Constipation is the most common gastrointestinal (GI) complaint in the United States, affecting between 2% and 28% of the population. Although it is usually relatively benign, the condition can be serious and can negatively affect a patient’s quality of life, as well as the ability to perform daily activities and overall work productivity.

Constipation represents a substantial economic burden on the US healthcare system. Constipation can have various etiologies, and diseases and conditions associated with constipation can be difficult to diagnose and to treat.

Laxatives are the mainstay of treatment for patients who self-diagnose constipation. More recently, newer drugs have been approved for the treatment of constipation in association with irritable bowel syndrome (IBS) and chronic idiopathic constipation.

Irritable Bowel Syndrome

IBS affects between 25 million and 55 million people in the United States, the majority of them female. IBS is often described as constipation predominant, diarrhea predominant, or an alternating pattern of constipation and diarrhea. Each of these types accounts for approximately 33% of all people with IBS.

An estimated 13 million Americans have IBS with constipation, which is considered a chronic GI disorder with symptoms that can be severe enough to compromise one’s ability to carry out daily activities.

IBS with constipation is associated with a substantial economic burden related to the direct costs of care and the indirect costs, including reduced employment and work productivity.

The symptoms associated with IBS include recurrent abdominal pain associated with defecation or a change in bowel habits with features of abnormal defecation that can include diarrhea, excess bloating, and either harder or looser stools than normal (hard stools in >25% of bowel movements and soft/watery stools in <25%).

According to the Rome III criteria for IBS, the symptoms of IBS involve recurrent abdominal pain or discomfort and a marked change in bowel habits for at least 6 months, with symptoms experienced on at least 3 days within at least 3 months. Two or more of the following symptoms must apply for the diagnosis of IBS:

- Pain is relieved by a bowel movement
- Onset of pain is related to a change in frequency of stool
- Onset of pain is related to a change in the appearance of stool

The causes of IBS are not completely understood. The proposed causes of IBS include bowel motility problems, hypersensitivity of the colon, dysregulation of neurotransmitters, and hormonal factors. None of these presumptive causes has been established with certainty. The triggers of IBS include specific foods, medications, the presence of gas or stool, and emotional stress.

Chronic Idiopathic Constipation

Chronic idiopathic constipation is a functional disorder with no identified anatomic or physiologic causes. Chronic idiopathic constipation is not relieved by standard therapy. Chronic idiopathic constipation can also be accompanied by a sensation of incomplete bowel movements and hard stools. Unlike IBS with constipation, patients with chronic idiopathic constipation do not have pain as a primary symptom.

The Rome III diagnostic criteria for chronic idiopathic constipation include the onset of ≥2 of the following symptoms for at least 6 months:

- Straining for at least 25% of bowel movements
- Lumpy or hard stools in at least 25% of bowel movements
- Sensation of incomplete evacuation at least 25% of the time
- Sensation of anorectal blockage/obstruction at least 25% of the time
- Manual maneuvers to facilitate at least 25% of bowel movements
- Fewer than 3 bowel movements weekly.

Medications Used to Treat Constipation

Laxatives are frequently used to treat chronic idiopathic constipation, with between 16% and 40% of patients with chronic idiopathic constipation using laxatives; no less than 66% of patients used them at least monthly.

Linzess: A Novel Treatment Option for Constipation Associated with Irritable Bowel Syndrome

By Alice Goodman, Medical Writer
However, many patients are dissatisfied with laxatives as a treatment, and these agents do not target the pathophysiologic abnormalities associated with constipation.8 Newer drugs developed for the treatment of chronic idiopathic constipation over the past decade include prucalopride (Resolor) and lubiprostone (Amitiza). A meta-analysis of randomized controlled trials of laxatives and some of these newer agents conducted in 2010 showed that laxatives (with the exception of lactulose) and the newer agents were more effective than placebo in the treatment of chronic idiopathic constipation.9 The most recent agent was approved at the end of 2012.10

**Linzess Receives FDA Approval**

Linaclotide (Linzess; Ironwood Pharmaceuticals/Forest Laboratories) was approved in December 2012 by the US Food and Drug Administration (FDA) for the treatment of constipation in adults in association with IBS or chronic idiopathic constipation. Linaclotide’s approval is limited to treatment of adults; the drug should not be used in pediatric patients or in patients younger than age 17.10 Linaclotide is the only FDA-approved guanylate cyclase-C (GC-C) agonist that acts locally in the intestinal tract. Furthermore, linaclotide is the first new FDA-approved treatment option for adults with constipation in 6 years.

**Mechanism of Action**

Linaclotide is believed to exert its effects via 2 mechanisms. The drug binds to the GC-C receptor within the intestinal epithelium. Activation of GC-C leads to increased secretion of intestinal fluid and then transit through the intestinal tract, as well as reduced visceral pain, which is mediated by reduced activity of sensory nerves that are involved in the perception of pain.5

**Dosing**

The oral capsule linaclotide that is taken once daily has been shown to alleviate the pain and constipation associated with IBS associated with constipation and the hard stools observed in patients with chronic idiopathic constipation. The recommended doses are 290 mcg for IBS with constipation and 145 mcg for patients with chronic idiopathic constipation.11 Linaclotide should be swallowed whole once daily on an empty stomach as prescribed.11

**Clinical Trials Data with Linaclotide**

Randomized, placebo-controlled clinical trials with a total of more than 2800 adults demonstrated that linaclotide alleviated abdominal pain in patients with constipation-predominant IBS and improved the frequency of bowel movements in these patients, as well as in patients with chronic idiopathic constipation.11

**Trials 1 and 2: IBS with Constipation**

Two double-blind, placebo-controlled, randomized, multicenter trials established the efficacy of linaclotide for the management of symptoms of IBS with constipation. Trial 1 and Trial 2 enrolled 800 and 804 patients, respectively, who met the Rome II criteria for IBS, and

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Trial 1</th>
<th>Treatment difference, %</th>
<th>Trial 2</th>
<th>Treatment difference, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Linaclotide 290 mcg (N = 405), %</strong></td>
<td>12.1</td>
<td>7.0 (95% CI, 3.2-10.9)</td>
<td>12.7</td>
<td>9.7 (95% CI, 6.1-13.4)</td>
</tr>
<tr>
<td><strong>Placebo (N = 395), %</strong></td>
<td>5.1</td>
<td></td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td><strong>Abdominal pain responder a (≥30% abdominal pain reduction)</strong></td>
<td>34.3</td>
<td>7.2 (95% CI, 0.9-13.6)</td>
<td>38.9</td>
<td>19.3 (95% CI, 13.2-25.4)</td>
</tr>
<tr>
<td><strong>Placebo (N = 403), %</strong></td>
<td>27.1</td>
<td></td>
<td>19.6</td>
<td></td>
</tr>
<tr>
<td><strong>CSBM responder a (≥3 CSBMs and increase ≥1 CSBM from baseline)</strong></td>
<td>19.5</td>
<td>13.2 (95% CI, 8.6-17.7)</td>
<td>18.0</td>
<td>13.0 (95% CI, 8.7-17.3)</td>
</tr>
<tr>
<td><strong>Placebo (N = 403), %</strong></td>
<td>6.3</td>
<td></td>
<td>5.0</td>
<td></td>
</tr>
</tbody>
</table>

*aPrimary end points. Analyses based on first 12 weeks of treatment for both trials 1 and 2. CI indicates confidence interval; CSBM, complete spontaneous bowel movement; IBS, irritable bowel syndrome. Source: Linzess [package insert]. St Louis, MO: Forest Laboratories, Inc; August 2012.
randomized them to treatment with linaclotide 290 mcg or placebo once daily.\textsuperscript{11}

Both trials had identical designs for the first 12 weeks; after that, Trial 1 included a 4-week randomized withdrawal period and Trial 2 continued double-blind treatment for 14 additional weeks, for a total of 26 weeks.

Efficacy was based on responder analyses and change from baseline based on individual patient diaries. Efficacy end points included analysis of response for at least 9 of the first 12 weeks of treatment or at least 6 of the first 12 weeks of treatment (Table 1). Both end points, which were complex, required at least a 30% reduction from baseline in mean abdominal pain and an increase in complete spontaneous bowel movements. For all efficacy end points, the percentage of patients who responded to linaclotide 290 mcg was statistically superior to placebo.

In Trial 1, 12.1% of the linaclotide group and 5.1% of the placebo-receiving patients met the primary end point of combined response—abdominal pain and complete spontaneous bowel movement response for at least 9 of 12 weeks. In Trial 2, the percentages were 12.7% and 3.0%, respectively, for response for at least 9 of 12 weeks. For efficacy response rates in at least 6 of 12 weeks, in Trial 1 the combined responder rates were 33.6% in the linaclotide group and 21.0% for placebo. In Trial 2, 33.7% and 13.9%, respectively, responded in at least 6 of 12 weeks.\textsuperscript{11}

In each trial, abdominal pain and complete spontaneous bowel movement frequency improved over the first 12 weeks of treatment. The use of linaclotide began to show distinct improvement in abdominal pain compared with placebo during the first week of treatment. The maximum effects of linaclotide were observed in weeks 6 through 9 and maintained until the studies were ended. At 12 weeks, according to an 11-point pain scale, the mean difference between linaclotide and placebo was 1 point in both trials. A beneficial effect on complete spontaneous bowel movement was seen during the first week of treatment, and the change from baseline in frequency of complete spontaneous bowel movement at week 12 was a difference between linaclotide and placebo of approximately 1.5 complete spontaneous bowel movements weekly in both trials.

In Trial 1, during the 4-week built-in randomized withdrawal period, linaclotide-treated patients who were then rerandomized to placebo experienced a return of abdominal pain severity and complete spontaneous bowel movement to baseline levels. By contrast, patients in the placebo arm who were rerandomized to linaclotide experienced an increase in complete spontaneous bowel movement frequency and a similar abdominal pain level as that observed in patients who were randomized to linaclotide during the treatment period.

**Trials 3 and 4: Chronic Idiopathic Constipation**

Two double-blind, placebo-controlled, randomized, multicenter clinical trials established the efficacy of linaclotide in adults with chronic idiopathic constipation. Trials 3 and 4 enrolled 642 and 630 patients, respectively, and randomized them to treatment with linaclotide 145 mcg, linaclotide 290 mcg, or to placebo, all once daily.\textsuperscript{10} All patients met the modified Rome II criteria for functional constipation. Patients with IBS with constipation and those with fecal impaction requiring emergency treatment were excluded from Trials 3 and 4.\textsuperscript{11}

Trials 3 and 4 had identical designs. Trial 3 also included an additional 4-week withdrawal period. As in Trials 1 and 2, efficacy was based on overall responder analyses and change from baseline end points according to patients’ daily diaries. The higher dose (ie, 290 mcg) of linaclotide did not offer any benefit over the 145-mcg daily dose in these trials, so the 145-mcg daily dose has been deemed the appropriate and recommended dose.

In both trials, the proportion of patients who responded to linaclotide with a complete spontaneous bowel movement was significantly greater with the recommended dose of linaclotide than with placebo. Criteria for overall response were at least 3 complete spontaneous bowel movements and an increase of at least 1 complete spontaneous bowel movement from baseline for 9 of 12 weeks (Table 2).

In Trial 3, the absolute treatment difference favoring linaclotide was 16.9% (95% confidence interval [CI], 11.0%-22.8%). In Trial 4, the absolute difference favoring linaclotide was 9.9% (95% CI, 4.2%-15.7%).\textsuperscript{11}

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Trial 3</th>
<th>Trial 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linaclotide, %</td>
<td>20.3</td>
<td>15.5</td>
</tr>
<tr>
<td>Placebo, %</td>
<td>3.3</td>
<td>5.6</td>
</tr>
</tbody>
</table>

Adverse Events and Precautions

Linaclotide should not be used for children under age 17 years or for patients with known or suspected obstruction of the GI tract.11

Pooled data from Trials 1, 2, 3, and 4 show that diarrhea was the most common adverse event related to linaclotide. Severe diarrhea occurred in 2% of the linaclotide-treated patients in these clinical trials, with a similar incidence in patients with IBS with constipation and those with chronic idiopathic constipation (Table 3).11

In the pooled IBS-with-constipation pivotal trials, diarrhea was reported in 20% of the linaclotide-receiving patients and in 3% of the placebo-receiving patients. Severe diarrhea was reported in 2% and 1%, respectively, of the patients. Diarrhea-related treatment discontinuations occurred in 5% of those randomized to linaclotide versus <1% of the placebo group.

In the pooled chronic idiopathic constipation trials, diarrhea was the most frequently reported adverse event in the linaclotide-treated patients (16% vs 5% of placebo patients). Severe diarrhea was reported in 2% and less than 1%, respectively. Diarrhea-related treatment discontinuations were reported in 5% and less than 1%, respectively.11

Conclusion

Constipation in association with IBS or chronic idiopathic constipation affects millions of people and can be difficult to treat. Linaclotide is the first oral medication to be approved by the FDA in the past 6 years for the treatment of patients with IBS associated with constipation or for those with chronic idiopathic constipation. This approval adds a new treatment option for these 2 patient populations, by reducing abdominal pain that is associated with chronic idiopathic constipation and improving complete spontaneous bowel movements in both groups of patients.11

References