CLINICAL UPDATE

Advances in the Treatment of Irritable Bowel Syndrome

New Treatment Option for Irritable Bowel Syndrome with Constipation and Chronic Idiopathic Constipation

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G&H What symptoms occur in irritable bowel syndrome with constipation and chronic idiopathic constipation? How do these 2 conditions differ?

PSS Irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) are very common gastrointestinal disorders that affect millions of Americans. Patients who suffer from these conditions experience a significant reduction in quality of life due to both lost productivity (ie, missing work days) and an inability to enjoy time with their families.

IBS-C is approximately twice as prevalent in women than men in the United States, but this condition has a relatively similar prevalence across all age groups. In contrast, CIC occurs at the same frequency in men and women, but it is more common in older individuals. This latter observation may be due, in part, to the increased frequency with which this age group experiences other risk factors for the development of constipation.

The chief complaint among patients with IBS-C is abdominal discomfort, with additional symptoms including bloating, cramping, and constipation (including difficulty passing stool, straining, and infrequent stools). Unlike patients with IBS-C, the chief complaints among patients with CIC are related to hard and lumpy stools, as well as a feeling of incomplete evacuation.

G&H What treatment options are currently available for IBS-C and CIC?

PSS Multiple agents have been approved by the US Food and Drug Administration (FDA) with an indication for occasional constipation, including fiber or psyllium products, osmotic laxatives, and stool softeners. While patients with IBS-C and CIC frequently use these agents, they are only approved for the treatment of occasional constipation. Lactulose is FDA-approved for long-term treatment of chronic constipation. Before the approval of linaclotide (Linzess, Ironwood Pharmaceuticals/Forest Laboratories), the only FDA-approved therapy for CIC and IBS-C was lubiprostone (Amitiza, Sucampo Pharmaceuticals), which is indicated for use in women with IBS-C and in men and women with CIC. Recently, the FDA approved linaclotide for the treatment of both IBS-C and CIC, thus giving clinicians another medical treatment option for these conditions.

G&H What is the mechanism of action of linaclotide?

PSS Linaclotide is a guanylate cyclase C receptor agonist. Guanylate cyclase C receptors are expressed on the surface of colonic mucosal cells, which are located on the luminal surface of the intestinal epithelium. Linaclotide (and its active metabolite) bind to and activate this receptor, thus stimulating production of cyclic guanosine monophosphate (cGMP). As a result, both intracellular and extracellular concentrations of cGMP are increased. Intracellular cGMP then stimulates the secretion of chloride and bicarbonate into the intestinal lumen, leading to an increase in intestinal fluid and thus accelerated transit. Extracellular cGMP is thought to decrease the activity of pain-sensing nerves, thus reducing visceral pain.

G&H What were the results of animal studies and early clinical trials of linaclotide?

PSS Testing in animal models supports the mechanisms of action of linaclotide in terms of both intracellular and

extracellular effects. In vitro animal studies also showed that linaclotide treatment was not associated with evidence of carcinogenicity, mutagenesis, or impairment of fertility. Clinical studies have shown that linaclotide increases stool frequency and changes stool consistency (measured by the Bristol Stool Form Scale). However, there are currently no head-to-head trials directly comparing linaclotide to other commonly used treatments for IBS-C or CIC. Finally, linaclotide appears to be minimally absorbed, and this drug has low systemic availability following oral administration.

G&H Could you please describe the 2 clinical trials that led to linaclotide's approval for IBS-C?

PSS Trial 1 was a 12-week, double-blind trial in which patients were randomized to receive either linaclotide at a dose of 290 µg once daily or placebo. After completion of the initial 12-week period, all patients in the placebo arm were switched over to linaclotide; patients in the linaclotide arm were re-randomized to either linaclotide or placebo for an additional 4 weeks. Both of these switches occurred in a blinded fashion.

Trial 2 also randomized IBS-C patients in a 1:1 fashion to treatment with either linaclotide or placebo. In this trial, however, double-blind treatment continued for a total of 26 weeks, which is a particularly long treatment duration for a clinical trial involving patients with IBS-C.

Overall, these 2 studies enrolled 1,604 IBS-C patients, all of whom met the Rome II criteria for IBS. Patients who were already being treated with a bulk laxative (eg, psyllium) prior to study enrollment were allowed to continue this treatment during the study; however, no other rescue medications were permitted.

G&H What endpoints were used to evaluate the efficacy of linaclotide in the IBS-C clinical trials?

PSS In the IBS-C trials, there were 4 primary efficacy responder endpoints. The first 2 endpoints were based on whether the patient was a weekly responder for at least 9 of the first 12 weeks of treatment or at least 6 of the first 12 weeks of treatment. The other primary endpoints were abdominal pain (≥30% reduction in abdominal pain) and complete spontaneous bowel movements (≥3 complete spontaneous bowel movements and an increase of ≥1 complete spontaneous bowel movements from baseline). For the 9-of-12–week combined primary responder endpoint, a patient had to have at least a 30% reduction from baseline in mean abdominal pain, at least 3 complete spontaneous bowel movements, and an increase of at least 1 complete spontaneous bowel movement from baseline, all in the same week. For the 6-of-12–week combined primary responder endpoint, a patient had to have at least a 30% reduction from baseline in mean abdominal pain and an increase of at least 1 complete spontaneous bowel movement from baseline, both in the same week. Having 3 complete spontaneous bowel movements per week was not required for the 6-of-12–week responder endpoint.

G&H What were the efficacy results with linaclotide in these 2 IBS-C clinical trials?

PSS For the 9-of-12–week endpoint, the proportion of patients who achieved a combined response (improvement in both abdominal pain and complete spontaneous bowel movements) was higher with linaclotide than placebo in both Trial 1 (12.1% vs 5.1%) and Trial 2 (12.7% vs 3.0%). The stringency of the 9-of-12–week endpoint is reflected in the fact that very few placebo-treated patients were able to meet this endpoint (5.1% and 3.0% in Trials 1 and 2, respectively). Linaclotide also showed a benefit over placebo in the 9-of-12–week endpoint when efficacy was assessed in terms of either abdominal pain improvement alone (Trial 1: 34.3% vs 27.1%; Trial 2: 38.9% vs 19.6%) or improvement in complete spontaneous bowel movements alone (Trial 1: 19.5% vs 6.3%; Trial 2: 18.0% vs 5.0%).

Similar results were observed for the 6-of-12–week endpoint: The proportion of patients who achieved a combined response (improvement in both abdominal pain and complete spontaneous bowel movements) was higher with linaclotide than placebo (Trial 1: 33.6% vs 21.0%; Trial 2: 33.7% vs 13.9%). Linaclotide also showed benefit over placebo when efficacy was assessed in terms of either abdominal pain improvement alone (Trial 1: 50.1% vs 37.5%; Trial 2: 48.9% vs 34.5%) or improvement in complete spontaneous bowel movements alone (Trial 1: 48.6% vs 29.6%; Trial 2: 47.6% vs 22.6%).

The maximum effect on complete spontaneous bowel movement frequency occurred within the first week of treatment, while the maximum effect on abdominal pain was observed up to 6–9 weeks later. This temporal difference supports the hypothesis that linaclotide's various effects occur via different mechanisms of action—namely, that the drug's intracellular effect results in improved stool transit, while the drug's extracellular effect modifies the activity of pain-sensing nerves.

G&H In Trial 1, what was the result of switching from placebo to linaclotide or vice versa?

PSS After the initial 12-week treatment period in Trial 1, patients in the placebo group who were switched to linaclotide showed an increase in complete spontaneous bowel movements and an improvement in abdominal pain; these improvements produced similar improvement

in symptoms compared with patients who had received initial linaclotide therapy. Patients who were originally randomized to linaclotide and continued linaclotide following re-randomization maintained their improvement in abdominal pain and complete spontaneous bowel movements. However, these outcomes quickly worsened among patients who were initially treated with linaclotide but were then re-randomized to placebo.

G&H Regarding linaclotide's approval for CIC, could you please describe the 2 clinical trials that led to this approval?

PSS The 2 pivotal studies that evaluated linaclotide for the treatment of CIC were both 12-week trials. Trial 3 randomized CIC patients in a 1:1 fashion to linaclotide or placebo; in this trial, linaclotide was administered at a dose of 145 µg once daily. Trial 3 also utilized a re-randomization scheme similar to the one used in Trial 1; again, this aspect of the study design allowed patients to either continue linaclotide or switch to placebo for the last 4 weeks of the study. Trial 4 was a simple, direct comparison study in which patients were treated for a period of 12 weeks.

A total of 1,272 patients with CIC were included in Trials 3 and 4; all patients met modified Rome II criteria for functional constipation, which does not require abdominal pain as part of the definition. Stable doses of bulk laxatives or stool softeners could be continued during these studies, but rescue doses of osmotic or stimulant laxatives were not permitted.

The only endpoint evaluated in the CIC trials was improvement in complete spontaneous bowel movements. A complete spontaneous bowel movement overall responder was defined as a patient who had at least 3 complete spontaneous bowel movements and an increase of at least 1 complete spontaneous bowel movement from baseline, both in the same week, for at least 9 of 12 weeks.

G&H What were the results of these 2 trials?

PSS For the 9-of-12–week endpoint, the proportion of patients who achieved an improvement in complete spontaneous bowel movements was higher with linaclotide than placebo in both Trial 3 (20.3% vs 3.3%) and Trial 4 (15.5% vs 5.6%).

G&H In Trial 3, what was the result of switching from placebo to linaclotide or vice versa?

PSS Linaclotide-treated patients with CIC who were re-randomized to placebo showed a decrease in the frequency of complete spontaneous bowel movements, with this rate returning to baseline. In contrast, linaclotide-treated patients who continued linaclotide maintained their improvements in complete spontaneous bowel movement frequency.

G&H What side effects have been observed with linaclotide?

PSS Diarrhea was the most common adverse event reported in both the IBS-C and CIC clinical trials of linaclotide. In the IBS-C trials, 20% of linaclotide-treated patients experienced diarrhea compared to 3% of placebo-treated patients; in the CIC trials, these rates were 16% and 5%, respectively. Severe diarrhea occurred in 2% of linaclotide-treated patients in the IBS-C and CIC studies, and 5% of linaclotide-treated patients discontinued therapy due to diarrhea. With the exception of diarrhea, adverse events did not occur at significantly different rates in the linaclotide versus placebo groups; this finding was observed in both the IBS-C and CIC trials.

G&H What other safety data are available for linaclotide?

PSS No drug-drug interactions have been associated with linaclotide, and this drug has not been found to interact with the cytochrome P450 enzyme system in the liver. Animal studies show no evidence of maternal toxicity or effects on fetal development, but we lack adequate human studies assessing linaclotide during pregnancy, so this drug is considered to be a pregnancy category C drug. Studies are currently assessing the amount of linaclotide in the milk of nursing mothers.

G&H Why is linaclotide contraindicated in children?

PSS Linaclotide has a boxed warning specifying that this drug is contraindicated in pediatric patients up to 6 years of age and that its use should be avoided in pediatric patients aged 6–17 years. The reason for this warning is that, in 2 separate toxicology studies, linaclotide caused deaths in juvenile neonatal mice whose ages were approximately equivalent to those of human infants and children less than 2 years of age. These deaths occurred following administration of a clinically relevant adult dose (either 1 or 2 doses at 10 µg/kg/day or a single dose at 100 µg/kg or 600 µg/kg). In a separate study, no deaths occurred among older juvenile mice with ages approximately equivalent to human ages between 12 and 17 years. Because the mechanism for the deaths in juvenile mice is not known and there is a lack of safety data in pediatric patient populations, the use of

linaclotide should be avoided in children aged 6–17 years. Linaclotide did not cause death in adult mice, rats, rabbits, or monkeys at doses up to 1,000-fold higher than the maximum recommended adult dose.

G&H Why should linaclotide be taken on an empty stomach?

PSS A crossover study in 18 healthy subjects suggested that linaclotide may have a food effect. Thus, the current indication for linaclotide is that it be taken on an empty stomach at least 30 minutes prior to the first meal of the day.

Suggested Reading

Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol*. 2012 Sep 18. Epub ahead of print.

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