Effect of Linaclotide on Severe Abdominal Symptoms in Patients With Irritable Bowel Syndrome With Constipation

Satish S. C. Rao,[*] Eamonn M. M. Quigley,[‡] Steven J. Shiff,[§] Bernard J. Lavins,[‖] Caroline B. Kurtz,[‖] James E. MacDougall,[‖] Mark G. Currie,[‖] and Jeffrey M. Johnston[‖]

*Section of Gastroenterology and Hepatology, Georgia Regents University, Augusta, Georgia; [‡]Gastroenterology Division, Houston Methodist Hospital and Weill Cornell Medical College, Houston, Texas; [§]Forest Research Institute, Jersey City, New Jersey; and [‖]Ironwood Pharmaceuticals, Cambridge, Massachusetts

BACKGROUND & AIMS: **Patients with irritable bowel syndrome with constipation (IBS-C) have abdominal symptoms that vary in severity. Linaclotide, a guanylate cyclase-C agonist, improves abdominal and bowel symptoms in these patients. We examined the prevalence of severe abdominal symptoms in patients with IBS-C and assessed the effects of linaclotide on abdominal symptoms, global measures, and quality of life (QOL).**

METHODS: **In two phase 3 trials, patients who met modified Rome II criteria for IBS-C were randomly assigned to groups given oral, once-daily linaclotide (290 μg) or placebo for 12 weeks. During the baseline (2 weeks prior to treatment) and treatment periods, patients rated abdominal pain, discomfort, bloating, fullness, and cramping daily (from 0 = none to 10 = very severe). Linaclotide's effects on abdominal symptoms, global measures, and IBS-related QOL were assessed in subpopulations of patients who rated specific individual abdominal symptoms as severe (≥7.0) at baseline.**

RESULTS: **In the intent-to-treat population (1602 patients; 797 receiving placebo and 805 receiving linaclotide), baseline prevalence values for severe abdominal symptoms were 44% for bloating, 44% for fullness, 32% for discomfort, 23% for pain, and 22% for cramping, with considerable overlap among symptoms. In patients with severe symptoms, linaclotide reduced all abdominal symptoms; mean changes from baseline severity scores ranged from −2.7 to −3.4 for linaclotide vs −1.4 to −1.9 for placebo ($P < .0001$). Linaclotide improved global measures ($P < .0001$) and IBS-QOL scores ($P < .01$) compared with placebo. Diarrhea was the most common adverse event of linaclotide in patients with severe abdominal symptoms (18.8%–21.0%).**

CONCLUSIONS: **Of 5 severe abdominal symptoms assessed, bloating and fullness were most prevalent in patients with IBS-C. Linaclotide significantly improved all abdominal symptoms, global measures, and IBS-QOL in subpopulations of IBS-C patients with severe abdominal symptoms. Clinicaltrials.gov Numbers: NCT00938717, NCT00948818.**

Keywords: Guanylate Cyclase-C; IBS-C; Abdominal Pain; Bloating.

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder affecting up to 15% of the population in developed countries.[1–3] IBS is characterized by abdominal pain or discomfort associated with altered defecation[4] and is classified on the basis of predominant stool form into 4 subtypes: IBS with diarrhea, IBS with constipation (IBS-C), mixed IBS, and unsubtyped IBS.[4]

Patients with IBS-C often experience an array of abdominal symptoms, including pain, discomfort, bloating, fullness, and cramping, that vary in severity. The severity of abdominal symptoms has significant clinical implications because patients with more severe symptoms tend to use more health care resources, have worse health-related quality of life (QOL), and be less likely to respond to treatment.[5,6] Symptom severity is also an important component of a patient's perception of his/her overall IBS severity.[5] Despite the importance of symptom

Abbreviations used in this paper: **AE, adverse event; ANCOVA, analysis of covariance; BM, bowel movement; cGMP, cyclic guanosine monophosphate; CMH, Cochran–Mantel-Haenszel; GC-C, guanylate cyclase-C; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; ITT, intent to treat; IVRS, interactive voice response system; LOCF, last observation carried forward; NNT, number needed to treat; NRS, numerical rating scale; QOL, quality of life.**

1542-3565
http://dx.doi.org/10.1016/j.cgh.2013.09.022

severity, there are scant data regarding the prevalence of symptoms that IBS-C patients rate as severe.

Linaclotide, a 14-amino acid peptide, is a guanylate cyclase-C (GC-C) agonist that is structurally related to the guanylin peptide family and is approved by the United States Food and Drug Administration for the treatment of IBS-C and chronic idiopathic constipation in adults and by the European Medicines Agency for the treatment of moderate to severe IBS-C in adults. Linaclotide binds to and activates GC-C, resulting in the intracellular generation of cyclic guanosine monophosphate (cGMP), which is then increased both intracellularly and extracellularly. Data from animal models show that the increase in intracellular cGMP results in a cascade of events leading to increased fluid secretion into the intestinal lumen and accelerated gastrointestinal transit; the increase in extracellular cGMP results in reduced visceral nociception.[7,8]

In two phase 3 clinical trials, linaclotide has been shown to improve abdominal and bowel symptoms in patients with IBS-C.[9,10] However, the efficacy of linaclotide in IBS-C patients with severe symptoms has not been examined. To address this issue, a post hoc analysis of pooled data from the two phase 3 trials was conducted with the following objectives: (1) to examine the baseline prevalence of severe abdominal symptoms (pain, discomfort, bloating, fullness, cramping) and (2) to assess the effects of linaclotide on these symptoms, as well as on global measures of improvement (adequate relief, degree of relief, and treatment satisfaction) and IBS-related QOL, in the subpopulations of IBS-C patients with severe abdominal symptoms at baseline.

Methods

Trial Design

Detailed study methods for both phase 3 clinical trials (Trials 31 and 302) have been recently published.[9,10] In brief, these multicenter, randomized, double-blind, placebo-controlled, parallel-group trials were identical through the first 12 weeks of treatment. The trials included a 2-week baseline period that was followed by randomization of patients in equal proportions to either placebo or linaclotide 290 μg once daily during treatment periods of either 12 weeks (Trial 31) or 26 weeks (Trial 302). Primary end points were assessed for both trials during the first 12 weeks of treatment.

Trial Patients

Inclusion and exclusion criteria for the trials have been published previously.[9,10] Briefly, female and male patients were eligible to participate if they were at least 18 years of age and met modified Rome II criteria for IBS-C.[11] Patients had to have a mean score $\geq$3.0 for daily abdominal pain at its worst (11-point numerical rating scale [NRS]) as well as a mean of $\leq$5 spontaneous bowel movements (a bowel movement [BM] occurring in the absence of laxative, enema, or suppository use on the calendar day of the BM or the calendar day before the BM) per week and $<$3 complete spontaneous BMs (a spontaneous BM that is associated with a sensation of complete emptying) per week during the 2-week baseline period.

Efficacy Assessments and Severe Subpopulation Criterion

Daily reports by patients to an interactive voice response system (IVRS) included symptom ratings of abdominal pain at its worst, abdominal discomfort, abdominal bloating, abdominal fullness, and abdominal cramping. All abdominal symptoms were measured by using the 11-point NRS (example question: "How would you rate your abdominal discomfort over the last 24 hours? Enter a number from 0 to 10, where 0 represents no abdominal discomfort and 10 represents very severe abdominal discomfort."). The severe subpopulation for each abdominal symptom included patients in the intent-to-treat (ITT) population with a baseline score $\geq$7.0[12] for that abdominal symptom. Patients were included in more than 1 subpopulation if they had more than 1 abdominal symptom scored $\geq$7.0 at baseline.

Weekly IVRS assessments of global measures of improvement included adequate relief of IBS-C symptoms (yes/no) and degree of relief of IBS symptoms (7-point balanced scale: 1 = completely relieved, 4 = unchanged, 7 = as bad as I can imagine). Satisfaction with the trial medication's ability to relieve IBS symptoms (5-point ordinal scale: 1 = not at all satisfied to 5 = very satisfied) was assessed at all trial visits. The IBS-QOL, a self-administered QOL instrument yielding an overall score ranging from 0 (poor QOL) to 100 (maximum QOL),[13] was assessed at baseline and at week 12.

End Points

Change-from-baseline end points for abdominal symptoms (pain, discomfort, bloating, fullness, and cramping) were analyzed at week 12. Responder end points for adequate relief of IBS-C symptoms, degree of relief of IBS symptoms, treatment satisfaction, and IBS-QOL overall score were also analyzed at week 12; the number needed to treat (NNT) was calculated for each of these end points. Adequate relief responders answered "yes" to the question "Overall, have you had adequate relief from your IBS symptoms during the past 7 days?" Degree of relief responders had a degree of relief of IBS symptoms score of $\leq$3 (somewhat relieved, considerably relieved, or completely relieved) on the 7-point balanced scale. Treatment satisfaction responders had a treatment satisfaction score of $\geq$3 (moderately, quite, or very satisfied) on the 5-point scale. IBS-QOL responders had a change-from-baseline improvement of $\geq$14 points on the