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REVIEW

Linaclotide: evidence for its potential use in irritable bowel syndrome and chronic constipation

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Abstract: Both irritable bowel syndrome (IBS), characterized by chronic and recurrent abdominal pain and altered bowel habits, and functional constipation are highly prevalent gastrointestinal problems for which many patients seek medical advice. A diverse number of treatment approaches are currently recommended to treat persons with chronic constipation as well as patients with IBS in which constipation is the main gastrointestinal symptom (IBS-C). These approaches have had somewhat limited success, and many patients remain dissatisfied with available therapy. Recently, linaclotide, a novel intestinal secretagogue, which works by activating the guanylate cyclase C receptor on the luminal surface of the intestinal epithelium, has been demonstrated to be efficacious in patients with both chronic functional constipation and with IBS-C in a series of randomized, placebo-controlled studies in these populations. Evidence for this assertion is provided in this systematic review of the pharmacologic properties of this novel agent and the published pivotal studies which support the efficacy of this agent in targeted populations.

Keywords: linaclotide, constipation, irritable bowel syndrome, safety, efficacy

Core evidence clinical impact summary for linaclotide in chronic constipation (CC) and irritable bowel syndrome (IBS)

Outcome measure	Evidence	Implications
Disease oriented evidence	Randomized clinical trials	
Response rate	Ref 16 (CC) Ref 19,20 (IBS)	Safe and effective but only 10%–20% above placebo responses
Improvement in QOL	Ref 16 (CC) Ref 21 (IBS)	Improvement significantly greater than placebo
Patient oriented evidence		
Safety	Ref 16 (CC) Ref 18,19,20 (IBS)	Appears to be safe
Diarrhea	Ref 16 (CC) Ref 18,19,20 (IBS)	3%–5% withdrawal rates for diarrhea
Economic evidence	Unknown	The drug has not yet been approved by US FDA for use in constipation or IBS

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Introduction

Irritable bowel syndrome (IBS) is a gastrointestinal disorder characterized by chronic abdominal pain and altered bowel habits in the absence of an organic cause. The prevalence of IBS in the US, based on population-based studies, is approximately 10%–15%, and it is the most commonly diagnosed gastrointestinal condition.[1] A population-based study in Europe found a similar overall prevalence of 11.5%.[2]

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Patients with IBS account for upto 25%–50% of all referrals to gastroenterologists,[3] and some studies estimate that annual direct and indirect health care costs in the US are as high as $30 billion.[4]

Patients with IBS can present in various ways, but the symptom complex of chronic abdominal pain and altered bowel habits remains the nonspecific yet primary characteristic of IBS. The abdominal pain is described as a cramping sensation, varying in intensity and with exacerbations. Patients with IBS also complain of altered bowel habits, ranging from diarrhea, constipation, alternating diarrhea and constipation, or normal bowel habits, alternating with either diarrhea and/or constipation.[5]

In contrast with IBS, chronic constipation is described as a combination of infrequent bowel movements, hard stools, straining during defecation, bloating, abdominal discomfort, and/or a sense of incomplete evacuation. Constipation affects between 12% and 19% of the US population and is also associated with substantial costs.[6] Although there is probably a considerable overlap with IBS-C, the focus of treating functional constipation centers predominantly on improving bowel habits, whereas the approach to patients with IBS-C must encompass improving abdominal pain as well as bowel habits. This makes the treatment of IBS-C more complicated and efficacy of such treatment more difficult to measure.

Unfortunately, there are no effective and safe treatments for all patients with IBS-C or for those with chronic constipation. Laxatives can help with constipation but do not treat the abdominal discomfort in IBS-C, and use of pain modulators, such as tricyclic agents, may worsen constipation. Therefore, many patients remain dissatisfied with current available treatments.

Linaclotide is a novel peptide agonist of guanylate cyclase which is minimally absorbed, and acts by actively transporting chloride ions into the intestinal lumen through the cystic fibrosis transmembrane conductance regulator channel. Similar to all laxatives, linaclotide acts to increase stool water content and to enhance the frequency and ease of defecation by a secretory mechanism.[7] This new agent has undergone clinical trials for the treatment of patients with IBS-C and chronic constipation. To date, results of these trials have been promising, and improvements in stool consistency, reduced straining, and reduced abdominal symptoms have been reported. These improvements are often seen in the first several days of drug administration with sustained effects.

Pharmacokinetics

The development of linaclotide as a novel compound was derived from the discovery of a family of cyclic guanosine-3′, 5′-monophosphate (cGMP)-regulating peptide hormones.[8] These peptides, guanylin and uroguanylin, are found in the gastrointestinal tract and are released into the intestinal lumen. Stimulation of guanylate cyclase C receptors by both peptides increases concentrations of cGMP, the second messenger which (among other actions) increases intestinal secretion of water and electrolytes.[9]

In nature, heat-stable bacterial endotoxins produce a secretory diarrhea by stimulating cGMP, and formed the conceptual basis for the pharmacologic development of a substituted homolog of stable endotoxins. Linaclotide is a 14-amino acid peptide homolog of stable bacterial endotoxins which incorporates the three disulfide bonds of the toxin to produce maximum potency. Removal of the C-terminal tyrosine residue by carboxypeptidase A produces a 13-amino acid peptide which enhances pharmacokinetic stability by resisting proteolysis and is associated with minimal intestinal absorption. In vivo animal studies and in vitro studies in T84 human colon carcinoma cells characterized the binding of linaclotide to guanylate cyclase C receptors with resultant stimulation of intracellular cGMP.[10]

Stability of linaclotide was demonstrated by showing no degradation after incubation in simulated gastric fluid (pH 1), and the compound was also completely resistant to degradation by pepsin after 3 hours of incubation. Also, orally administered linaclotide was minimally absorbed in rat studies. While linaclotide stimulated significant secretion when injected into rat duodenal, jejunal, and ileal loops, increased cGMP levels were highest in the duodenum and jejunum.[10]

Initial clinical studies

The initial Phase I studies in 30 healthy subjects were published in 2005 and established that linaclotide was safe and well tolerated in single oral doses of up to 3000 μg. Drug administration elicited a decrease in stool consistency as measured on the Bristol Stool Form Scale with an increase in stool weight.[11] In a subsequent multiple ascending-dose Phase I trial of linaclotide in 48 healthy subjects, oral doses of 30, 100, 300, or 1000 μg were administered once daily for 7 days. Linaclotide at all doses was again well tolerated, with a statistically significant increase in stool frequency and weight from baseline Bristol Stool Form Scale scores at the 30 μg, 300 μg, and 1000 μg doses. Mean ease of stool

passage increased significantly from baseline in the 1000 μg group.[12]

Studies in chronic functional constipation

The efficacy of linaclotide in patients with chronic constipation was initially evaluated in a randomized, double-blind, placebo-controlled pilot study. Forty-two patients with chronic constipation were randomized to linaclotide (100, 300, or 1000 μg) or placebo once daily for 14 days to evaluate the safety, tolerability, and efficacy of the drug. A significant increase in the frequency of spontaneous bowel movements occurred with the 100 μg dose compared with placebo (change 6.18 versus 2.76 for placebo, $P = 0.047$). Frequency of complete and spontaneous bowel movements (CSBMs) also increased, with mean changes of 2.16, 2.90, and 3.19 for the 100, 300 and 1000 μg doses, respectively, versus 1.30 for placebo. The authors considered CSBM to be a more clinically meaningful endpoint than spontaneous bowel movement because epidemiologic surveys have found that many constipated persons do not qualify for constipation by Rome II criteria based on stool frequency alone. This is because most constipated persons complain of defecation difficulties and/or a sense of incomplete evacuation.[13] Stool consistency also improved in a dose-related manner in all three drug groups, with a statistically significant increase with the 1000 μg dose versus placebo (change 2.58 versus 0.43 for placebo, $P = 0.014$). Straining improved in all groups, with the greatest improvement with the higher doses (change 1.33 and 1.51 for 300 μg and 1000 μg, respectively, versus 0.36 for placebo). Dose-related improvements were also seen in abdominal discomfort (mean scores decreased from baseline by –0.58, –0.76, and –0.85 for linaclotide 100, 300, and 1000 μg, respectively, versus –0.16 for placebo), overall relief, and severity of constipation. The effect on bowel habits occurred within the first few days of treatment and overall relief of constipation occurred within the first week. The improvement scores regressed towards baseline after the drug was stopped. Because there was no worsening compared with baseline, the authors concluded that there was no evidence of a rebound effect.[14]

A subsequent dose-ranging study of chronic constipation was done with larger numbers of patients and a longer duration of treatment. In this multicenter, double-blind trial, 310 patients with chronic constipation, as defined by Rome II criteria, were randomized into groups given 75, 150, 300, or 600 μg oral linaclotide or placebo once daily for 4 weeks. Rescue medications were allowed, including oral bisacodyl (up to 15 mg daily), Fleets enema, or bisacodyl suppositories, but no more than two rescue medications were allowed in the pretreatment period. Mean increases in frequency of spontaneous bowel movement exhibited a linear dose response with increases of 2.6, 3.3, 3.6, and 4.3 for doses of 75, 150, 300, and 600 μg, respectively, compared with 1.5 for placebo ($P < 0.05$). Patients receiving drug were more likely to have a spontaneous bowel movement within the first 24 hours (50.8%, 55.4%, 54.8%, and 75.8%, respectively, for the four doses) compared with placebo (36.8%, $P < 0.05$). The median time to first spontaneous bowel movement was 24.0, 21.9, 23.1, and 13.0 hours for the four doses versus 32.6 hours for placebo ($P = 0.0005$ for overall log-rank test). Similar changes were seen for mean weekly CSBM frequency. Improvement in overall stool consistency was also dose-related, as was overall straining. Bowel habits returned to baseline patterns during the post-treatment period, suggesting no rebound worsening of constipation. The percentage of patients who reported a decrease in the abdominal discomfort score (defined as ≥0.5 for 3 of 4 weeks) ranged from 27% to 32% for the four linaclotide doses versus 12% for placebo ($P < 0.05$ for each dose). Similarly, the percentage of patients who reported a decrease in the bloating score (defined as ≥0.5 for 3 of 4 weeks) ranged from 29% to 39% for linaclotide versus 12% for placebo ($P < 0.05$). All three global measures, including constipation severity, adequate relief of constipation, and relief of constipation, improved in dose-dependent manner. Of note, there was no significant change in rescue medication use between the placebo and linaclotide groups.[15]

In 2011, the results of two Phase III trials in chronic constipation were reported. Two randomized, 12-week, multicenter, double-blind, parallel-group, placebo-controlled trials were performed at 204 clinical centers in the US and at eight clinical centers in Canada. The trials were identical except that one trial included a 4-week period of randomized withdrawal at the conclusion of the 12-week treatment period. In a ratio of 1:1:1, patients were randomly given 145 μg or 290 μg of linaclotide, or placebo. After completing the treatment period, patients in one trial who had received linaclotide during the preceding treatment period were randomly assigned to either the same linaclotide dose or placebo, whereas patients who had received placebo during the treatment period were given 290 μg of linaclotide for a 4-week period.

Eligible patients who met the criteria for chronic constipation reported fewer than three spontaneous bowel movements

per week (without laxatives, enemas, or suppositories in the preceding 24 hours) and straining, lumpy, or hard stools or a sensation of incomplete evacuation for more than 25% of bowel movements for at least 12 weeks within the preceding 12 months. In addition, during the 14-day baseline period, patients had to report an average of fewer than six spontaneous bowel movements and fewer than three CSBMs per week. The primary endpoint of both trials was defined as both three or more CSBMs per week and an increase of at least one CSBM per week from baseline for at least 75% of the weeks of the treatment period. Secondary endpoints included stool frequency, stool consistency, severity of straining, abdominal discomfort, bloating, and constipation severity. Additional endpoints such as constipation relief, satisfaction with treatment, the likelihood of treatment continuation, and health-related quality of life were determined.

A total of 1272 patients (642 in trial 303 and 630 patients in trial 01) were included in the intention-to-treat analysis; rates of compliance during the treatment period were over 86%. In the two trials, 21.2% and 16.0% of the patients who received the 145 μg dose and 19.4% and 21.3% of the patients who received the 290 μg dose, respectively, met the primary endpoint versus 3.3% and 6.0% with placebo ($P < 0.01$ for each dose). In both trials, differences in overall response rates between the two linaclotide doses were not statistically significant. For all secondary endpoints, linaclotide-treated patients had significant improvements versus placebo. Weekly CSBM rates increased significantly with linaclotide in the first week and were maintained throughout the 12-week period. In both trials, scores for constipation relief, treatment satisfaction, and treatment continuation were significantly greater in both treatment groups than in the placebo group. At week 12, 44.9% and 42.2% of respective patients who received 145 μg and 35.5% and 46.8% of those who received 290 μg of linaclotide had improved by one point or more from baseline in overall Patient Assessment of Constipation Quality of Life score, compared with 18.7% and 27.8% who received placebo ($P < 0.01$). In trial 303, which included an additional 4 weeks, patients who continued to take linaclotide and those who were switched from placebo to linaclotide had sustained increases in the frequency of CSBMs similar to levels reported during the treatment period, whereas patients who switched from linaclotide to placebo had a decreased frequency of CSBMs.[16]

Studies in IBS-C

The first Phase IIA, randomized, double-blind, placebo-controlled single-site study evaluated the effects of oral linaclotide 100 μg and 1000 μg once daily for 5 days in 36 women with IBS-C. The primary endpoint was the effect on ascending colon emptying and colonic transit as determined by scintigraphy. There were no demonstrable effects of linaclotide on gastric emptying or colonic filling at 6 hours, the latter being a marker for small intestine transit time. However, there was significant acceleration of ascending colon emptying, but only with 1000 μg compared with placebo ($P = 0.004$). The acceleration of ascending colon transit may have been due to decreased colon fluid absorption, because there is a high capacity of fluid absorption in this part of the colon. Acceleration of overall colonic transit occurred at 48 hours ($P = 0.02$), but not at 24 hours. As with ascending colon emptying, the geometric center at 48 hours was significantly faster only with 1000 μg ($P = 0.01$). As determined by daily stool diaries, linaclotide shortened the time to first bowel movement ($P = 0.013$), increased stool frequency ($P = 0.037$), decreased stool consistency ($P < 0.001$), and improved ease of stool passage ($P < 0.001$). There was no significant effect on sense of complete evacuation.[17]

In a subsequent Phase IIB trial, Johnston et al performed a randomized, double-blind, multicenter, placebo-controlled

Table 1 Rome III criteria for functional constipation and IBS-C[5]

Functional constipation	IBS-C
Loose stools not present and insufficient criteria for IBS	Recurrent abdominal discomfort ≥3 days per month for ≥3 months associated with ≥2 of the following
Symptoms for >6 months and at least two of the following symptoms for >25% of defecations during past 3 months	Improvement with defecation
Straining	Onset associated with change in frequency in stool
Lumpy or hard stools	Onset associated with change in form of stool
Sensation of incomplete evacuation	<25% of bowel movements were loose stools
Sensation of anorectal obstruction/blockage	
Manual maneuvers to facilitate defecations	
<3 defecations/week	

Abbreviations: IBS, irritable bowel syndrome; IBS-C, IBS in which constipation is the main gastrointestinal symptom.

Table 2 Trials in patients with IBS-C

Reference	Phase	Patients (n)	Linaclotide dose (μg)	Duration (days)	Primary endpoint	Results	Other endpoints
Andresen et al[17]	IIA	36	100 or 1000	5	Effect on ascending and total colonic transit times	Acceleration of ascending colon transit with 1000 μg only at 24 and 48 hours	Shorter time to first BM. Increased stool frequency decreased stool consistency Improved ease of stool passage
Johnston et al[18]	IIB	420	75, 150, 300, or 600	84	Change in mean weekly complete spontaneous BM	Increased complete spontaneous BM (mean 2.9, 2.5, 3.6, and 2.7 for each dose versus 1.0 for placebo)	Stool consistency and straining improved with linaclotide; decreased abdominal pain scores
Rao et al[19]	III	600	266	112	Percentage reaching composite endpoint (≥30% reduction in abdominal pain, ≥3 CSBMs per week, and an increase >1 CSBM per week for 9 of 12 weeks)	12.1% drug versus 5.1% placebo ($P = 0.0004$)	Decreased abdominal pain, discomfort, bloating straining Increased number of CSBMs and SBMs
Chey et al[20]	III	804	266	182	Same as above	12.7% drug versus 3% placebo ($P \leq 0.0001$)	39% of patients given drug had >30% reduction in abdominal pain versus 19% with placebo; significant decrease in abdominal pain, discomfort, bloating; increased number of CSBMs and SBMs
Carson et al[21]	III	748	266	84	Mean change from baseline to week 12 on the IBS-QOL Scale	Drug 17.5 versus placebo 13.1 ($P < 0.0001$)	Significant improvement on dysphoria, body image, health worry, food avoidance, social reaction, sexual, and relationship subscales

Abbreviations: BM, bowel movement; CSBMs, complete spontaneous bowel movements; SBMs, spontaneous bowel movements; IBS-QOL, Irritable Bowel Syndrome Quality of Life score.

Table 3 Trials in patients with chronic constipation

Trial	Phase	Patients (n)	Linaclotide dose (μg)	Therapy duration (days)	Primary endpoint	Results	Other endpoints
Johnston et al[14]	IIA	42	100, 300, or 1000	14	Frequency of spontaneous BM	Change, 6.18 versus 2.76 for placebo for increased spontaneous BM with frequency of complete BM in dose-related manner	Statistically significant increase in stool consistency with the 1000 μg dose versus placebo; straining improved in all three doses
Lembo et al[15]	IIB	310	75, 150, 300, or 600	28	Change in mean weekly spontaneous BM frequency	Linear dose-response with weekly spontaneous BM frequency (2.6, 3.3, 3.6, and 4.3 for each dose versus 1.5 for placebo)	Median time to first SBM was 24.0–13.0 hours for the 4 linaclotide doses versus 32.6 hours for placebo; changes in stool consistency (1.35–2.0 versus 0.50 for placebo $P \leq 0.0005$); in overall straining (–0.71–1.14 versus –0.52 for placebo; $P < 0.001$); decrease in abdominal discomfort score of ≥0.5 for 3 of 4 weeks 27%–32% for the 4 linaclotide doses versus 12% for placebo ($P \leq 0.05$)
Lembo et al[16]	III	1272 (trial 303: 642 trial 01: 630)	145 or 290	84	3+ CSBMs/week and an increase of one or more CSBM per week from baseline for at least 9 of 12 weeks	21% (trial 303) and 16% (trial 01) for doses 145 μg versus 3% placebo and 19% (trial 303) and 21% (trial 01) for dose 290 μg versus 3% placebo ($P < 0.01$)	Scores for constipation relief, treatment satisfaction, treatment continuation, improvement of >1 point on PAC-QOL score were all significantly greater in the linaclotide groups

Abbreviations: BM, bowel movement; CSBM, complete spontaneous bowel movement; PAC-QOL, Patient Assessment of Constipation Quality of Life.

study of 420 patients with IBS-C using oral linaclotide doses of 75, 150, 300, or 600 μg or placebo once daily for 12 weeks. With all doses, there were mean increases of daily stool frequency ranging from 2.5 to 3.6 versus 1.0 for placebo ($P < 0.01$) which were evident within 24 hours of treatment. Stool consistency and straining also improved with linaclotide compared with placebo ($P < 0.001$), and decreases in abdominal pain scores were significantly greater for all doses, with mean changes of –0.7 to –0.9 versus –0.5 for placebo on a scale of 1–5 ($P < 0.05$). Improvement in pain occurred within the first week and persisted throughout the study; those who reported "severe" or "very severe" abdominal pain for at least 50% of the pretreatment period had the greatest reduction of abdominal pain. Patient-reported satisfaction to relief of symptoms IBS symptoms was greater with all except the 75 μg dose.[18]

A double-blind randomized controlled Phase III trial evaluated the efficacy and safety of linaclotide 266 μg (n = 405) versus placebo (n = 395) for 12 weeks. An additional 4 weeks after the initial 12-week treatment period were included to assess the effects of therapy withdrawal; during this time, patients previously randomized to placebo received linaclotide, and patients who originally received linaclotide were randomly assigned to either linaclotide or placebo. After 12 weeks, the percentage of patients meeting the composite endpoint was significantly greater with linaclotide compared with placebo (12.1 versus 5.1, respectively; $P = 0.0004$). All secondary endpoints (abdominal pain/discomfort, bloating, straining, stool consistency, and number of CSBMs and spontaneous bowel movements per week) demonstrated statistically significant improvements with drug compared with placebo. Abdominal pain, discomfort, and bloating had a mean change from baseline of approximately –2 (rated on a 10-point scale), compared with –1.1 with placebo ($P < 0.0001$), and straining –1.3 (rated on a five-point scale) compared with –0.7 with placebo ($P < 0.0001$). The number of weekly CSBMs and spontaneous bowel movements increased to 2.3 and 3.9, respectively, compared with 0.7 and 1.1 with placebo ($P < 0.0001$). After the initial 12 weeks, patients originally given linaclotide and who remained on linaclotide showed continued improvements, but a return of symptoms was seen in those patients who were switched to placebo therapy. On the other hand, patients given placebo showed improvement in abdominal pain in just one week after being switched to linaclotide.[19]

In another double-blind Phase III trial, the long-term use of linaclotide was assessed, in which patients were randomized to receive either linaclotide 266 μg (n = 401) or placebo

(n = 403) for a period of 26 weeks. The primary endpoint of the trial was a composite endpoint identical to the previous study. In total, 12.7% of patients randomized to linaclotide demonstrated significant improvement in the primary endpoint compared with only 3% given placebo ($P \leq 0.0001$); these improvements were sustained throughout the 26 weeks of the trial. Approximately 39% of patients given linaclotide had a >30% reduction in abdominal pain as compared with 19% for placebo. A significant decrease in abdominal pain, discomfort, and bloating of −1.9 (rated on a 10-point scale) occurred with linaclotide versus −1.1 with placebo at 12 weeks ($P \leq 0.0001$ for all measures), and a further decrease of −2.2 in the linaclotide group compared with −1.2 with placebo was seen at 26 weeks. At 12 and 26 weeks, the number of weekly CSBMs and spontaneous bowel movements increased to 2.2 and 4.0 for linaclotide-treated patients, compared with 0.7 and 1.2 for placebo-treated patients.[20]

A randomized, double-blind, placebo-controlled, Phase III trial in IBS-C studied the overall quality of life scores and several subset scores of the IBS-Quality of Life questionnaire. These scores improved in patients receiving linaclotide compared with placebo over 12 weeks. A mean change of 17.45 in overall quality of life scores versus 13.1 with placebo ($P < 0.0001$) including significant improvements on dysphoria, body image, health worry, food avoidance, social reaction, sexual, and relationship subscales ($P < 0.0001$).[21]

Safety and tolerability

Both Phase I trials showed no significant adverse effects and no differences between placebo-treated and linaclotide-treated subjects. The medication was well tolerated at all dose levels, and with no systemic exposure detected.[11,12]

In the first Phase II trial for chronic constipation, there were 22 mild or moderate adverse effects among the 42 patients, all but one occurring in the linaclotide-treated patients. The diarrhea in four patients was not dose-dependent. Two patients discontinued the medication due to rash and moderate diarrhea.[14] No clinically significant adverse effects were reported in the second Phase II trial for chronic constipation; 34% of patients receiving linaclotide had an adverse effect compared with 32% receiving placebo; this was slightly higher with the 600 μg dose (38%) compared with the other groups. Not unexpectedly, diarrhea was the most common gastrointestinal adverse effect, ranging from 5% to 14% of patients receiving from 75 μg to 600 μg versus 3% of patients receiving placebo. Half of all reports of diarrhea occurred within 2 days of starting the study medication, and most were mild or moderate. Only two adverse effects were graded as severe diarrhea and both occurred with the highest dose.[15]

As expected, the most common adverse effect in both Phase III trials for chronic constipation was diarrhea. There was a single death which was attributed to an overdose of fentanyl. Serious adverse effects were reported in 1.4% of patients receiving 145 μg of linaclotide, 2.6% of patients receiving 290 μg of linaclotide, and 2.1% of patients receiving placebo. Due primarily to diarrhea, discontinuation of treatment during the 12 weeks was higher among the linaclotide-treated patients, occurring in 7.9% of patients who received 145 μg and in 7.3% of those who received 290 μg, compared with 4.2% receiving placebo. The first occurrence of diarrhea for many patients occurred during the initial 2 weeks of therapy; 13 of the 852 patients (1.5%) who received linaclotide had severe diarrhea, versus only one of 424 patients (0.2%) on placebo. There were no clinically significant differences in other laboratory parameters, electrocardiographic results, or vital signs between the drug and placebo groups.[16]

In the initial Phase II trial in IBS-C, linaclotide was safe and well tolerated at 1000 μg but the duration of treatment was brief.[17] In the more recent trial for IBS-C, adverse effects occurred in 3% of all linaclotide-treated patients; diarrhea was the most common adverse effect and was more frequent with higher doses (18% of patients receiving the 600 μg dose versus 1.2% in placebo). Nine of the diarrhea adverse effects were graded as severe, but there were no clinical consequences, such as dehydration or electrolyte imbalances. The only severe adverse effect was fecal impaction which occurred from withholding the study medication, but this resolved with treatment.[18] In the Phase III trials, the most common adverse effect again was diarrhea, but it was mostly well tolerated.

Discussion

The treatment of IBS-C and chronic constipation continue to be problematic for many patients and their health care providers. The goals of therapy in each of these disorders overlap to some degree, but there are additional issues in the IBS-C population.

The goal of treatment for chronic constipation is to relieve altered bowel habits, i.e. to increase (complete) spontaneous bowel movements and to have a sense of complete evacuation. The clinical effectiveness of linaclotide versus placebo for chronic constipation has been demonstrated in a series of clinical trials, culminating in the recently published two large

Phase III trials.[16] Using the number of CSBMs as a primary endpoint, 21.2% and 16.0% of patients who received the 145 µg dose of linaclotide, and 19.4% and 21.3% of the patients who received the 290 µg dose of linaclotide, respectively, in the dual trials, met the primary endpoint. Although this is clinically significant, it is worthwhile to emphasize that only a minority of treated patients met the primary endpoint. Furthermore, it is not established that this drug would be more effective than widely available osmotic laxatives, such as bisacodyl[22] and polyethylene glycol,[23] the efficacy of which versus placebo has been previously established in several randomized, placebo-controlled trials. It seems important to conduct head-to-head comparison trials with these agents in the future and also to determine if linaclotide is more efficacious in certain constipated individuals than are currently available laxatives. Another point to emphasize is that linaclotide is unlikely to benefit in patients with pelvic floor dyssynergia, another cause of chronic constipation that responds poorly to laxatives. Polyethylene glycol and bisacodyl are widely and relatively inexpensive and likely will continue to be first-line agents for constipation. Therefore, the appropriate indication for linaclotide is likely to be as a second-tier agent where cost, efficacy, and side effects compared with other second-tier agents such as lubiprostone will play important roles.

In patients with IBS-C, simply increasing the frequency of spontaneous bowel movements is insufficient, as treatment also needs to target the abdominal discomfort often exhibited by these patients. In both Phase II and Phase III trials, the efficacy of linaclotide has been promising, with significant improvement in stool consistency and straining as well as decreases in abdominal pain scores versus placebo. Its ability to target many of the symptoms of irritable bowel syndrome with relatively few adverse effects makes it a potentially attractive medication for this subgroup of IBS patients. Nevertheless, it has proven effective in only a minority of patients, with improvement over placebo of approximately 10%. IBS is a heterogeneous disorder and not likely to respond to monotherapy in many cases. The precise role of linaclotide in IBS-C remains to be established.

In addition to their efficacy in past trials, linaclotide has been well tolerated with similar adverse effects to placebo. Not surprisingly, the most common side effect has been diarrhea, but very few cases of diarrhea have been severe. This is in contrast with other agents for IBS-C, such as tegaserod,[24] with its (admittedly tiny) risks of cardiovascular events, and lubiprostone,[25] with its more frequent side effects of nausea and headaches.

In conclusion, linaclotide has certainly been shown to be effective in chronic constipation and IBS-C in the recently published Phase II and Phase III trials. Future studies are needed in patients with chronic constipation to compare this new agent with widely available and less expensive agents, such as polyethylene glycol and bisacodyl. Linaclotide is an attractive drug because of its apparent ability to alleviate symptoms of irritable bowel syndrome with a single daily dose. In addition, it is well tolerated and has been proven to be a safe medication to use. At the time of writing, the US Food and Drug Administration has accepted the new drug application for linaclotide for review in chronic constipation and IBS-C.

Disclosure

The authors report no conflicts of interest in this work and received no payment for preparing this manuscript.

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