Linaclotide: A Novel Therapy for Chronic Constipation and Constipation-Predominant Irritable Bowel Syndrome

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Abstract: Chronic constipation and irritable bowel syndrome (IBS) are functional gastrointestinal disorders that significantly affect patients' quality of life. Chronic constipation and IBS are prevalent—12% of the US population meet the diagnostic criteria for IBS, and 15% meet the criteria for chronic constipation—and these conditions negatively impact the healthcare system from an economic perspective. Despite attempts at dietary modification, exercise, or use of over-the-counter medications, many patients have persistent symptoms. Alternative treatment options are limited. This article describes linaclotide (Linzess, Ironwood Pharmaceuticals/Forest Pharmaceuticals), a new, first-in-class medication for the treatment of chronic constipation and constipation-predominant IBS.

Constipation is a common chief complaint among patients presenting to any primary care or gastrointestinal practitioner. In fact, nearly 15% of the US population meet the criteria for chronic constipation (CC), and 12% meet the criteria for irritable bowel syndrome (IBS).[1-3] Both CC and constipation-predominant IBS (IBS-C) present with infrequent bowel movements, hard stools, a sensation of incomplete evacuation, rectal pressure or pain, straining, and occasional need for evocative or manual maneuvers to evacuate stool. The main difference between the 2 conditions is that, by definition, IBS-C includes lower abdominal pain that is associated with defecation and is temporally related to a change in stool form or frequency (Table 1).[4] This difference is a clinically key distinction between the 2 conditions.

Both CC and IBS-C inflict significant morbidity, decreasing patients' quality of life compared to nonconstipated matched groups and/or patients with other typical presenting complaints, such as asthma or migraines.[5-10] Not only do CC and IBS-C cause significant individual discomfort, but these conditions also have a large economic impact on the healthcare system. In 2001, an estimated $235 million was spent on the primary diagnosis of constipation, and this figure does not include costs of over-the-counter medications.[11] Women

Table 1. Rome III Criteria for Chronic (Functional) Constipation and Constipation-Predominant Irritable Bowel Syndrome (IBS-C)

Chronic constipation	IBS-C
• Symptom onset at least 6 months prior to diagnosis • Presence of symptoms for the last 3 months (see below) • Loose stools are rarely present without the use of laxatives. • Fewer than 3 bowel movements per week • Symptoms include 2 or more of the following during at least 25% of defecations: – Straining – Lumpy or hard stools – Sensation of incomplete evacuation – Sensation of anorectal obstruction or blockade – Manual maneuvers to facilitate evacuation	• Symptom onset at least 6 months prior to diagnosis • Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with 2 or more of the following: – Improvement with defecation – Onset associated with a change in stool frequency – Onset associated with a change in stool form (appearance) • 1 or more of the following symptoms on at least 25% of occasions for subgroup identification: – Abnormal stool frequency (<3/week) – Abnormal stool form (lumpy/hard) – Abnormal stool passage (straining/incomplete evacuation) – Bloating or feeling of abdominal distension – Passage of mucous

Modified from Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC.[4]

with the diagnosis of constipation had direct medical costs twice those of controls over a 15-year period, and any patient with a diagnosis of CC had annual healthcare costs of $7,522.[12,13] In addition, the conservative estimate for annual healthcare expenditures for IBS in the United States is at least $10 billion, and the total cost of IBS (including the cost of absenteeism) is at least $20 billion.[14-16]

Multiple prescription and over-the-counter medications are available to treat CC and IBS-C.[17-21] Despite these products, many patients have persistent symptoms. Linaclotide (Linzess, Ironwood Pharmaceuticals/Forest Pharmaceuticals) was developed for these groups of patients.

Guanylyl Cyclase, Guanylyl Cyclase Receptors, and the Mechanism of Action of Linaclotide

Linaclotide—a protease-resistant, acid-stable, 14–amino acid peptide—is a first-in-class medication that stimulates guanylyl cyclase C (GC-C) receptors (Figure 1).[22] In order to understand how this drug affects both IBS-C and CC, clinicians need to understand the roles of guanosine 3',5'-monophosphate (GMP) and guanylyl cyclase in the enteric system. Cyclic GMP (cGMP), originally discovered in 1963, helps to regulate multiple essential functions throughout the body, including blood pressure, long bone growth, and lipolysis; more crucial to the gut, it also regulates intestinal fluid secretion and visceral pain.[23] Guanylyl cyclase, discovered in 1969, catalyzes the conversion of guanosine triphosphate to cGMP.[24] Guanylyl cyclase can be found in either particulate or soluble forms. The membrane-bound, particulate form of guanylyl cyclase found in mammals is comprised of 5 different transmembrane enzymes (A, B, C, E, and F). Each of

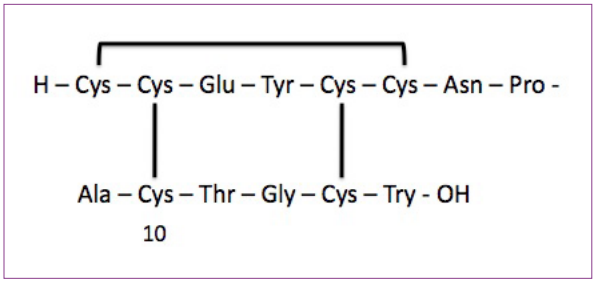

Figure 1. Structure of linaclotide.

these enzymes has a different function. GC-C, which was cloned in 1990, binds heat-stable enterotoxin, the endogenous intestinal peptides guanylin and uroguanylin, and linaclotide.[22,25,26] The other transmembrane enzymes are either associated with natriuretic peptides (GC-A, GC-B) or are found in the retina (GC-E, GC-F).

GC-C receptors are primarily found on the luminal or apical side of enterocytes. When GC-C receptors are bound and stimulated, the level of intracellular cGMP increases, thus activating a protein kinase–dependent pathway (PKGII), which then activates the cystic fibrosis transmembrane regulator (CFTR; Figure 2). Activation of the CFTR leads to increased secretion of bicarbonate (HCO_3^-) and chloride (Cl^-) into the gastrointestinal lumen, thus inhibiting the sodium/hydrogen exchanger, which leads to fluid secretion into the intestinal lumen. In addition to stimulating CFTR via PKGII, the increase in intracellular cGMP also leads to increased levels of extracellular cGMP, which may affect visceral nociception.

Linaclotide mimics the endogenous intestinal peptides guanylin (15 amino acids) and uroguanylin (16 amino acids) that activate GC-C, thus increasing intracellular and

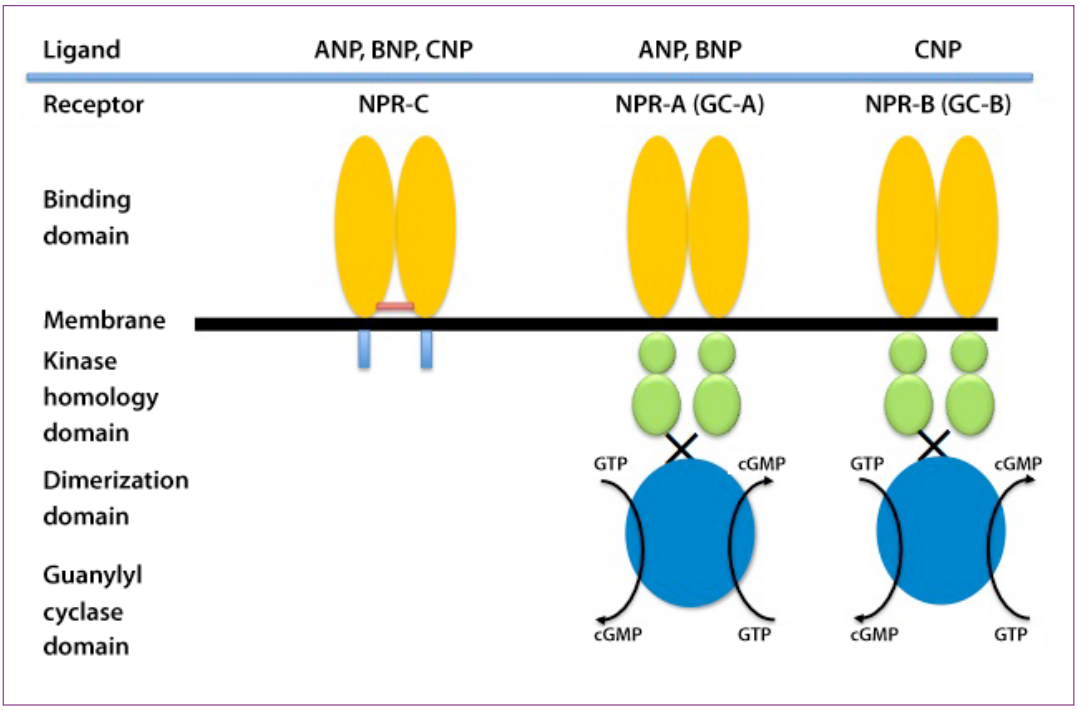

Figure 2. Guanylyl cyclase C receptors.

ANP=atrial natriuretic peptide; BNP=brain natriuretic peptide; cGMP=cyclic guanosine 3'5'-monophosphate; CNP=C-type natriuretic peptide; GC-A=guanylyl cyclase A; GC-B=guanylyl cyclase B; GTP=guanosine triphosphate; NPR=natriuretic peptide receptor.

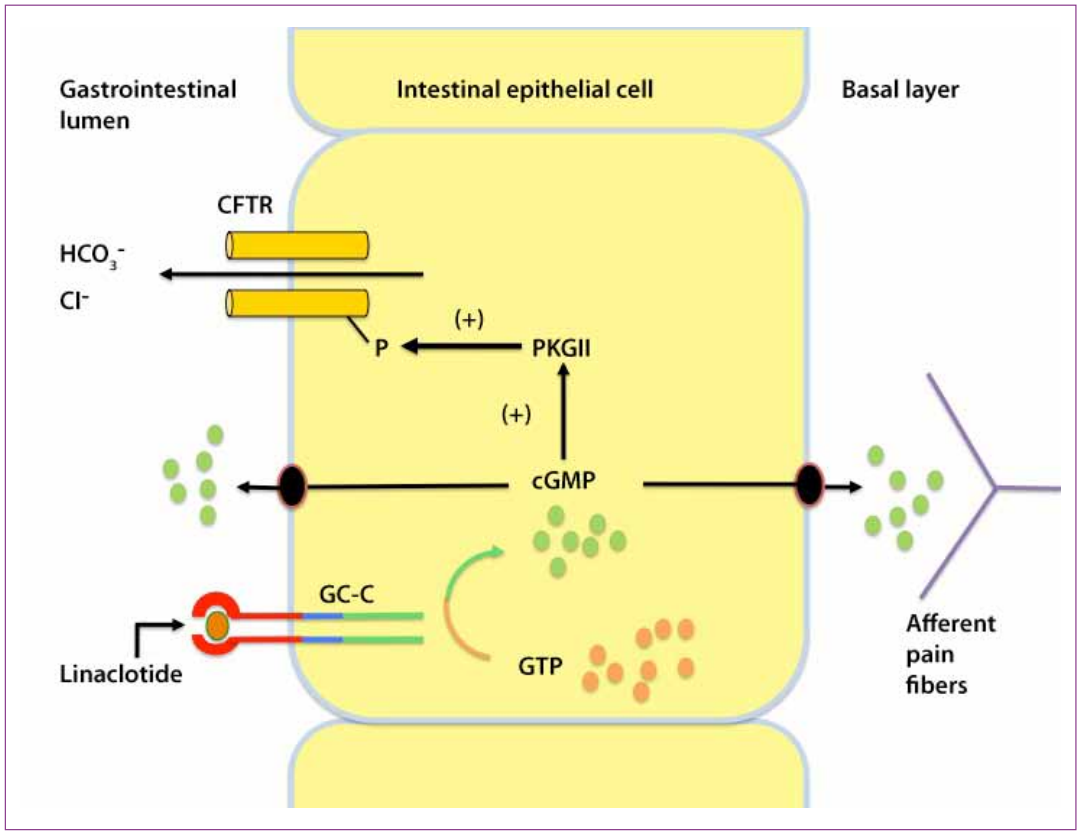

Figure 3. Mechanism of action of linaclotide.

CFTR=cystic fibrosis transmembrane regulator; cGMP=cyclic guanosine 3'5'-monophosphate; Cl^-=chloride; GC-C=guanylyl cyclase C; GTP=guanosine triphosphate; HCO_3^-=bicarbonate; P=phosphate; PKGII=protein kinase–dependent pathway.

extracellular cGMP and activating PKGII. In turn, this cascade activates CFTR, which leads to increased levels of HCO_3^-, Cl^-, and water in the intestinal lumen (Figure 3).[22,26-29] This increase in electrolytes and water accelerates gastrointestinal transit.

Pharmacology and Pharmacokinetics

Linaclotide is both acid-stable and pepsin-stable.[30] It is also minimally absorbed. In mice, the bioavailability of linaclotide was approximately 0.10%; in healthy volunteers, linaclotide could not be detected in the serum when administered at doses up to 1,000 μg.[28,31] Linaclotide is nearly completely broken down within the lumen of the gastrointestinal tract, but a small amount of the drug may be recovered intact in feces (Ironwood Pharmaceuticals; data on file). When incubated in mouse jejunal fluid, linaclotide was completely broken down within 30 minutes, with a first-order half-life of 30 minutes.[32] The parent compound is broken down from a 14–amino acid chain to a 13–amino acid chain by removing the C-terminal tyrosine, leaving a fully biologically active metabolite that is completely broken down within 60 minutes (Ironwood Pharmaceuticals; data on file).

In vitro and in vivo studies have helped to characterize the pharmacology of linaclotide.[30] In both rat intestinal mucosal cells and rat T84 cells, low-affinity and high-affinity binding sites were found, and linaclotide inhibited these receptors in a concentration-dependent fashion at a neutral pH level. In human colonic enterocytes, linaclotide binds GC-C receptors with high affinity at any pH level. This observation suggests that linaclotide may be active not only in human colonic cells but throughout the gut. In human T84 cells, linaclotide stimulated cGMP accumulation in a concentration-dependent manner, leading to significantly increased cGMP levels compared to those seen following administration of either uroguanylin or guanylin.[32]

Preclinical Data on Linaclotide

Given its direct effect on GC-C receptors, linaclotide stimulates fluid secretion and increases cGMP production in wild-type mice but not GC-C–null mice.[30] Using the progression of activated charcoal through the small bowel to measure the effect of linaclotide, wild-type mice treated with 100 μg/kg of linaclotide were found to have significantly accelerated transit times compared to either wild-type mice given charcoal only or GC-C–null mice treated with or without linaclotide. There was no difference in transit times between the vehicle-only groups (wild-type mice or GC-C–null mice).[32] Linaclotide at doses of 5 μg/kg, 10 μg/kg, and 20 μg/kg significantly increased gastrointestinal transit equally in both male and female rats compared to vehicle-treated rats.[30]

Several animal models have shown the potent antinociceptive effects of linaclotide. In 1 study, wild-type and GC-C–null rats were treated with trinitrobenzene sulphonic acid; this drug produces a well-accepted model of colonic inflammation that can cause visceral allodynia. Linaclotide significantly reduced abdominal contractions in response to colorectal balloon distension in wild-type mice but not in GC-C–null mice, again supporting linaclotide's mechanism of action on the GC-C receptor.[33] Linaclotide also significantly decreased colonic hypersensitivity induced by stress due to partial restraint or water avoidance testing ($P<.05$).

How linaclotide improves visceral pain or hypersensitivity is unknown. The precise mechanism of action is obscure and will be better understood over the coming years, although this mechanism is thought to work through the increase in extracellular cGMP. This drug appears to modulate visceral pain via several pathways; in addition to having a direct effect on the enteric nervous system, it also acts through cGMP-dependent protein kinases and phosphodiesterases, mast cells, and/or nitric oxide.

Clinical Studies of Linaclotide

Constipation-Predominant Irritable Bowel Syndrome

Linaclotide was first studied in women with IBS-C in a 5-day colonic transit study.[34] Forty-seven patients were screened, and 36 females with IBS-C (mean age, 39 years) who were not on any medications specifically for constipation or IBS were eligible, randomized, and completed 5 days of treatment with either linaclotide (100 μg or 1,000 μg) or placebo. Inclusion criteria included IBS-C diagnosed by Rome II criteria and evidence of slow colonic transit (defined by geometric center); patients were excluded if an evacuation disorder was present. The 1,000-μg dose of linaclotide, but not the 100-μg dose, significantly decreased ascending colonic transit time and total colonic transit time at 48 hours compared to placebo (ascending, $P=.015$; total, $P=.020$). Time to first bowel movement, stool frequency, stool consistency, and ease of stool passage were all significantly improved compared to placebo, although linaclotide had no effect on sensation of complete evacuation. There were no serious adverse events (SAEs) and no adverse events (AEs) that prevented completion of the study.

A subsequent, 12-week, randomized, double-blind, placebo-controlled, dose-ranging trial was completed to evaluate the efficacy and safety of linaclotide for the treatment of IBS-C (Table 2).[35] A total of 420 patients with IBS-C (92% female; 80% white; mean age, 44.4 years) were randomized to either

Table 2. Summary of a Study Assessing Linaclotide for Treatment of Constipation-Predominant Irritable Bowel Syndrome

	Johnston JM, et al.[35]		
Female (%)	92		
Mean age (years)	44.4		
Total number of patients randomized	420		
Total number of patients who completed the study	337		
Total number of patients analyzed	419		
CSBMs/week		Baseline	Treatment
	Placebo	0.3	1.47
	75 µg	0.4	3.55*‡
	150 µg	0.2	2.79*†
	300 µg	0.2	3.93*‡
	600 µg	0.3	3.10*‡
SBMs/week	Placebo	3.1	4.55
	75 µg	3.2	7.69*‡
	150 µg	2.5	6.67*‡
	300 µg	3.2	7.98*‡
	600 µg	3.1	8.59*‡
Abdominal pain	Placebo	3.0	–0.49
	75 µg	3.1	–0.71**
	150 µg	3.1	–0.71**
	300 µg	2.9	–0.90**
	600 µg	3.1	–0.86**

*Based upon change from baseline. **P<.05. †P<.01. ‡P<.001.

CSBM=complete spontaneous bowel movement; SBM=spontaneous bowel movement.

placebo or 1 of 4 doses of linaclotide (75 µg, 150 µg, 300 µg, or 600 µg) daily for 12 weeks. The primary efficacy endpoint was the change from baseline in the number of complete spontaneous bowel movements (CSBMs) per week. Patients were identified as a "75% responder" if they had 3 or more CSBMs weekly and an increase of at least 1 CSBM per week for 75% of the treatment period. This study included men and women older than 18 years who met Rome II criteria for IBS with fewer than 3 spontaneous bowel movements (SBMs) per week and straining, a sensation of incomplete evacuation, or hard stools during at least 25% of all bowel movements within the preceding 12 weeks.

This study yielded positive results for every dose of linaclotide studied. CSBM rates were 2.90, 2.49, 3.61, and 2.68 for the 75-µg, 150-µg, 300-µg, and 600-µg doses of linaclotide, respectively, compared to 1.01 for placebo (P<.01 for all doses). All doses of linaclotide improved SBM rates, straining, and stool consistency compared to placebo (P<.001). Abdominal pain was improved in 31.1–38.7% of linaclotide-treated patients compared to 22.7% of placebo-treated patients (P≤.01 for the 300-µg and 600-µg doses of linaclotide; P≤.05 for the 75-µg dose of linaclotide); this effect was more pronounced among patients with severe or very severe pain (4 or 5 on a 5-point scale) at baseline (35.5–52.9% vs 10.3%; P<.05 for all doses). Pain returned to baseline levels after linaclotide was stopped. Constipation severity, IBS severity, and global relief of IBS were all significantly improved with linaclotide. Diarrhea was the most frequent AE, occurring in a dose-dependent manner in 11.4–18% of linaclotide-treated patients versus 1.2% of placebo-treated patients. The only reported SAE was a fecal impaction in a patient receiving 300 µg of linaclotide. There were no differences between groups in terms of vital signs, physical examinations, electrolyte levels, or electrocardiogram recordings.

Another study evaluated the long-term efficacy of linaclotide in patients with IBS-C (Rome III criteria), fewer than 3 CSBMs per week, 5 or fewer SBMs per week, and abdominal pain scores greater than 3 out of 10.[36] A novel primary endpoint was established for this study: Patients were considered to be responders if they achieved at least a 30% reduction in pain, an increase of more than 1 CSBM per week, and at least 3 CSBMs per week for 9 of the first 12 weeks of the study. A total of 804 patients (90% female; mean age, 44 years) were randomized to either 266 µg of linaclotide (n=401) or placebo (n=403) daily for 26 consecutive weeks. At 12 weeks, the unique primary endpoint was met in 12.7% of linaclotide-treated patients compared to 3% of placebo-treated patients (P≤.0001). Abdominal pain, bloating, straining, and stool frequency were all improved at both 12 weeks and 26 weeks.

Chronic Constipation

The safety and efficacy of linaclotide for the treatment of CC were first evaluated in a placebo-controlled, randomized, multicenter, phase IIa, pilot study that compared 3 doses of daily linaclotide (100 µg, 300 µg, and 1,000 µg) versus placebo over a period of 2 weeks (Table 3).[37] Men and women aged 18–70 years were eligible for this study if they had 3 or fewer SBMs per week plus symptoms of incomplete evacuation, straining, or lumpy or hard stools at least 25% of the time. Exclusion criteria included known laxative abuse, pelvic floor dysfunction, and prior colonic surgery. Seventy-seven patients were entered into the study using modified Rome II criteria; 35 patients were excluded during the screening and pretreatment periods. Of the 42 patients randomized (88% women; 71% white; mean age, 45.4 years), 38 completed the treatment period. This

Table 3. Summary of Studies Assessing Linaclotide for Treatment of Chronic Constipation

	Johnston JM, et al.[37]		Lembo AJ, et al.[38]		Lembo AJ, et al.[39] Trial 01*		Lembo AJ, et al.[39] Trial 303*	
Female (%)	88		92		90		87	
Mean age (years)	45.4		47.3		48			
Total number of patients randomized	42		310		630		642	
Total number of patients who completed the study	38							
Total number of patients analyzed	37				630		642	
Mean CSBMs/week (baseline)			0.4		0.3		0.3	
Mean SBMs/week (baseline)			2.3		1.9		2.0	
CSBMs/week	Placebo 100 µg 300 µg 1,000 µg	1.30 2.16 2.90 3.19	Placebo 75 µg 150 µg 300 µg 600 µg	0.5 1.5 1.6** 1.8† 2.3**	Placebo 145 µg 290 µg	0.6 2.0‡ 2.7‡	Placebo 145 µg 290 µg	0.5 1.9‡ 2.0‡
SBMs/week			Placebo 75 µg 150 µg 300 µg 600 µg	1.5 2.6** 3.3** 3.6† 4.3†	Placebo 145 µg 290 µg	1.1‡ 3.4‡ 3.7‡	Placebo 145 µg 290 µg	1.1‡ 3.0‡ 3.0‡

*12-week data. **$P \leq .01$. †$P \leq .001$. ‡$P < .0001$.

CSBM=complete spontaneous bowel movement; SBM=spontaneous bowel movement.

study found a dose-dependent increase in SBMs per week among patients using daily linaclotide compared to the pretreatment baseline; comparison of the 100-µg dose versus placebo was statistically significant (6.18 vs 2.76; $P=.047$). This study also noted an improvement in CSBMs (2.16–3.19 with linaclotide vs 1.3 with placebo; P-value not provided), stool consistency ($P<.01$ for linear dose-related trend), and straining ($P=.36$). Severity of constipation, abdominal discomfort, and overall relief of constipation symptoms were all significantly improved ($P<.05$). Diarrhea was the most common AE, occurring in 21% of linaclotide-treated patients. This study reported no SAEs, although 2 patients discontinued therapy due to AEs possibly related to linaclotide (rash and diarrhea).

In 2010, Lembo and coauthors published a large, randomized, multicenter, dose-ranging study comparing daily linaclotide versus placebo for the treatment of CC.[38] Men and women older than 18 years who met modified Rome II criteria were eligible to participate in this study. The primary efficacy endpoint was the change in weekly SBM rate from the 14-day pretreatment baseline. SBM frequency was also analyzed using a responder definition: A responder was defined a priori as a patient who had a weekly SBM frequency of at least 3 and an increase of at least 1 in the number of weekly SBMs compared to baseline for at least 3 of the 4 treatment weeks. A total of 310 patients (92% women; 84% white; mean age, 47.3 years) were treated with daily linaclotide (75 µg, 150 µg, 300 µg, or 600 µg) or placebo for 4 weeks. Weekly SBMs were significantly increased with all linaclotide doses compared to placebo (2.6, 3.3, 3.6, and 4.3 for the 75-µg, 150-µg, 300-µg, and 600-µg doses of linaclotide, respectively, vs 1.5 for placebo; $P<.01$), while CSBMs were significantly improved for the 150-µg, 300-µg, and 600-µg doses of linaclotide ($P<.01$) but not for the 75-µg dose ($P=.057$). The median time to first SBM was shorter for patients treated with linaclotide (24 hours, 21.9 hours, 23.1 hours, and 13 hours for the 75-µg, 150-µg, 300-µg, and 600-µg doses of linaclotide, respectively) compared to those treated with placebo (32.6 hours; $P<.0005$). Stool consistency, straining, abdominal discomfort, and bloating were improved in all linaclotide groups compared to placebo ($P<.05$ for all doses). When global measures of constipation were evaluated, significant improvements compared to placebo were observed for constipation severity ($P<.001$), adequate relief of constipation ($P<.001$ for the 150-µg and 600-µg doses), global relief of constipation ($P<.01$), and treatment satisfaction ($P<.01$).

Health-related quality of life, measured using the validated Patient Assessment of Constipation Quality of Life questionnaire, was significantly improved compared

to placebo in 3 of the 4 linaclotide groups ($P<.05$ for the 75-µg, 150-µg, and 600-µg groups; $P=.0515$ for the 300-µg group). At least 1 AE was reported in 31.9% of the placebo group compared to 33.8% of the linaclotide-treated patients; this difference was not significant. The most common AE was diarrhea, which occurred in 5.1%, 8.9%, 4.8%, and 14.3% of the patients taking 75 µg, 150 µg, 300 µg, and 600 µg of linaclotide, respectively, compared to 2.9% of patients taking placebo. Nine patients discontinued therapy due to AEs: 2 patients in the placebo group and 7 patients in the linaclotide groups. No patients developed dehydration or suffered clinically meaningful electrolyte disturbances during the study period. No SAEs were reported.

Lembo and colleagues subsequently published the results of 2 large, multicenter, randomized, placebo-controlled, double-blind trials in which linaclotide (145 µg or 290 µg) was compared to placebo over a 12-week period.[39] Trial 01 consisted of 630 patients, while Trial 303 consisted of 642 patients (89% female; 76% white; median age, 48 years). The primary efficacy endpoint was 3 or more CSBMs and an increase of at least 1 CSBM from baseline during at least 9 of the 12 study weeks. Men and women 18 years of age or older were eligible for inclusion if they met modified Rome II criteria for CC.

Among patients treated with 145 µg of linaclotide, the primary endpoint was achieved in 21.2% and 16% of patients in Trial 303 and Trial 01, respectively, compared to 3.3% of patients treated with placebo ($P<.01$). Among patients taking 290 µg of linaclotide, 19.4% and 21.3% of patients met the primary endpoint, compared to 6% of patients who received placebo. Linaclotide-treated patients also improved compared to placebo-treated patients (in both studies and for each dose of linaclotide) in terms of all secondary endpoints: CSBMs per week ($P<.0001$), SBMs per week ($P<.0001$), stool consistency ($P<.001$), straining ($P<.001$), constipation severity ($P<.001$), abdominal discomfort ($P\leq.01$), and bloating ($P\leq.005$). Quality of life improved significantly in terms of overall satisfaction, worries, overall discomfort subscore, and physical discomfort subscore for all doses of linaclotide in both studies ($P<.0001$).

To assess whether stopping linaclotide would cause a rebound worsening of symptoms, Trial 303 (N=538) included a planned, randomized, 4-week withdrawal period. All placebo-treated patients were switched to 290 µg of linaclotide, and patients who were receiving linaclotide were either continued at the same dose or switched to placebo. CSBM rates for placebo-treated patients who were transitioned to 290 µg of linaclotide increased to levels seen during the primary treatment period. CSBM rates for linaclotide-treated patients who were switched to placebo decreased to rates seen among placebo-treated patients; patients who continued on linaclotide had sustained CSBM rates (complete data not available). No rebound effect was observed.

AEs were similar among patients taking linaclotide (60.5% and 55.7% for the 145-µg and 290-µg groups, respectively) compared to those taking placebo (52.1%). The most common AE was diarrhea, which was reported by approximately 15% of linaclotide-treated patients. Discontinuation rates were marginally higher in the linaclotide groups (7.9% and 7.3% for the 145-µg and 290-µg groups, respectively) compared to the placebo-treated group (4.2%). Linaclotide-treated patients showed no clinically significant differences in electrocardiogram recordings, blood work (complete blood count and serum electrolytes), or urinalysis.

Summary

IBS-C and CC are prevalent functional gastrointestinal disorders that are frequently encountered in clinical practice. Many patients can achieve symptomatic improvements with dietary modification or over-the-counter medications. Unfortunately, many patients do not improve and seek additional medical attention. Many clinicians try to treat the constipation associated with both CC and IBS-C, which is reasonable given the large overlap between these 2 disorders.

Until recently, only 2 agents had been approved by the US Food and Drug Administration (FDA) for treatment of CC: lubiprostone (Amitiza, Sucampo) and tegaserod (Zelnorm, Novartis), the latter of which was subsequently removed from the market following concerns about possible cardiovascular side effects.[19] Polyethylene glycol is only approved for treatment of occasional constipation, not for CC. For treatment of IBS-C, lubiprostone had been the only FDA-approved medication available; as such, it was frequently a first-line medication for global symptom relief in women with IBS and constipation.

Linaclotide, which received FDA approval on August 30, 2012, is now the third FDA-approved agent for the treatment of CC and the second FDA-approved medication for the treatment of IBS-C. This drug is indicated for treatment of adults with chronic idiopathic constipation or IBS with constipation.[40] With this approval, clinicians now have another choice in the small armamentarium of therapeutic options for treating CC and improving IBS symptoms.

Dr. Lacy is on the Scientific Advisory Board for Given, Ironwood, Ono Pharmaceutical Co, Prometheus, and Takeda. Dr. Levenick and Dr. Crowell have nothing to disclose.

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