CLINICAL INVESTIGATION

Clinical evidence for the role of linaclotide for the treatment of irritable bowel syndrome

Clin. Invest. (2012) 2(10), 1039–1046

JR Malagelada

Digestive System Research Unit, Autonomous University, Barcelona, Spain
E-mail: juanrmalagelada@gmail.com

Linaclotide is an synthetic peptide that binds to the external domain of enteric guanylate cyclase C, activating a molecular pathway that increases intestinal secretion into the lumen and may simultaneously reduce pain sensitivity. These pharmacological properties make linaclotide specially well suited for the management of irritable bowel syndrome with constipation (IBS-C) a condition characterized by abdominal pain and decreased bowel movement frequency and/or increased stool consistency. Linaclotide has been evaluated by a series of clinical trials in both, patients with chronic constipation and patients with IBS-C. In both groups, reported trials have shown that this new drug is both efficacious and appears to be quite safe. Thus, linaclotide is an exciting new drug arriving timely to assist clinicians in the management of IBS-C, a benign yet common, and extremely inconvenient symptomatic condition that currently poses a significant therapeutic challenge

Keywords: abdominal pain • bloating • constipation • irritable bowel syndrome • linaclotide

Irritable bowel syndrome (IBS), as we recognize it today, is a clinical entity that was the subject of a structured consensus process initiated at a meeting in Rome approximately 20 years ago and refined through a series of subsequent meetings. The outcomes have been published and received Roman numeral indices from Rome I, the first, to Rome IV, the current consensus process due to be reported in 2016. IBS, in a more imprecise semantic state was, prior to the Rome process, well known to clinicians but received many different names and sub groupings, which was confusing. The contribution of the Rome I criteria and subsequent consensus gatherings has been to provide a single definition based on easily recognizable symptom criteria. A secondary, but nonetheless valuable outcome of the Rome process has been to facilitate the discrimination between IBS and organic intestinal diseases, thus helping to prevent unnecessary and costly diagnostic investigations in patients fulfilling IBS criteria.

IBS has been divided into various subcategories, a process that facilitates the clinical recognition of more homogeneous groups of patients susceptible to respond consistently to pharmacologic treatment. Short-term stability of the subcategories allows clinical trial evaluation of potential therapeutic drugs, albeit most IBS patients change subtype over time [1]. IBS with constipation (IBS-C) is a major subcategory characterized by the duopoly abdominal pain plus constipation. The abdominal pain feature distinguishes it from functional constipation; the latter being a common occurrence in the general population. Functional constipation is managed (self-managed in many instances) with dietary measures and laxatives. Rarely, idiopathic constipation is refractory enough to require pharmacological use of bowel stimulants. Protracted cases may enter into the category of colonic inertia where ineffective colonic motility becomes the overriding issue. Pelvic floor dysfunction with obstructed defecation is another important mechanism of constipation where, unlike colonic inertia, there

FUTURE SCIENCE part of fsg

is a disturbance of visceral–somatic coordination rather than primary motility failure.

In IBS-C, the abdominal pain component manifests as a symptom complex, not unlike in IBS with diarrhea. Thus, the discriminating criteria between diarrhea- and constipation-predominant forms of IBS are a function of the opposite bowel habit disturbance. However, the matter is complicated by the existence of a third IBS subgroup; named mixed IBS that combines defecatory features of both diarrhea- and constipation-predominant IBS. Mixed IBS may eventually shift towards IBS with constipation in many patients [2].

Deficiencies in current pharmacologic agents to treat IBS-C

IBS is essentially managed symptomatically, as there is insufficient knowledge of the underlying disease mechanisms of IBS to allow etiologic or even pathogenetically based treatment. Thus, patients with IBS-C whose symptoms lead them to seek medical assistance are conventionally managed by a combination of laxatives and agents that modulate abdominal pain such as spasmolytics, visceral analgesics or other. This approach is largely unsatisfactory for several reasons. First, patients quickly recognize that they are being prescribed symptomatic treatment, essentially pain-relieving visceral analgesics and purged to move their bowels, rather than treatment for 'cure'. Second, it is difficult to modulate this pharmacologic mixture since laxatives themselves may increase cramp pains and bloating and certain visceral analgesics, most notably tricyclic antidepressants, which may aggravate constipation. Third, some associated symptoms such as bloating or straining with defecation may not be adequately relieved by current medications and continue to reduce the patient's quality of life.

Relatively mild IBS patients may obtain relief from implementing appropriate changes in lifestyle and the aforementioned common therapeutic armamentarium. However, moderate-to-severe IBS-C may require a more intense and complex pharmacologic approach. Remarkably, even at subspecialist level therapeutic efforts are largely directed towards visceral pain relief whereas management of defecatory troubles follows the standard line of osmotic, bulk and other laxatives. The bloating component remains for the most part unaffected by standard therapies.

Thus, at present, there is a perceived need for a single pharmacological agent that could safely and effectively control all clinical facets of IBS-C. Such an ideal agent should provide simultaneous relief of impaired evacuation, abdominal pain and bloating. An exciting new agent, linaclotide, is a candidate for such an integrated therapeutic role in IBS-C. This review will attempt to summarize the pertinent evidence to date and point out potential pitfalls, as well as future expectations.

▪ What is linaclotide & how does it work?

Linaclotide is an orally active, 14-amino acid peptide that binds to the external domain of GC-C, activating the intracellular guanylyl cyclase domain of the receptor [3]. As a result of GC-C activation, there is generation and intracellular increase of the second messenger cGMP, which, through certain signaling pathways, activates CFTR. This molecular pathway induces an electrogenic chloride current that drives the secretion of water into the lumen of the intestine [4,5]. The resulting increase in luminal fluid load appears to be the main mechanism for the anticonstipating effects of linaclotide. In essence, linaclotide produces an intestinal segretagogue action that mimics in many respects that produced by heat stable enterotoxins in bacterially induced diarrhea. Increased luminal water content is the main mechanism accelerating colonic transit and improving bowel functions. There is no evidence that linaclotide directly stimulates peristaltic bowel motility.

Since the normal gastric mucosa expresses negligible levels of GC-C, in contrast to intestinal epithelial cells, no gastric effects are observed. However, both the small intestinal and colonic mucosa are sensitive to the secretagogue effects of linaclotide. It is likely that its pharmacodynamic effects begin in the duodenum and extend along the entire intestine, depending on mucosal exposure to the drug. The site of activity of linaclotide is restricted to the luminal side of the intestinal epithelium where GC-C receptors are mostly expressed. There is only minimal absorption of linaclotide, its bioavailability being estimated to be ≤0.2%.

In addition to promoting fluid secretion into the intestinal lumen, linaclotide possesses relevant antinociceptive effects that have been largely established in experimental rodent models of visceral hyperalgesia, including the rat model of trinitrobenzene sulphonic (TNBS)-induced chronic inflammation and the rat model of stress-induced visceral hyperalgesia through acute restraint or water avoidance. Interestingly, in these models linaclotide had no effect on visceral sensitivity under basal conditions but was effective in correcting TNBS-induced colonic allodynia and colonic hypersensitivity in both acute stress models. Furthermore, it was shown that in GC-C null mice linaclotide was unable to reduce hypersensitivity. Thus, the antinociceptive effects of linaclotide appear to be largely exerted by its activation of enteric GC-C. There is, apparently, an important component of neuromodulation of afferent sensory fibers by cGMP [6] particularly mechanosensitive fibers located in the serosa and mesentery. These particular fibers mediate colonic pain and may be sensitized in a post-inflammatory state.

The antihyperalgesic effect of linaclotide in some of the animal models evaluated so far, as in the water-restraint model are not linearly dose dependent but rather bell-curve shaped. At higher doses of linaclotide, the antihyperalgesic effect diminishes in the TNBS model of colonic inflammation [7], possibly in relation to a loss of pharmacological specificity with cGMP that would also be acting upon other signaling pathways that neutralize the hypoalgesic effect. Interestingly, the most efficacious doses of linaclotide administered orally in experimental models may be extrapolated to the doses observed to be therapeutically efficacious in human clinical studies. The antihyperalgesic effects of linaclotide, moreover, are not associated with relevant changes in colonic muscular tone, suggesting that colonic relaxation is not involved as a mediator of linaclotide antihyperalgesia. The extracellular accumulation of cGMP may activate signaling pathways that modulate both immune cell systems and enteric nerves, hence diminishing the sensory response associated with inflammation and stress-induced central modulation of pain. As mentioned earlier, studies conducted in GC-C-null nice demonstrate that linaclotide is unable to reverse the hypersensitivity response induced by TNBS, further confirming that the drug-induced hypoalgesia in this model is mediated through the CG-C receptor. These studies have been refined by examining the effect of linaclotide on colorectal afferent mechanosensitivity in healthy mice and in mice recovering from TNBS-induced inflammation. Post-TNBS mice develop chronic visceral hypersensitivity, which, to some extent, models human IBS colonic hypersensitivity. Results show that linaclotide as a GC-C agonist is more potent at inhibiting mechanosensitive serosal nociceptor afferents than exogenously applied cGMP. The inhibitory effect of linaclotide is observed in chronically hypersensitive animals [8].

Although the visceral analgesic effects of linaclotide observed in experimental animals have not been shown in visceral hypersensitivity studies in man, they provide some mechanistic basis for the relief of abdominal pain induced by linaclotide, subsequently shown by clinical trials in IBS-C patients. However, the antinociceptive effects demonstrated in experimental animals may relate to pain thresholds well above those observed in human visceral hypersensitivity in IBS. Besides, in human IBS, central mechanisms are also likely to be involved.

Clinical evidence of linaclotide therapeutic potential in IBS-C

Oral linaclotide has been shown to be effective in chronic constipation, most likely on account of its notable stimulatory effects on intestinal fluid secretion and transit. However, IBS-C differs from chronic constipation in a key aspect: pain and discomfort are both mandatory criteria for the diagnosis of IBS-C [9]. A number of clinical studies have specifically addressed IBS-C.

Andresen *et al.* reported the results of a small trial that evaluated the effects of acute 100 and 1000 µg of linaclotide and placebo on 36 women with IBS-C [10]. The trial was single-site, double-blind, randomized and placebo-controlled. To establish the mechanism through which linaclotide exerted its therapeutic effects, participants underwent simultaneous measurement of gastrointestinal transit by a scintigraphic method. Bowel function was assessed by daily diaries. The study consisted of three successive periods. First, there was a baseline period during which patients were screened and observed. As a part of the baseline period there was a 5-day assessment period during which the baseline scintigraphic colonic transit test was conducted and quantification of defecation pattern and stool characteristics was performed. Next, there was a 5-day treatment phase again including scintigraphic measurement of colonic transit and stool diaries obtained. Finally, there was a 3- to 5-day post-treatment observation period. For a candidate patient to be enrolled in the treatment period, the baseline colonic transit study had to demonstrate slow colonic transit. This prerequisite was important to ensure that the expected accelerating effect of linaclotide on colonic transit could be observed and quantified.

The relevant results of the study were as follows: Linaclotide had no significant effects on gastric emptying or colonic filling, as evaluated by the scintigraphic test. Ascending colonic emptying and overall colonic transit time were significantly accelerated by the 1000-µg dose of linaclotide over placebo. Linaclotide also significantly shortened the interval time from start of treatment to first bowel movement and also significantly decreased stool consistency. The study was not designed to evaluate the effects of linaclotide on abdominal discomfort or bloating. Thus, no conclusions as to potential therapeutic effects of linaclotide on these IBS features could be ascertained. No substantial adverse effects were observed beyond those related to known pharmacological drug effects, such as diarrhea.

A Phase IIb study of the effects of linaclotide on abdominal pain and bowel habits in 420 patients with IBS-C (defined according to Rome II) was conducted in North America as a randomized double-blind, multicenter, placebo-controlled study [11]. Linaclotide was administered at doses of 75, 150, 300 or 600 µg or placebo daily for 12 weeks. During the 2-week baseline period patients had to meet two criteria: less than three complete spontaneous bowel movements per week and mean daily abdominal pain/discomfort of at least mild severity. End points included change in daily bowel habits, change in daily abdominal pain and weekly global assessments. The results showed that all evaluated doses

of linaclotide significantly improved constipation and pain. Other associated symptoms, including abdominal discomfort and bloating, were also significantly relieved. Interestingly, the favorable effects of linaclotide appeared during the first week of treatment and were sustained for the entire 3-month duration of the study. Adverse effects were insubstantial except for diarrhea, linked to the pharmacodynamics of linaclotide, that developed in a dose-related manner in up to 18% of treated patients at the highest dose. Only 7% of those receiving the 600-µg dose, however, discontinued the medication and their participation in the trial due to this side effect. Remarkably, the pain relief obtained with linaclotide tended to be most apparent in patients reporting frequent 'severe' or 'very severe' pain during baseline, suggesting that the drug may be most effective in patients suffering the worse symptoms.

Patients who successfully completed the trial were observed for a further 2 weeks post-treatment period and their symptoms tended to return towards baseline levels, but were generally better than baseline levels. The results of this trial suggested that linaclotide was very effective in IBS-C and that its positive effects were sustained as long as the medication was continued. However, once patients were taken off linaclotide, the benefits rapidly disappeared.

Additional analyses were conducted on the clinical material gathered in this Phase IIb trial. A *post hoc* analysis conducted by Johnston *et al.* assessed the effect of linaclotide on co-primary end points: abdominal pain/discomfort and a patient global assessment [12]. These co-primaries had been specified as a requirement by the European Medicines Agency. Results of the analysis showed that abdominal pain/discomfort improved in all linaclotide dose groups compared with placebo. Global assessments of adequate relief also showed significant improvement for all, but the lowest linaclotide dose. Thus, patients with linaclotide in this Phase IIb study experienced significant and clinically relevant improvement using the specified coprimary end points, in addition to the single symptom-specific primary end point concerning complete spontaneous bowel movements per week.

Another *post hoc* analysis by Lavins *et al.* examined the effects of linaclotide on study patients whose mean baseline abdominal pain score was more than mild [13]. It was observed that linaclotide improved abdominal pain using any of four different end points: absolute change; percent change; change in percent days with mild or no pain and change in percent pain-free days. There was a moderately strong correlation between the four abdominal pain end points and the patients' global assessments.

Psychometric evaluation of patient-reported outcome measures was also analyzed [14]. Twelve IBS-C measures (three daily abdominal symptoms, five daily bowel function and four weekly global items) showed high tests–retest reliability. Comparing linaclotide and placebo groups reinforced these results. It was observed that the 12 patient reported measures assessing IBS-C symptom severity and global change induced by linaclotide are reliable, valid and good indicators of favorable response to the agent.

Since the two highest doses of linaclotide tested by the Phase II study were of comparable efficacy, the lower of the two was chosen for Phase III evaluation. The Phase III clinical program aimed at conclusively establishing the efficacy and safety of linaclotide in the treatment of IBS-C by comparing a daily 290 µg dose of linaclotide against placebo (Figure 1). The 290-µg dose was chosen as equivalent to the 300-µg dose in Phase IIb studies. Again, the Phase III clinical program was conducted in several centers in the US and Canada. A 12-week Phase III clinical trial included 800 patients (intention to treat) who received once daily, capsules containing either 290 µg of linaclotide or placebo according to a randomized, double-blind design [15]. Patients entered a pretreatment 2-week period of observation prior to a 12-week treatment phase and afterwards completed a 4-week randomized withdrawal period. Patient's baseline characteristics were similar to those selected for the Phase IIb studies. These were: less than three complete spontaneous bowel movements per week; five, or less, spontaneous small bowel movements overall and abdominal pain equal or greater than three on 0–10 point scale.

Four primary efficacy parameters (responder end points) and ten secondary end points were selected. Among the end points, two composite responder end points consisted of:

- Equal or greater than 30% reduction in abdominal pain and at least three complete spontaneous bowel movements per week implying an increase of at least one from baseline for a minimum of 9 out of the 12 weeks of the treatment period;
- Equal or greater than 30% reduction in pain and an increase of at least one complete spontaneous bowel movement per week for at least 6 out of the 12 weeks of treatment.

Trials outcome supported the efficacy of linaclotide in the treatment of IBS-C. For the first composite responder end point, 12.1% of patients in the linaclotide arm were responders versus 5.1% in the placebo arm. The difference was highly statistically significant ($p < 0.0004$). For the second composite responder end point the equivalent figures were 33.6% for linaclotide and 21.0% for placebo ($p < 0.0001$).

There were ten secondary efficacy parameters among

them: the complete spontaneous bowel movements frequency rate, measured as the weekly rate over the 12 weeks of treatment; the stool consistency index measured on the seven point Bristol scale; the severity of straining, measured on a five-point scale and the severity of bloating, measured on an 11-point numerical scale. All ten secondary efficacy parameters for linaclotide showed responses significantly above placebo.

Two additional efficacy end points were evaluated for submission of trial outcomes to the European Medical Agency – first, at least 30% reduction from baseline in mean abdominal pain or discomfort score for at least 6 of the first 12 weeks of treatment with neither score worsening, and second, patients considerably relieved/completely relieved on the 'degree of relief' of the IBS symptoms for at least 6 out of the first 12 weeks of treatment. Linaclotide amply met the prestablished response criteria: for the first end point, 41.8% of the patients on placebo versus 54.8% on linaclotide, a highly significant difference ($p < 0.0002$) and for the second end point 37.0% of patients on linaclotide responded versus 18.5% on placebo ($p < 0.0001$) [16].

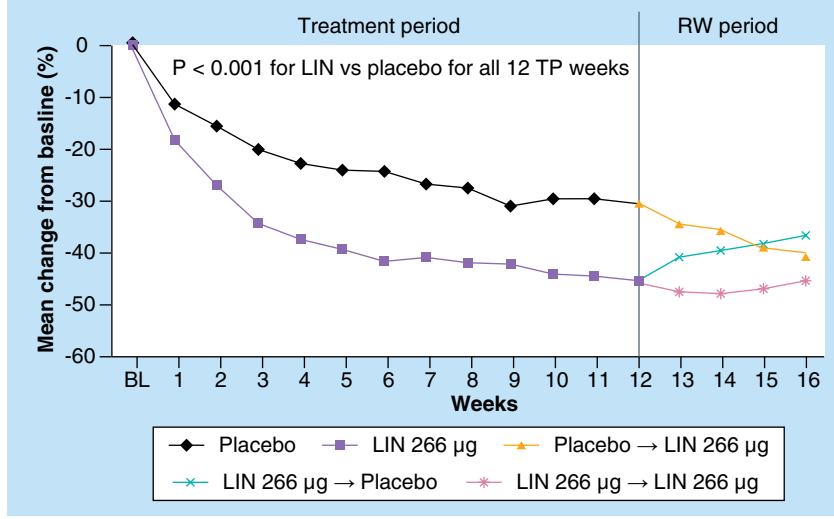

Figure 1. Percentage change in abdominal pain per week for patients treated for 12 weeks with either linaclotide or placebo.

BL: Baseline; LIN: Linaclotide; RW: Retreatment or withdrawal; TP: Treatment period. Reprinted with permission from [15].

An additional Phase III clinical trial has been conducted and reported [17]. This consisted of 26 weeks of treatment with either linaclotide (290 µg daily) or placebo. The trial was multicenter, double-blind and randomized. The screening period was up to 3 weeks followed by a 2-week baseline pretreatment period and then a 26-week treatment period. As expected for IBS, there was a predominance of females in both study arms. Patients (n = 804, intend-to-treat population) included met modified Rome II criteria for IBS-C verified during the 2-week baseline period that were identical to those specified earlier and used for the first trial.

There were four primary end points including composite responder end points that were similar to those required for efficacy in the 12-week study. At the completion of the 26-week treatment period patients treated with linaclotide showed significant improvement for primary and all secondary parameters. For instance, for the first 12-week treatment period, abdominal pain/discomfort responder proportions were 54.1% in the linaclotide group and 38.5% in the placebo group ($p < 0.0001$). Sustained response rates for abdominal pain/discomfort and IBS degree of relief at 12 and 26 weeks were significantly greater with linaclotide than placebo (all $p < 0.0001$).

The co-primary parameter indices, similar to those required for the 12-week Phase III controlled trial evaluated for EMA submission were also met [18]. As an example, for the second co-primary parameter (considerably relieved or completely relieved, on the degree of relief of IBS symptoms question for at least 6 out of the first 12 weeks) 39.4% in the linaclotide group versus 16.6% in the placebo group were responders ($p < 0.0001$).

With regard to the secondary efficacy end points the 26-week abdominal pain/discomfort sustained responder defined as for the 12 weeks, but extending into 26 weeks, yielded a 53.6% response rate for linaclotide and 36.0% response for placebo ($p < 0.0001$) for a difference in response between linaclotide and placebo of 17.6%. The rest of the secondary efficacy parameters all gave significant advantage to linaclotide over placebo. The bloating response was particularly appealing because of its resistance to other pharmacotherapy approaches.

Several subanalyses of Phase III trial data have recently been reported in abstract form adding valuable information. Data from the two Phase III trials of linaclotide in IBS-C have been pooled and the global responder end points compared with the FDA interim end point (6/12 week abdominal pain and constipation [+1]). The agreement among these end points was high indicating that the observed improvement in both abdominal pain and complete spontaneous bowel movement frequency closely reflects overall improvement in IBS-C symptoms [19]. Another analysis examined whether improvement of the FDA interim end point, described above, is representative of clinically meaningful improvement in IBS-C symptoms. Anchor-based methodology was utilized to estimate clinically meaningful thresholds of symptomatic change in IBS-C and to establish that end

points demonstrated in the Phase III trials exceeded the thresholds for clinical relevance [20].

Another interesting analysis attempted to show that linaclotide relieves abdominal pain through a direct effect not necessarily linked to correction of constipation. To this end, Phase III trial patients observed for at least a week without producing a complete spontaneous bowel movement were selected for linaclotide versus placebo comparison. The results of such analysis suggest that linaclotide was more effective than placebo in relieving the patient's abdominal pain in the absence of spontaneous bowel movements [21]. Further indication of sustained effects of linaclotide over time was provided by an analysis of weekly end points: adequate relief, IBS symptom severity and degree of relief of IBS symptoms. After 26 weeks of either linaclotide or placebo, linaclotide end point improvements relative to placebo that were observed after the first week remained stable throughout the 26-week trial [22]. Since linaclotide may induce diarrhea in a subset of patients receiving the drug, satisfaction with treatment was measured and compared in patients who experienced an adverse event of diarrhea and those who did not. The comparison showed that IBS-C patients experiencing diarrhea during treatment reported similar degree of treatment satisfaction than those who did not [23]. These results suggest that diarrhea may not be perceived negatively as an adverse event by these constipated patients with IBS.

Baseline pain severity may be an important factor in self assessment of treatment efficacy by patients. By comparing baseline abdominal pain scores to the absolute magnitude of improvement in abdominal pain it was shown that relief was of greater magnitude in those with more severe pain. However, percent rating of pain relief was similar in patients with mild, moderate and severe pain subgroups [24].

Adverse events

Linaclotide appears to be, at this point, a particularly safe drug. Diarrhea is the most commonly observed side effect (approximately two in ten patients receiving linaclotide). Mild-to-moderate diarrhea accounts for most events and severe diarrhea is only reported by 2% of the patients. It would seem that diarrhea would not be considered, by the constipated subjects entering trial, such an unwelcome side effect but, nevertheless, led to a trial withdrawal rate of 4.5 versus 0.2% in the placebo-treated group. There were other reported side effects occurring in a minority of linaclotide-treated patients. These included nausea, abdominal pain, flatulence and others. Although some of these side effects did occur more frequently in the linaclotide than in the placebo group they did not appear to be as substantial as diarrhea.

Time effects of linaclotide on abdominal pain patterns

Remarkably, the effects of linaclotide-relieving abdominal pain appeared relatively early and were sustained through 26 weeks [17]. Abdominal pain relief, although already apparent in the first or second week, was gradually strengthening with a slow plateau till the end of the 26-week observation period. In the randomized double-blind drug withdrawal period allotted after completion of the 12-week clinical trial, pain returned rather rapidly towards the level observed in the placebo group [15]. The explanation for these time related responses can only be speculative. The visceral analgesic properties of linaclotide, observed in animal studies, may indeed play a role. However, we cannot rule out the possibility that the luminal clearing effects of linaclotide would gradually diminish the sensitizing effect of stool accumulation inside the bowels and hence provide gradual relief of abdominal pain/discomfort. Only additional studies would be able to ascertain the mechanism behind these trial data.

Linaclotide in chronic constipation

The positive effects of linaclotide in chronic constipation must be at least summarized here because of its impact on explaining part of the positive effects of linaclotide on IBS-C.

A pilot study of the effects of linaclotide on chronic constipation was conducted in 42 patients who were randomized to receive placebo or either 100, 300 or 1000 µg of linaclotide daily for 2 weeks [25]. Bowel habits and degree of abdominal discomfort were monitored daily. The results of this pilot study clearly showed the ability of linaclotide to increase spontaneous bowel movement frequency, decrease stool consistency scores and reduce straining. Abdominal discomfort was also clinically improved.

A Phase IIb trial was subsequently performed and reported [26]. It compared the effects of either 75, 150, 300 or 600 µg of linaclotide or placebo given daily for 4 weeks. The trial was a multicenter, double-blind parallel-group study conducted in a total of 310 patients with chronic constipation. All doses of linaclotide were found to improve bowel evacuation pattern and provide significant relief to patients including improvements in abdominal pain.

Two Phase III randomized trials of linaclotide in patients with chronic constipation have been subsequently reported [27]. A total of 1276 patients with chronic constipation were include in these multicenter, double-blind, parallel-group, placebo-controlled trials of two different daily doses of linaclotide (145 or 290 µg) for 12 weeks. Again, linaclotide significantly reduced both constipation and associated

symptoms including abdominal pain. The primary efficacy end point was 12-week complete spontaneous bowel movement overall responder. Responses were 21.3 and 19.4% (for either trial) in the linaclotide arms versus 6 and 3.3% in the placebo arms, respectively. The difference was highly statistically significant ($p < 0.0001$). Again both constipation and abdominal discomfort and also bloating were improved by the drug.

Potential impact of linaclotide in the treatment of IBS-C

Linaclotide is a drug with substantial pharmacodynamic assets and may become a useful addition to an, as yet, relatively meager therapeutic armamentarium for IBS-C. Patients with IBS-C are likely to welcome the introduction of linaclotide because of its dual effects promoting bowel evacuation and inducing analgesia, albeit the latter through a mechanism not fully elucidated in humans. Thus, this novel agent may enable clinicians to act therapeutically on the two primary manifestations of IBS-C by using a single drug. Currently, combinations of agents are often needed: drugs to normalize bowel movements and others to reduce pain perception, be it through peripheral or central mechanisms or both.

Thus linaclotide comes to the clinical arena well equipped to do the job, and clinical trials so far substantiate its efficacy. An additional asset of linaclotide is that it may do it quite safely on account of its very limited bioavailability and trial substantiated lack of major side effects. Only diarrhea appears to signal a hint of caution. Usually mild, it may be perceived, in fact, by many IBS-C patients as helpful rather than a drawback. However, extended experience will be needed to calibrate its clinical impact and the development of potential electrolyte/water imbalances in IBS-C patients whose age or comorbidities could render them especially vulnerable to substantial diarrhea spurts. The latter appear to occur relatively rarely but not exceptionally based on reports of published controlled trials.

Another relevant safety aspect on which there is currently insufficient data is the potential impact of linaclotide therapy on concomitant drug absorption on account of increased intraluminal fluid flow.

Linaclotide may also alleviate currently difficult to treat associated symptoms of IBS such as bloating. It is too early to determine whether this bothersome symptom may become a future indication for linaclotide use, but tantalizing hints have been noted in clinical trial analysis.

In conclusion, linaclotide is an exciting new drug arriving timely to assist clinicians in the management of IBS-C, a benign yet common, and extremely inconvenient symptomatic condition that currently poses a significant therapeutic challenge.

Future perspective

Linaclotide is an innovative step forward in the development of new agents for the treatment of IBS that act predominantly on the luminal side of the gut. This approach reduces the chance of systemic side effects and interactions with other agents. Over the next 5–10 years I would anticipate future drug developments along the same lines because the concept is attractive, results of clinical trials are, so far, encouraging and linaclotide is likely to be clinically successful

Financial & competing interests disclosure

JR Malagelada is an advisory board member for Ironwood Pharmaceuticals, Forest Laboratories, Almirall and Shire Pharmaceuticals. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Irritable bowel syndrome (IBS) is a challenging medical ailment. No definitive treatment is available.
- Current pharmacologic therapies for IBS are symptom-oriented and often have to be administered as a combination of different agents.
- Linaclotide is a nonabsorbable, orally administered peptide drug, that increase intestinal secretion and has antinociceptive properties.
- It alleviates both chronic constipation and the symptoms of IBS, as proven by clinical trials.
- Its therapeutic effects are sustained for at least 6 months while the drug is administered, but it provides no lasting relief after treatment is interrupted.
- Linaclotide is likely to be used in clinical practice.

References

Papers of special note have been highlighted as:

- ▪ of interest

1 Engsbro AL, Simren M, Bytzer P. Short-term stability of subtypes in the irritable using the Rome III classification. *Aliment. Pharmacol. Ther.* 35(3), 350–359 (2012).

- ▪ **Interesting study that provides data on the probability that irritable bowel syndrome (IBS) subtypes (based on a specific symptom profile) will either remain stable or change overtime.**

2 Mearin F, Balboa A, Badia X *et al.* Irritable bowel syndrome subtypes according to bowel habits: revisiting the alternating subtype. *Eur. J. Gastroenterol. Hepatol.* 15, 165–172 (2003).

3 Bryant AP, Busby RW, Bartolini WP *et al.* Linaclotide is a potent and selective guanylate cyclase C agonist that elicits pharmacological effects locally in the gastrointestinal tract. *Life Sci.* 86, 760–765 (2010).

4 Bharucha AE, Linden DR. Linaclotide – a secretagogue and antihyperalgesic agent – what next? *Neurogastroenterol. Motil.* 22, 227–231 (2010).

- ▪ **Good review on the mechanism of action of linaclotide and future perspectives.**

5 Busby RW, Bryant AP, Bartolini WP *et al.* Linaclotide, through activation of guanylate cyclase C, acts locally in the gastrointestinal tract to elicit enhanced intestinal secretion and transit. *Eur. J. Pharmacol.* 649, 328–335 (2010).

6 Castro J, Martin C, Hughes PA *et al.* A novel role of cyclic GMP in colonic sensory neurotransmission in healthy and TNBS-treated mice. *Gastroenterology* 140(5 Suppl. 1), S538 (2011).

- ▪ **Evidence that cyclic GMP has an antinociceptive role in mice providing an experimental basis for the observed pain-relieving effects of linaclotide in clinical trials in humans.**

7 Eutamene H, Bradesi S, Larauche M *et al.* Guanylate cyclase C-mediated antinociceptive effects of linaclotide in rodent models of visceral pain. *Neurogastroenterol. Motil.* 22, 312–322 (2010).

8 Castro J, Harrington AM, Hughes PA *et al.* Mechanism of action for linaclotide induced abdominal pain relief. *Gastroenterology* 142(5 Suppl. 1), S699 (2012).

9 Longstreth G, Thompson WG, Chey WD *et al.* Functional Bowel Disorders. In: *Rome III. The Functional gastrointestinal disorders.* Drossman DA (Ed.). Allen Press, KA, USA, 487–555 (2006).

10 Andresen V, Camilleri M, Busciglio IA *et al.* Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. *Gastroenterology* 133, 761–768 (2007).

- ▪ **Translational study on the effects of linaclotide on colonic transit quantified by a scintigraphic imaging technique.**

11 Johnston JM, Kurtz CB, Macdougall JE *et al.* Linaclotide improves abdominal pain and bowel habits in a Phase IIb study of patients with Irritable bowel syndrome. *Gastroenterology* 139, 1877–1886 (2010).

- ▪ **Reports the results of a large Phase IIb study with details on efficacy and safety of linaclotide administered over a wide dose range to patients with IBS with constipation.**

12 Johnston JM, MacDougall JE, Lavins B *et al.* Linaclotide significantly improved abdominal pain/discomfort and global assessments in adults with irritable bowel syndrome with constipation. *Am. J. Neurogastroenterol. Motil.* 20(13) S460–461 (2008).

13 Lavins B, MacDougall J, Shiff S, Schneier H, Lembo A, Johnston J. Comparison of abdominal pain end points: results from a Phase 2b study of linaclotide in adults with IBS-C. *Am. J. Gastroenterol.* 104, S486–S487 (2009).

14 Carson R, Williams V, Nelson L, MacDougall J, Johnston J. Psychometric evaluation of patient-reported outcome measures for assessing IBS-C symptom severity and global change: results from a Phase 2b study of linaclotide. *Am. J. Gastroenterol.* 104, S409–S410 (2009).

15 Rao S, Lembo A, Shiff SJ, Shi K, Johnston JM, Schneier H. Efficacy and safety of once daily linaclotide in patients with irritable bowel syndrome with constipation: a 12-week, randomized, double-blind, placebo-controlled Phase 3 trial followed by a 4-week randomized withdrawal period. *Gastroenterology* 140 (5 Suppl. 1), S138 (2011).

16 Quigley EM, Lembo AJ, Diaz C *et al.* Significant improvements in abdominal pain and bowel symptoms in a Phase 3 trial of linaclotide in patients with irritable bowel syndrome with constipation (IBS-C): a European perspective. *Gut* 60(Suppl 3), A80 (2011).

17 Chey W, Lembo A, MacDougall JE, Bernard L, Schneier H, Johnston JM. Efficacy and safety of once-daily linaclotide administered orally for 26 weeks in patients with IBS-C: results from a randomized, double-blind, placebo-controlled Phase 3 trial. *Gastroenterol.* 140(5 Suppl. 1), S138 (2011).

- ▪ **Reports the results of the longest clinical trial to date on the effects of linaclotide on IBS with constipation. Various primary and secondary efficacy parameters were used and linaclotide provided significant relief advantage over placebo in all of them.**

18 Lembo AJ, Fortea J, Diaz C *et al.* 26-week efficacy and safety of once-daily oral linaclotide in patients with irritable bowel syndrome with constipation: a European perspective. *Gut* 60(Suppl 3), A41 (2011).

19 Locke GR III, Chang L, Currie MC *et al.* Comparison of responder rates and degree of agreement for symptom-specific and global-relief end points in two Phase 3 trials of linaclotide in IBS-C. *Gastroenterology* 142(5 Suppl. 1), S737 (2012).

20 Spiegel BMR, Locke GR III, Spiegel BM *et al.* Developing benchmarks for clinically meaningful change for IBS-C symptoms using data from two Phase 3 trials of linaclotide. *Gastroenterology* 142(5 Suppl. 1), S214–S215 (2012).

21 MacDougall JE, MacKinnon DP, Lavins BJ *et al.* Mediation analysis supports a direct effect of linaclotide on relief of abdominal pain independent of constipation improvement. *Gastroenterology* 142(5 Suppl. 1), S215–S216 (2012).

22 Chey WD, Quigley EMM, Chey WD *et al.* Effects of 26 weeks of linaclotide treatment on adequate relief and IBS severity in patients with irritable bowel syndrome with constipation. *Gastroenterology* 142(5 Suppl. 1), S218 (2012).

23 Lembo AJ, Carson RT, Shiff SJ *et al.* Factors contributing to treatment satisfaction in patients with irritable bowel syndrome with constipation (IBS-C) trated with linaclotide versus placebo. *Gastroenterology* 142 (5 Suppl. 1), S822–S823 (2012).

24 Schoenfeld PS, Chey WD, Lavins BJ *et al.* Linaclotide significantly improved abdominal pain compared with placebo in patients with irritable bowel symptoms regardless of baseline pain severity in two Phase 3 trials. *Gastroenterology* 142(5 Suppl. 1), S701 (2012).

25 Johnston JM, Kurtz CB, Drossman DA *et al.* Pilot study on the effect of linaclotide in patients with chronic constipation. *Am. J. Gastroenterol.* 104, 125–132 (2009).

26 Lembo AJ, Kurtz CB, Macdougall JE *et al.* Efficacy of linaclotide for patients with chronic constipation. *Gastroenterology* 138, 886–895 (2010).

27 Lembo AJ, Schneier HA, Shiff SJ *et al.* Two randomized trials of linaclotide for chronic constipation. *N. Engl. J. Med.* 365, 527–536 (2011).