**NEW PRODUCTS**

**Constella: new treatment for constipation-predominant IBS**

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Linaclotide (Constella) is guanylate cyclase-C receptor agonist for the treatment of constipation-predominant IBS. In our New products review, Steve Chaplin presents the clinical data relating to its efficacy and adverse effects and Dr Nigel Trudgill discusses its place in therapy.

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**KEY POINTS**

- Linaclotide (Constella) is a guanylate cyclase-C receptor agonist for the treatment of moderate to severe constipation-predominant irritable bowel syndrome (IBS-C) in adults.
- It acts locally to increase fluid secretion into the intestine and speed colonic transit.
- After 12–26 weeks’ treatment, it increased bowel frequency and reduced IBS symptoms, notably pain and bloating, compared with placebo.
- The most frequent adverse event in clinical trials was mild to moderate diarrhoea, reported by approximately 20 per cent of patients.
- At the recommended dose of 290µg once daily, a month’s treatment costs £37.56.
- It should play a role in the treatment of patients with IBS-C who fail to respond to lifestyle measures, laxatives, antispasmodics and tricyclic antidepressants.

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The 2008 NICE guideline on the management of irritable bowel syndrome (IBS) recommends dietary and lifestyle advice and as-required antispasmodic agents.1 Drug therapy should then be tailored to symptoms, and laxatives (other than lactulose) should be considered for individuals with constipation-predominant IBS (IBS-C).

If this is unsuccessful, further options for drug therapy include a low-dose tricyclic antidepressant and, if this also fails, an SSRI.

A psychological intervention, such as cognitive behavioural therapy or hypnotherapy, should be considered if drug treatment fails and symptoms persist for one year.

**Linaclotide**

Linaclotide (Constella; Almirall) is a 14-amino acid synthetic peptide that acts as an agonist at guanylate cyclase-C receptors. It is not significantly absorbed from the gastrointestinal tract, where it is converted to the active metabolite des-tyrosine. Linaclotide increases secretion of chloride and bicarbonate into the intestinal lumen, increasing intestinal fluid and speeding colonic transit. It also has visceral analgesic activity in an animal model.

Linaclotide is licensed for the symptomatic treatment of moderate to severe IBS-C in adults when organic disease has been excluded and the diagnosis of IBS-C is established. The recommended dose is 290µg once daily, taken 30 minutes before a meal.

No dose adjustment is recommended in patients with renal or hepatic impairment, or in older people.

Treatment should be reconsidered if there is no improvement in symptoms after four weeks.

**Clinical trials**

The efficacy and safety of linaclotide have been evaluated in two phase 3 trials of similar design (n=8002, n=8043). Patients (mean age 43–45, approximately 90 per cent women) had moderate to severe IBS-C (mean number of complete spontaneous bowel movements in both trials 0.2 per week and mean spontaneous bowel movements 1.7 and 1.9 per week) with abdominal symptoms (pain, discomfort, bloating, fullness, cramping), firm stool consistency and straining.
Each trial specified four primary end-points after 12 weeks’ treatment (see Table 1). Linaclotide was significantly superior to placebo in increasing bowel movements and reducing abdominal pain, with a number needed to treat (NNT) of approximately 10–14 for the most consistent improvements. Outcomes were similar when assessed over a 26-week treatment period.

Linaclotide also improved secondary end-points including abdominal symptoms, bloating severity, straining and cramping severity,2–4 and IBS-related and general health-related quality-of-life scores.4

Table 1. Primary end-points at 12 weeks in phase 3 trials of linaclotide

<table>
<thead>
<tr>
<th>End-point</th>
<th>Rao et al2 placebo ( % pts)</th>
<th>Linaclotide* ( % pts)</th>
<th>NNT (CI95%)</th>
<th>Chey et al3 placebo ( % pts)</th>
<th>Linaclotide* ( % pts)</th>
<th>NNT (CI95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement of ≥30% from baseline in the average of the daily worst abdominal pain scores and increase of ≥1 CSBM from baseline6</td>
<td>21.0</td>
<td>33.6</td>
<td>8.0 (5.4–15.5)</td>
<td>13.9</td>
<td>33.7</td>
<td>5.1 (3.9–7.1)</td>
</tr>
<tr>
<td>Improvement of ≥30% in abdominal pain7</td>
<td>27.1</td>
<td>34.3</td>
<td>13.8 (7.4–116.1)</td>
<td>19.6</td>
<td>38.9</td>
<td>5.2 (3.9–7.6)</td>
</tr>
<tr>
<td>≥3 CSBMs and an increase of ≥1 CSBM from baseline6</td>
<td>6.3</td>
<td>19.5</td>
<td>7.6 (5.6–11.6)</td>
<td>5.0</td>
<td>18.0</td>
<td>7.7 (5.8–11.5)</td>
</tr>
<tr>
<td>Meet both of the above 2 criteria in the same week8</td>
<td>5.1</td>
<td>12.1</td>
<td>14.2 (9.2–31.3)</td>
<td>3.0</td>
<td>12.7</td>
<td>10.3 (7.5–16.4)</td>
</tr>
</tbody>
</table>

*p <0.0001–0.0262 for all end-points vs placebo; 7 in the same week for at least 6 of the 12 weeks of the treatment period; 8 for at least 9 of the 12 weeks of the treatment period; NNT = number needed to treat vs placebo; CSBM = complete spontaneous bowel movement.

Adverse events
The most frequent adverse event associated with linaclotide in phase 3 trials was diarrhoea (approximately 20 per cent vs 2–4 per cent with placebo).2 In one trial, 17.5 per cent of patients rated this as mild2 but in the other 10 per cent rated it as moderate and 2 per cent as severe.3

About 6 per cent of patients treated with linaclotide discontinued treatment due to diarrhoea compared with 0.2–0.3 per cent with placebo. Other adverse events included abdominal pain, flatulence and bloating.

References

Declarations of interests
None to declare.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics

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Place in therapy

IBS is characterised by abdominal pain or discomfort relieved by defecation or a change in stool frequency or form. IBS-C is associated with hard stools at least 25 per cent of the time and never or rarely with loose or mushy stools.¹

In the absence of alarm symptoms (age >50, short history, nocturnal symptoms, weight loss, anaemia, rectal bleeding, abdominal mass, or family history of bowel/ovarian cancer) it can be confidently treated in primary care without referral or investigation, other than a blood count and tissue transglutaminase (tTG) antibody to exclude coeliac disease.²

Current NICE guidelines for IBS-C recommend increasing exercise and soluble fibre (fruit/vegetable rather than cereal based), bulking laxatives (eg ispaghula) for episodic and osmotic laxatives (eg PEG based) for persistent hard stools, and antispasmodics for discomfort or pain.²

Low-dose tricyclic antidepressants have some value in managing pain, and psychological therapies or hypnotherapy, although efficacious, have limited availability.² However, further therapies for this common and disabling condition are clearly needed.

Efficacy

Two large randomised placebo-controlled trials over three and six months have shown that, compared with placebo, linaclotide increases the number of complete spontaneous bowel movements per week, improves abdominal pain or discomfort, provides greater overall relief from IBS-C symptoms and also improves quality-of-life measures and even bloating (a particularly difficult symptom to treat).³⁻⁵

Effects were seen on bowel frequency in the first week of treatment and sustained over the trial period.³⁻⁴

The NNT to achieve the primary trial end-points of increasing spontaneous bowel movements and reducing pain or discomfort varied from 5 to 14.

Tolerability

Given its low systemic absorption, linaclotide is generally well tolerated and not associated with any significant drug interactions.

The most common side-effect is related to its mode of action, with 19.5 per cent of patients reporting diarrhoea and 5.7 per cent needing to discontinue the drug due to this.³ Patients should therefore be counselled about the possibility of diarrhoea during linaclotide therapy.

Role of linaclotide in management of IBS-C

Linaclotide moderately improves a variety of symptoms in IBS-C, unlike other agents (eg laxatives) that tend to be of benefit for only single symptoms. It should play a role in the treatment of patients with IBS-C in primary or secondary care who fail to respond to lifestyle measures, laxatives, antispasmodics and, if appropriate, tricyclic antidepressants.

References


Declaration of interests

Dr Trudgill has served on an advisory board for Almirall and is a member of the Unlocking GI education programme supported by Almirall.

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