STATE-OF-THE-ART TREATMENT OF IRRITABLE BOWEL SYNDROME: RECENT ADVANCES AND EMERGING THERAPEUTIC ALTERNATIVES

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ABSTRACT

Irritable bowel syndrome (IBS) is a highly prevalent functional disorder characterised by chronic and recurrent abdominal pain and altered bowel habit. Numerous pharmacological and nonpharmacological treatment options have proven to have some benefit in the condition, and a multidisciplinary approach should ensure that treatment is tailored to the individual. Recently, an enhanced understanding of the pathophysiological processes underlying the condition has led to the development of new therapies, including prokinetic agents targeting serotonin (5-HT) pathways, and pro-secretory agents. Many are still at an early stage of clinical development, however, some have demonstrated improved outcomes in clinical trials and have gained regulatory approval. Lubiprostone, a calcium channel activator and linaclotide, a novel secretagogue that activates the guanylate cyclase C receptor, have demonstrated improvement of abdominal pain as well as improved bowel function in patients with IBS with constipation (IBS-C) in a series of randomised, placebo-controlled studies.

Keywords: Irritable bowel syndrome, constipation, linaclotide.

INTRODUCTION

Irritable bowel syndrome (IBS) is the one of the most common disorders in modern medicine. Its prevalence varies between countries, and depends on the criteria used to define it, but global prevalence has been estimated at around 15%; 9% when criteria include patients with persistent symptoms for at least 12 months.[1] IBS predominantly affects women[1] and imposes a substantial burden on healthcare systems, with reduced health-related quality of life (HR-QoL), repeated medical care visits and high costs, as well as indirect costs arising from reduced work productivity.[2,3] IBS is a functional bowel disorder characterised by intermittent episodes of abdominal pain or discomfort and altered bowel habit (diarrhoea, constipation, or alternating hard and loose stools),[4] which according to the Rome III diagnostic criteria, should be interrelated (Table 1).[5] IBS can be subtyped based on the predominant bowel habit into IBS with constipation (IBS-C), IBS with diarrhoea (IBS-D), mixed IBS (IBS-M), and unsubtyped IBS (IBS-U).[6] Besides abdominal pain or discomfort and abnormal bowel habit, patients with IBS often complain of other gastrointestinal (GI) symptoms, such as abdominal bloating, visible abdominal distention, straining, urgency, and incomplete evacuation, as well as symptoms emanating from the upper GI tract, other somatic symptoms, and psychological comorbid symptoms.[5]

The treatment of IBS requires a structured approach, accounting for both doctor and patient preferences. Given the fact that response to placebo in clinical trials of IBS is strong,[7] a good, patient-doctor relationship is of pivotal importance, with patient reassurance and education being central to management of the condition. Treatment options for IBS include pharmacological and nonpharmacological interventions and are summarised in the paper by Halland and Talley.[8] However, the development of effective drugs has been hindered by the

Table 1. ROME III diagnostic criteria and subtypes for irritable bowel syndrome.

Diagnostic criteria	IBS subtypes
Recurrent abdominal pain or discomfort for at least 3 days within the last 3 months in association with two 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)	• IBS with constipation when at least 25% of stools are hard and fewer than 25% are loose or watery • IBS with diarrhoea when at least 25% of stools are loose or watery and fewer than 25% are hard • IBS mixed type when at least 25% of stools are loose or watery and at least 25% are hard • IBS un-subtyped when changes in stool consistency do not fit any of the previous subtypes

Longstreth et al.[5]

complex pathophysiology of the condition. IBS is a functional disorder and as such its aetiology cannot be attributed to any underlying specific disease process or structural abnormality. However, it may be associated with abnormal GI motility, visceral hypersensitivity, low-grade gut inflammation, previous intestinal infections, changes in microflora, food hypersensitivity, and psychosocial dysfunction.[9] Recent advances in the understanding of the pathogenesis of IBS have led to the development of several promising pharmaceutical agents.[10] This article aims to review the current treatment options in IBS, with a specific focus on recent advances and emerging therapeutic alternatives.

NON-PHARMACEUTICAL TREATMENT APPROACHES TO IBS

The majority of patients with IBS report that their GI symptoms worsen in response to food intake, in particular foods rich in carbohydrates and fats.[11,12] Up to half of all IBS patients have also reported intolerance to histamine-releasing food items such as milk, red wine and pork and foods rich in biogenic amines such as wine, salami, and cheese.[12] Dietary advice is frequently sought by IBS patients,[13] and represents a cost-effective therapeutic approach. Although limited clinical evidence exists in support of dietary modification, restricting rapidly fermentable, short-chain carbohydrates (FODMAPs) has proven effective in subgroups of IBS patients.[14-16] Fibre supplementation is a widely used treatment approach in IBS-C but clinical evidence in support of its use is weak.[17,18] Soluble fibre (such as psyllium) has proven more beneficial than insoluble fibre (bran).[19]

Other lifestyle interventions may be useful in the management of IBS. A randomised clinical study showed that physical activity improves GI symptoms in IBS.[20] Psychological treatment approaches may also be beneficial, and numerous approaches, including cognitive behavioural therapy (CBT), dynamic psychotherapy, biofeedback, hypnotherapy, and relaxation therapy have been studied.[21] The availability, duration, cost, and patient reluctance have limited such interventions but a growing body of evidence supports the fact that such interventions may bring about clinically meaningful improvements in symptoms and QoL, particularly in patients with low-to-moderate QoL at baseline.[22-24] In order to increase the availability of such therapies, self-administered, internet and group-based CBT are promising options.[25-27] Gut directed hypnotherapy may provide long-term benefits in terms of symptom relief and reduced medication usage.[28] A report of two recent randomised, controlled studies concluded that the treatment is effective for patients with refractory IBS, but treatment effectiveness is lower when administered outside specialist research centres.[29]

SYMPTOM-SPECIFIC TREATMENT OF IBS

Treatment directed towards specific symptoms of IBS form the backbone of IBS therapy. Osmotic laxatives such as polyethylene glycol have demonstrated efficacy in providing relief from constipation.[30] Diarrhoea may be treated

successfully with loperamide (see below), but has also been associated with bile acid malabsorption in up to one-third of patients with IBS-D; these patients respond well to the bile acid agent cholestyramine.[31,32] In terms of abdominal pain, the use of antispasmodics including hyoscine, peppermint oil, mebeverine, otilonium bromide, pinaverium bromide, and cimetropium bromide is supported by clinical data.[16,17,24] Moreover, several studies have demonstrated that antidepressants are effective in the treatment of IBS symptoms in general, and pain in particular.[20] The α2δ ligands gabapentin and pregabalin are beneficial to some IBS patients with severe abdominal pain and anxiety.[33] However, these approaches target the patient's individual symptoms at the time of the acute episode[4,34,35] and are associated with varied efficacy and poor patient satisfaction.[36]

AGENTS TARGETING PATHOPHYSIOLOGICAL PROCESSES IN IBS

Several mediators and receptors involved in IBS-related abdominal pain have been identified, including serotonin (5-hydroxytryptamine [5-HT]), tachykinins, cholecystokinin (CCK), and nerve growth factor (NGF). Their corresponding receptor antagonists have been investigated in clinical trials. However, not all have fulfilled their promise as therapeutic targets and several clinical studies have not met their primary endpoints.[37]

Opioid Receptors

Endogenous opioids regulate nervous visceral sensitivity as well as visceral motor function. Loperamide, a μ-opioid-receptor agonist, which decreases GI motility, is the first choice treatment for patients with IBS-D,[38] and others are in clinical development. In a Phase II study of IBS-D patients, the μ-opioid receptor agonist and δ-opioid receptor antagonist eluxadoline improved abdominal pain and stool consistency.[39] Kappa-opioid receptor agonists are effective analgesics in visceral pain. Asimadoline, an orally administered kappa opioid-receptor agonist,[40,41] is currently in clinical development for IBS-D.

5-HT Pathways

One proposed pathophysiological pathway in IBS involves neurotransmission through serotonergic nerves that help regulate GI motility, sensation, and secretion. IBS-C is associated with impaired serotonin (5-HT) response.[42] Pharmacotherapies directed at 5-HT receptors therefore offer a promising treatment approach to IBS by stimulating or inhibiting GI motility. The 5-HT4 receptor agonist tegaserod (Zelnorm®, Zelmac®) was indicated for the short-term treatment of women with IBS-C who are <55 years of age, but was refused marketing approval by the European Medicines Agency (EMA) owing to safety concerns.[43] It was previously withdrawn by the US Food and Drug Administration (FDA) in 2007 following postmarketing reports of serious adverse events (AEs), including an increased risk of cardiovascular events, and is currently available only upon request for women who fail to respond to other treatments.[3] Cisapride was also withdrawn as a result of serious cardiac AEs. Other 5-HT4 receptor agonists have failed to demonstrate significant clinical benefit in IBS.[44]

The potential for cardiac and vascular AEs with 5-HT receptor agonists has been demonstrated in other therapeutic areas.[45,46] As a result, any new drugs in this category must demonstrate selectivity for the 5-HT4 receptor over other receptors. Three 5-HT4 receptor agonists in clinical development have greater selectivity for 5-HT4 over other receptors. Prucalopride (Resolor®), a selective, high affinity 5-HT4 receptor agonist, demonstrated efficacy in three large randomised, placebo-controlled, clinical trials of chronic idiopathic constipation (CIC), but has not yet been studied in IBS-C.[47-49] Its most common AE is headache, followed by nausea and diarrhoea. Prucalopride has been approved for use in Europe[50] but not yet in the US. Velusetrag and ATI-7505 are 5-HT4 antagonists in early stage clinical development.[51]

Other therapies targeting the 5-HT system include 5-HT3 antagonists such as cilansetron and alosetron.[52,53] These significantly improve the symptoms of IBS-D but have been associated with ischaemic colitis and constipation. Alosetron was withdrawn from the US market in 2000 and reintroduced in 2002 with availability and use restricted, and the development of cilansetron was stopped.[53] Alosetron is not available in Europe. In a recent study from the UK, ondansetron, a 5-HT3 antagonist approved for the treatment of chemotherapy-induced nausea,

has also been found to be effective for patients with IBS-D.[54] Pumosetrag (DDP-733), an orally available prokinetic agent and locally acting 5-HT3 partial agonist, is currently in clinical development for IBS-C.[55]

Gastrointestinal Secretion

An emerging concept in IBS therapy is the use of non-absorbed, luminally-acting molecules, minimising the likelihood of systemic AEs. Inducing fluid secretion into the GI tract, which softens stools, increases motility, and promotes spontaneous bowel movements, has proved a promising therapeutic target. Currently, two intestinal secretagogues are available: lubiprostone and linaclotide. Clinical trial data demonstrating their efficacy and safety in IBS are summarised in Table 2.

Table 2. Randomised, placebo-controlled trials of linaclotide and lubiprostone in constipation-predominant irritable bowel syndrome (IBS-C).

Author	Study design	Patients (n)	Main outcomes
Linaclotide (100 or 1000 μg)	Phase IIa, n=36, 100% women[96]	5 days	Ascending colon emptying time Time to first bowel movement Stool frequency Stool consistency Ease of stool passage
Linaclotide (75, 150, 300, or 600 μg QD)	Phase IIb, n=420, 92% women[64]	12 weeks	CSBM and SBM frequency CSBM responder SBM responder Adequate relief responder Global relief responder Stool consistency Straining Abdominal pain Abdominal discomfort Bloating
Linaclotide (290 μg QD)	Phase III study, n=804, 90% women[65]	26 weeks	FDA responder CSBM and SBM frequency Abdominal pain, discomfort, bloating, fullness, and cramping Stool consistency Straining Adequate relief Treatment satisfaction
Linaclotide (290 μg QD)	Phase III, n=800, 91% women[66]	12 weeks	FDA responder CSBM and SBM frequency Abdominal pain, discomfort, bloating, fullness, and cramping Stool consistency Straining Adequate relief Treatment satisfaction
Lubiprostone (8 μg BID)	Two Phase III trials, n=1171[58]	12 weeks	Using a balanced seven-point Likert scale ranging from significantly relieved (+3), to significantly worse (-3), patients responded on their electronic diary to the question: 'How would you rate your relief of IBS symptoms over the past week compared to how you felt before you entered the study?'
Lubiprostone (8 μg BID)	Open-label extension study of Phase III trials	36 weeks	Long-term safety and tolerability, monitored via adverse events (AEs), laboratory parameters and vital signs. Monthly responder rates Patient evaluations of IBS-C symptom severity Quality of life

BID: twice daily; QD: once daily; CSBM: complete spontaneous bowel movement; SBM: spontaneous bowel movement.

Table 3: Primary endpoints specified by the European Medicines Agency (EMA) and US Food and Drugs Administration (FDA).

EMA[67]	FDA[68]
Abdominal pain or discomfort responder: 30% reduction in mean abdominal pain or discomfort score, with neither condition worsening from baseline for at least 6 weeks. IBS degree of relief responder: symptoms considerably or completely relieved for at least 6 weeks.	FDA responder: decrease of at least 30% in the average daily worst abdominal pain score (measured daily) compared with baseline weekly average, and an increase of at least one complete spontaneous bowel movement (CSBM) from baseline.

Lubiprostone (Amitiza®) is an analogue of endogenous prostones (bicyclic fatty acids), and directly activates chloride channels in epithelial cell membranes, inducing fluid secretion.[56] It is approved by the FDA for the treatment of CIC and IBS-C. In a Phase II trial, lubiprostone showed significantly greater improvements in mean abdominal discomfort/pain scores after 2 months compared with placebo, but at 3 months the trend was no longer significant.[57] In a combined analysis of two Phase III clinical trials, a significantly higher percentage of lubiprostone-treated patients were considered overall responders compared with those treated with placebo.[58] An extension study found that lubiprostone demonstrated sustained efficacy and was safe and well tolerated over 9–13 months of treatment.[59] Common AEs of lubiprostone include nausea, diarrhoea, abdominal pain, and bloating, and, rarely, dyspnoea.[60] Nausea is mostly mild-to-moderate, and is best managed by taking the drug with food.[35]

Further studies have focused on the mechanism of action of lubiprostone. An 8-week crossover study demonstrated that lubiprostone has no effect on visceral pain thresholds. The reductions in clinical pain associated with its use appear to be secondary to changes in stool consistency.[61] An *in vitro* study found that lubiprostone, but not active linaclotide, promotes repair of the epithelial barrier and cell function, a finding of potential clinical importance for IBS patients with compromised barrier function.[62]

Linaclotide (Constella®) is a first-in-class 14-amino acid peptide agonist of guanylate cyclase (GC-C). It activates GC-C receptors on the luminal surface intestinal enterocytes, causing a signal transduction cascade that results in chloride channel activation and enhanced secretion of intestinal fluid and accelerated intestinal transit.[63] Linaclotide received EMA marketing authorisation in November 2012 and FDA approval in August 2012 for the symptomatic treatment of moderate-to-severe IBS-C in adults after demonstrating efficacy and safety in Phase II[64] and Phase III clinical trials, based on FDA endpoints[65,66] (Table 3),[67,68] as well as an analysis based on EMA recommended endpoints.[69] Linaclotide also significantly improved abdominal symptoms and QoL in a subgroup of patients who rated specific abdominal symptoms as severe at baseline.[70] A higher rate of AEs was reported in the linaclotide treatment arm compared with placebo; however, most were mild or moderate in severity. The most common of these was diarrhoea. The use of linaclotide in clinical practice requires further evaluation of the significance of this AE and the best strategies to minimise its impact. Animal studies have found that linaclotide has an analgesic mechanism of action that is independent of its action on gut motility or stool consistency.[71] Another GC-C agonist, plecanatide, is currently in clinical development for IBS-C, and demonstrated efficacy in a Phase II study of patients with CIC.[72] A Phase II placebo-controlled trial in IBS-C patients is ongoing.[73]

Intestinal Microbiota

Alterations in intestinal microbiota are increasingly being recognised as an important factor in the pathophysiology of IBS. Recent evidence suggests that a proportion of patients with IBS may have small intestinal bacterial overgrowth (SIBO), although this suggestion is controversial.[74-76] This has provided a rationale for antibiotic-based therapies for IBS. Rifaximin

is a nonabsorbable antibiotic that demonstrates no clinically relevant bacterial resistance and has been associated with improvement of IBS symptoms, but symptoms seem to return when the treatment is stopped, and repeated dosing has not been formally evaluated.[77]

Probiotics have also proven safe and effective in IBS, and may be administered as functional foods such as yoghurts and drinks or in pharmaceutical forms. The most widely used probiotics are *Lactobacillus plantarum* 299v, *Lactobacillus rhamnosus LGG*, *Lactobacillus reuteri*, *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium infantis*, *lactis* or *brevis*. However, not all probiotics have been shown to be equally effective. Clinical trials to date have varied in design, probiotic strain used, dosage and formulation, but a number of studies have reported beneficial effects.[78-82] A recent review concluded that probiotics are associated with modest clinical benefits but are unlikely to benefit all patients.[83] A larger body of good quality clinical trial data is needed to draw firm conclusions.

Faecal microbiota transplantation has demonstrated efficacy in recurrent *Clostridium difficile* infections,[84] and interest is growing in the technique as a potential treatment for IBS. However, the technique remains controversial and to date has only been used in experimental settings.[85,86]

OTHER THERAPEUTIC APPROACHES TO IBS

Stress and concomitant psychological conditions such as somatisation, anxiety and depression play a major role in the development, clinical course, and response to treatment in IBS.[87,88] Psychotropic drugs, including selective serotonin/serotonin-norepinephrine receptor antagonists and tricyclic antidepressants, therefore play a key role in the treatment of moderate-to-severe IBS.[89]

It is well known that bile acids in the colon stimulate motility and increase secretion. Following their role in digestion, bile acids are reabsorbed by ileal bile acid transporters (IBATs). Inhibiting IBATs by luminally acting drugs may increase the amount of bile reaching the proximal colon and benefit patients with IBS-C. In a Phase II clinical trial, the IBAT inhibitor A3309 increased stool frequency and improved constipation-related symptoms in CIC.[90] Agents in clinical development for IBS-D include ibodutant, a neurokinin 2 receptor antagonist,[91] anti-inflammatory approaches including mesalazine[92] and ketotifen,[93] and the centrally acting agent dextofisopam.[94]

CONCLUDING REMARKS

Until recently, pharmacotherapy directed at individual symptoms has been the standard of care for IBS. However, new treatments are improving clinical outcomes and changing the treatment algorithm, especially as clinical trial data are becoming available. While systemic prokinetic agents, such as the 5-HT4 receptor agonist prucalopride, and 5-HT3 receptor agonists, offer considerable potential, the largest body of clinical data to date supports the use of the pro-secretory agents - lubiprostone and linaclotide. There is a need for head-to-head trials comparing the efficacy and cost-effectiveness of these treatments.

In conclusion, the treatment armamentarium for IBS is expanding. However, there remains a need for a multidisciplinary and individualised approach to IBS. While some patients will benefit primarily from symptom-based pharmacological treatment, others may benefit more from behavioural therapy and/or the use of psychotropic drugs. A graduated treatment approach has been suggested, with diagnosis being the most important treatment step.[95] Individualising management remains the key to achieving the optimal outcomes in IBS with currently available therapeutics.

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