Experimental therapies in Irritable Bowel Syndrome

Jakub Włodarczyk[1], Patrycja Szałwińska[1], Anna Waśniewska[1,2], Jakub Fichna[1]

[1]Department of Biochemistry, Medical University of Lodz, Poland
[2]Department of Normal and Clinical Anatomy, Medical University of Lodz, Poland

Corresponding author: Jakub Włodarczyk, M.D.
Department of Biochemistry, Medical University of Lodz
ul. Mazowiecka 6/8, 92-215 Łódź, Poland
Phone: +48 42 272 57 07; E-mail: dr.jwlodarczyk@gmail.com

Abstract: Irritable bowel syndrome (IBS) is a multifactorial gastrointestinal disorder with still not fully understood pathogenesis. At first, the treatment of IBS was mainly focused on alleviating symptoms (with the use of laxatives, anti-diarrheals, anti-spasmodics and painkillers) and then became more specific by targeting discovered pathways responsible for proper functioning of the gastrointestinal system, for instance: 5HT3, 5HT4, cannabinoid and opioid receptors, guanylyl cyclase C, chloride channels and sodium-hydrogen exchanger. Nowadays, there is a growing number of experimental IBS treatment strategies and in this article we discuss these novel and therapeutic options in IBS, their efficacy and future perspectives.

Introduction

Irritable bowel syndrome (IBS), sometimes also called "spastic colon" is a heterogenous, chronic disease with multifactorial pathogenesis [1]. Depending on diagnostic criteria, evaluated population, access to the health care and cultural impact, prevalence of IBS fluctuates between 10 and 25%. IBS affects mostly adults in Europe and North America, especially females and generally manifests between the age of 15 and 65 years [1–3]. This condition belongs to the group of functional bowel disorders (FBD) and is mainly manifested by recurrent abdominal pain or discomfort, bloating, distension and abnormal gut contractions (resulting in irregular stool pattern: diarrhea in IBS-D, constipation in IBS-C or both in IBS-M). It is a growing problem worldwide and since

its pathogenesis is not completely understood — the treatment is mainly symptomatic and generally based on diet modifications or alleviating symptoms. Still, IBS symptoms can be very troublesome for the patients, highly affecting their quality of life and many previous methods are ineffective. In consequence, more efficacious treatment with the smallest number of side effects is needed. In this narrative review, we discuss novel and emerging therapies vs. currently approved therapies for IBS, highlighting their mechanisms of action, effectiveness and safety.

Current approaches in IBS treatment

Pharmacotherapy used in IBS, depending on the subtype, includes antidepressants, antibiotics, peripherally restricted opioids, as well as more specific or experimental ones, such as serotonin receptor ligands, cystic fibrosis transmembrane conductance regulator (CFTR) channel antagonists, guanylate cyclase C (GC-C), and type 2 chloride ion channels activators [2]. FDA accepted the following drugs with division into IBS-D and IBS-C [1]:

1. IBS-D: antispasmodics (dicyclomine, hyoscyamine, peppermint oil), 5HT3 antagonists (alosetron), targeting opioid receptors (loperamide, eluxadoline), and antibiotics (rifaximin);

2. IBS-C: laxatives (polyethylene glycol [PEG], lactulose), chloride channels activator (lubiprostone), targeting guanylyl cyclase C (linaclotide), and sodium-hydrogen exchanger inhibitor (tenapanor).

Many of these drugs are included in the most recent American College of Gastroenterology (ACG) Clinical Guideline [4]. It strongly recommends the use of chloride channel and GC-C activators to treat general IBS symptoms in IBS-C. Another recommendation is the use of rifaximin with the same indication but in IBS-D. Tricyclic antidepressants are also strongly recommended (to treat global symptoms of IBS) but with moderate quality of evidence. Conditional recommendations with low or moderate quality of evidence include avoiding PEG products alone — for general symptoms in IBS-C, use of 5-HT4 agonists (tegaserod) — in IBS-C symptoms in women under age of 65, 5-HT3 antagonists (alosetron) — in IBS-D symptoms in women with acute symptoms and conventional therapy failure; and mixed opioid agonists/antagonists — in global IBS-D symptoms. Noteworthy, ACG also mentions some non-pharmacological paths of IBS management such as low FODMAP diet (recommended as a limited trial to improve IBS symptoms) and fecal microbiota transplantation (FMT — not recommended) — both of them have very low quality of evidence [4].

Recent trials regarding IBS treatment

Heat-inactivated Bifidobacterium bifidum MIMBb75 (SYN-HI-001)

Probiotics are live or attenuated microorganisms which can affect gut microbiota composition and functions with the benefit for the host and are widely used in IBS management since disruptions in gut microbiome (dysbiosis) may play an important role in IBS pathogenesis [1]. One of the fundamental mechanisms in IBS pathology is increased visceral permeability (state in which intestinal barrier is impaired what allows for translocation of intraluminal contents including pathogenic bacteria) and it is believed that probiotics can strengthen intestinal barrier through adherence of some strains to the epithelial cells [5, 6]. However, the efficacy of viable probiotics strains is highly strain-specific and not every strain can meaningly alleviate IBS symptoms [7]. One study focused on beneficial influence of *Bifidobacterium bifidum* MIMBb75 which noticeably improves IBS symptoms and patients quality of life [8]. Its adhesion to intestinal epithelial cells was also higher in comparison to other commercial probiotics [8].

In this mentioned randomized, double-blind, placebo-controlled trial patients diagnosed with IBS on the basis of Rome III criteria after meeting particular inclusion/exclusion criteria received for 8 weeks non-viable undisturbed B bifidum HI-MIMBb75 obtained by heat-inactivation of viable strain [7]. The results turned out to be promising — the study showed that this strain of *Bifidobacterium bifidum* notably reduced IBS symptoms of all subtypes. It had 1.7 times greater response rate for at least 30% improvement of abdominal pain with relief of general IBS symptoms in contrast to placebo group. Moreover, patients reported considerable relief of individual symptoms like abdominal pain, bloating, distension and frequent bowel movement.

Apart from this, it was suggested that the effect of non-viable form of bacteria seems to exceed the effects of corresponding viable type [8]. In fact, the use of non-viable form of bacteria may occur advantageous especially for severely ill or immunocompromised patients as these preparations are associated with better standardization, stability and safety [9, 10].

β-Galactooligosaccharide in Conjunction with Low FODMAP Diet

Low FODMAP diet is a non-pharmacological way of IBS management. In general, FODMAP stands for fermentable oligosaccharides, disaccharides, monosaccharides and polyols, therefore this diet requires exclusion of such products as legumes, vegetables, fatty foods, artificial sweeteners, stone fruits and lactose-containing foods from everyday life [11]. Despite being quite restrictive, it is proved to have a positive impact on preventing abdominal pain, bloating, and general symptoms, and improving quality of life and stool pattern, especially in patients reporting loose stool or

diarrhea [12, 13]. However, there is some data about a negative influence of low FODMAP diet on fecal bifidobacterial concentration — bacteria responsible for regulation of colonic pH, immune modulation and pathogen removal [14]. What is more, the low FODMAP diet restricts — due to opposite effects — the use of prebiotics. Nevertheless, both treatments improve some IBS symptoms and it is believed that they can be complementary [15].

There were some attempts already to investigate whether the detrimental impact of low FODMAP diet on microbiota can be avoided. For example, in a study by Wilson *et al.* the influence of B-galactooligosaccharides (B-GOS) supplementation (which alone can reduce IBS symptoms and increase bifidobacteria) together with low FODMAP diet was investigated [16]. In this randomized, placebo-controlled, 3-arm trial with adults diagnosed with IBS on the basis of Rome III criteria, patients were divided into 3 groups: control group (sham diet with placebo supplement), group with low FODMAP diet plus placebo and low FODMAP diet with 1.8 g/d B-GOS (1.4 g active ingredient) for 4 weeks. This study showed that B-GOS can be safely added to the low FODMAP diet keeping its effects on symptom improvement. What is more, combined therapy (diet + prebiotic) turned out to be more effective than placebo, as after 4 weeks more patients reported milder symptoms on the IBS symptom severity score. However, the performed study did not allow to state without a doubt that B-GOS makes low FODMAP diet more effective, as the prebiotic supplementation did not markedly ameliorate any symptom in comparison with low FODMAP diet alone [16]. Moreover, in this investigation the prebiotic did not prevent the reduction of bifidobacteria, what allowed to confirm the theory of negative "anti-prebiotic" effect of this diet. Additionally, according to mentioned study low FODMAP diet decreases butyrate concentration and fecal *Actinobacteria*, and increases fecal pH so it should not be used for a long time [16].

Faecal microbiota transplantation (FMT) administered via colonoscopy

FMT is the process of transferring fecal microbes from a healthy donor to the host via colonoscopy, gastroscopy or fecal capsules [17]. This procedure is proved to be highly effective in recurrent *Clostridioides difficile* infections and some data show that it can relieve functional gastrointestinal (GI) symptoms. Hence, FMT is increasingly being used for IBS treatment trials as changes in gut microbiota are believed to play a part in IBS pathogenesis. However, the results of previous investigations vary, what can depend on donor microbiota, other not known stool elements or microbiota survival while the stool is processed [17–20].

In the most recent randomized, double-blinded and placebo-controlled clinical trial by Lahtinen *et al.* the long-term efficacy of FMT via colonoscopy in reducing IBS symptoms as well as its influence on patient's mental health (including depression and anxiety) and quality of life was evaluated using validated questionnaires: IBS symptom

severity score, Rome-III questionnaire and IBS Quality of Life questionnaire [17, 21–23]. Patients were divided into 2 groups and received 30 g of autologic (placebo) or allogenic FMT into the caecum and were monitored for a year. The IBS symptoms decreased significantly after FMT but the effect was not significant when compared with placebo. Of note, the biggest difference in transient reduction of symptoms between the groups was at week 12 (3 months after FMT). This stays in line with another study by Johnsen *et al.* in which temporary symptom relief was also observed in the same period of time. The mental health and quality of life also did not reveal any notable differences between the groups after the procedure — what, as authors say, may be caused by many other factors affecting quality of life apart from IBS symptoms [18]. Nevertheless, after separate analysis of the responders (patients whose IBS symptoms improved after FMT) it turned out that the depression score decreased and the quality of life increased in contrast to placebo patients who also reported symptoms relief [18]. What is more, FMT increased microbiota richness (but not diversity) and it resembled donor's microbiota in the contrary to placebo group in which these changes were not observed. Consequently, as these changes lasted for 52 weeks, FMT seems to quite permanently alter gut microbiota composition. Furthermore, stool water content decreased in the FMT group and did not change through the follow-up. To conclude, this study did not reveal significant and long-lasting benefits of FMT over placebo and therefore this procedure cannot be recommended in daily clinical practice; however, it showed that FMT can cause some constant stool alternations and that there is a possible connection between gut microbes and depression [18].

Serotonin receptor agonists

Serotonin 4 (5-hydroxytryptamine 4: 5-HT4) receptor agonists promote GI motility, by leading to release of acetylcholine in GI tract. Despite many trials, so far only one 5-HT4 receptor agonist has been approved for IBS-C therapy: tegaserod. However, new 5-HT4 agonists are still being assayed in IBS treatment [24].

Hamatani *et al.* investigated the effectiveness of a new, highly selective 5-HT4 receptor agonist, minesapride, which presents enterokinetic effect [25]. In their trial, 411 patients who suffered from IBS-C were randomized into four groups: patients received 10, 20 or 40 mg/d of minesapride or placebo for 12 weeks, respectively. The primary endpoint was defined with accordance to a FDA definition: responder was a person who noticed an increase in one or more complete spontaneous bowel movements from baseline and with an improvement of 30% or more from baseline in weekly average of worst abdominal pain score [25]. Throughout the treatment period, a significant difference was noticed between placebo group and the patients who received 40 mg of minesapride. Adverse events, such as diarrhea, abdominal pain, or an increase in blood creatine phosphokinase, were rare. According to Hamatani *et al.* minesapride seems to be a promising, new agent for IBS [25].

Future perspectives

Endocannabinoid system in irritable bowel syndrome

Since the recognition of cannabinoid (CB) receptors 1 and 2 followed by identification of the endogenous cannabinoid (CB) receptor ligands — anandamide (arachidonoylethanolamide) and 2-arachidonoylglycerol, numerous studies were focused on the endocannabinoid (eCB) system and possible ways of its pharmacological modulation [26, 27]. This system consists of the endocannabinoid ligands, their "classical" receptors (CB1 and CB2) as well as transporter molecules and degradation enzymes. The CB1 receptors are mainly located in the peripheral and central neurons; in the GI tract, the CB1 receptors can be found in enteric nervous system and sensory terminals of spinal and vagal neurons. Activation of these receptors in the GI tract is inhibited mainly by ongoing contractile transmitter release and leads to a decreased motility [28]. Moreover, CB receptors influence intestinal secretion, promotion of fibrosis and secretion of inflammatory mediators. The CB2 receptors are located in the nerve terminals and immune cells. Activation of the CB2 receptors results in modification of inflammatory expression by neutrophils, B and T cell subtypes and macrophages. These activities of the CB2 receptors mediate anti-inflammatory effect of mucosa and support the integrity of the epithelium [28].

Cannabis has been long used in the treatment of multiple GI disorders, such as nausea, vomiting, constipation, diarrhea, abdominal pain and other symptoms of dysmotility and inflammation. Moreover, sensation of visceral pain, which is precepted by majority of patients with IBS, is partly mediated by the cannabinoid receptors. Therefore, cannabis has also been used for IBS treatment. Wong *et al.* reported that dronabinol, which is a non-selective cannabinoid agonist, in patients with IBS-M and IBS-D was highly effective by reducing fasting colonic motility index and increasing colonic compliance [29].

Taranabant and rimonabant, which are CB1 receptor inverse agonists and were previously tested as potential anti-obesity drugs with high efficiency, were later used as potential treatment for IBS-C. However, in some clinical trials, taranabant and rimonabant revealed more side effects than placebo such as nausea, vomiting and diarrhea. What is more, the phase III studies of rimonabant were suspended, because patients suffered from serious psychiatric adverse events, depression and suicidal intentions [30].

Recently, a novel CB2 receptor agonist, olorinab, was tested as a new therapy for GI tract diseases [31]. Olorinab decreased abdominal pain and improved bowel movement, hence ongoing clinical trials of this CB2 receptor agonist in IBS are quite promising.

Effect of resolvins on sensitization of TRPV1 and visceral hypersensitivity in IBS

Transient receptor potential vanilloid type 1 (TRPV1) is a receptor located in the peripheral nerve endings (i.e. of the GI tract) and thought to play a crucial role in nociception. It can be directly or indirectly activated by proinflammatory mediators, which results in TRPV1 depolarization and release of algogenic compounds responsible for ascending pain transmission pathway. Any alternations in this process lead to the visceral hypersensitivity, which is a critical aspect of IBS pathogenesis. The increased expression of TRPV1 was confirmed in preclinical models of visceral hypersensitivity and in rectal samples of IBS patients [32, 33]. Moreover, the evidence of TRPV1 sensitization in patients with IBS was recently provided [34]. Therefore, targeting TRPV1 may have positive implication on IBS symptoms and related pain, whereas the results of preclinical studies suggest the need for novel compounds to be further assessed as IBS treatment [34].

Resolvins (RvD1, RvD2 and RvE1) are endogenous anti-inflammatory lipid mediators that modulate the TRPV1 activation [35]. Their analgesic properties were proved in *in vitro* and *in vivo* murine model studies. Resolvins prevented histamine-induced TRPV1 sensitization and reversed TRPV1 sensitization by histamine and IBS supernatant. Moreover, RvD2 treatment normalized pain responses to colorectal distension in murine models of VHS and post-inflammatory irritable bowel syndrome (PI-IBS).

Another study regarding TRPV1 employed its fast desensitizing agonist — palvanil [36]. The research targeting the murine GI tract proved that TRPV1 palvanil provides antinociceptive actions and inhibition of colonic contractions and motility.

Endogenous opioid system

Endogenous opioid system (EOS) participates in the control of the GI functions through its receptors: μ (MOP) — engaged in the control of motility, δ (DOP) — secretion and absorption, and κ (KOP) — immunomodulation. The MOP receptor agonist, loperamide, is the most commonly used drug to treat acute diarrhea [37]. Loperamide may be used in some patients with IBS-D, but it is not currently recommended in long term treatment because of a lack of high-quality evidence [38]. However, many recent studies attempt at modulating the endogenous opioid system in order to alleviate IBS symptoms [39].

Conventional opioids, upon binding to MOP induce analgesia through activation of G protein-mediated pathways; however, they also inhibit the GI motility and depress central nervous function by the activation of β-arrestin. Recently, a new biased MOP ligand — TRV130 was proposed as analgesic therapy; it activates exclusively the G protein pathway without gastrointestinal side effects [40].

Some recent studies regarding the EOS in GI tract have focused on enkephalinases — metalloproteases which play a crucial role in modulation of the EOS activity [41]. Consequently, enkephalinase inhibitors (EIs) allow obtaining therapeutic concentrations of selected endogenous opioid peptides, i.e. enkephalins. EIs are characterized by low potency for developing serious adverse events in the treatment of patients with chronic d46iseases; moreover, they possess antidiarrheal effects and the ability to modulate pain signaling and activities in both peripheral and nervous centers [41].

In line, Fabisiak *et al.* conducted an experiment verifying the analgesic properties of enkephalins and enkephalinase inhibitors in a mouse model of visceral pain [42]. The results showed that subcutaneous administration of sialorphin at 1 mg/kg reduced the visceromotor response to balloon insufflation in the intestinal lumen. Noteworthy, no analgesic activity was shown by opiorphin, the human functional homologue of the rat sialorphin, what may indicate the presence of specific enzymes in the organism that degrade this compound or interspecies specificity.

Oridonin

Lately, a diterpenoid compound isolated from *Rabdosia rubescens* — oridonin, was proposed as a potential treatment in PI-IBS [43]. In *in vivo* and *in vitro* studies oridonin had beneficial anti-inflammatory effect and helped in proper intestinal barrier function restoration. Its mechanism of action is based on restoration of tight junction protein level and on inhibition of NF-κBp65 as well as its downstream gene product (iNOS, COX-2, IL-1β, and IL-6) level. Moreover, it was proved that oridonin has a strong relation with PXR (ligand-activated nuclear receptor, which is abundantly expressed in intestine), that also has been proposed as a therapeutic target of PI-IBS [44].

Inhibition of miRNA-29a regulates intestinal barrier function in IBS-D by upregulating ZO-1 and CLDN1

MiRNAs have only recently become the center of interest for researchers and clinicians focusing on intestinal diseases. These are small non-coding RNAs with the ability of post-transcriptional regulation by mRNA cleavage or repression of translation, depending on the degree of complementarity miRNA-mRNA. MiRNAs were seen being implicated in biological processes underlying inflammation, carcinogenesis and cell proliferation [45].

A study by Zhou *et al.* suggested that miRNA-29a plays a role in regulation of intestinal membrane permeability in IBS-D patients. They observed that glutamine synthetase gene (GLUL), modified by miR-29a, regulates intestinal membrane permeability [46].

In a study by Zhu *et al.*, the role of miRNA-29a in the maintaining of the intestinal mucosal barrier in IBS-D was analyzed [47]. Based on samples from IBS-D patients they noted that miRNA-29a was upregulated while tight junctions (such as ZO-1, CLDN1) were downregulated. Following they have tested miRNA-29a inhibitor in a IBS-D mouse model, during which they observed amelioration of junction protein complex.

SGLT1 inhibitor

SGLT1 is a transporter widely expressed in a human body (i.e. in the small intestine, kidney, heart, and colon). In the small intestine, SGLT1 is localized in the apical membrane of the epithelial cells involved in glucose uptake by sodium gradient [48]. Recently, drugs which inhibit the glucose transport or reduce uptake of sodium ions from the intestinal lumen were proposed as potential IBS agents. These drugs include mizagliflozin — a SGLT1 inhibitor and DRAinh-A250 — an inhibitor of intestinal anion exchanger DRA (downregulated in adenoma). Through the inhibition of glucose transport in the intestine mizagliflozin restrained water absorption, which resulted in the stool softening and alleviation of constipation. Results of a phase 2 controlled trial of mizagliflozin in patients with chronic constipation proved its effectiveness over placebo [49]. Whereas intraluminal administration of DRAinh-A250 in mouse blocked fluid absorption and reversed loperamide induced constipation [50].

Histamine 1 receptor antagonists

While serotonin has already proved to be implicated in the pathogenesis of IBS, histamine has emerged as an important biogenic amine in this disease. Although the pathophysiological role of histamine in IBS is not entirely clear, there is evidence that supports the use of agents targeting histamine receptors (HRs) as a potential therapeutic option [51]. In line, treatment of IBS patients with the H1R antagonist — Ebastine resulted in a significant improvement of abdominal pain in 46% of patients with IBS compared with 13% in the placebo group. Moreover, it was proved that ebastine attenuates visceral hypersensitivity in vitro [34].

Conclusion

In summary, increased understanding of the pathophysiological mechanisms in IBS was followed by the development of novel IBS treatment strategies to manage patients, particularly the abdominal pain component. Numerous therapeutics currently available on the pharmaceutical market are proposed to IBS patients, when non-pharma-

cological approach is not sufficient. Unfortunately, the effectiveness of these drugs, in general, is still not satisfactory. Therefore, more detailed research on new pharmacological targets, IBS biomarkers and biomarkers of drug response are warranted.

Acknowledgments

Conflict of interest

None declared.

Abbreviations

ACG	— American College of Gastroenterology
B-GOS	— B-galactooligosaccharides
CB	— cannabinoid
CFTR	— cystic fibrosis transmembrane conductance regulator
eCB	— endocannabinoid
EIs	— enkephalinase inhibitors
EOS	— endogenous opioid system
FBD	— functional bowel disorder
FMT	— fecal microbiota transplantation
FODMAP	— Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols
GC-C	— guanylate cyclase C
GI	— gastrointestinal
GLUL	— glutamine synthetase gene
5-HT4	— 5-hydroxytryptamine 4
IBS	— irritable bowel syndrome
PEG	— polyethylene glycol
PI-IBS	— post-inflammatory irritable bowel syndrome
PXR	— ligand-activated nuclear receptor
TRPV1	— t ransient receptor potential vanilloid type 1

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