Review of Rifaximin: Latest Treatment Frontier for Irritable Bowel Syndrome Mechanism of Action and Clinical Profile

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ABSTRACT

BACKGROUND: Irritable bowel syndrome is classified as a functional gastrointestinal disorder with the primary symptom of abdominal pain in conjunction with bloating and bowel movement disorder. It affects up to 15% of the world's population. Among its subtypes, the most common is diarrhoea predominant. However, the current treatment options for diarrhoea-predominant irritable bowel syndrome have had not very promising results; most, such as antispasmodics, only provide partial symptomatic relief. Treatment with antidepressants and alosetron (a 5HT3 antagonist) has shown the most promise to date. The latest drug to be approved for the treatment of irritable bowel syndrome-diarrhoea is rifaximin, which was approved in May 2015. It is a minimally absorbed antibiotic that is used to change the gut microbiota. Small intestinal bacterial overgrowth is one of the causes suggested for irritable bowel syndrome, particularly for the diarrhoea-predominant type. There are various methods for detecting bacterial overgrowth, the simplest of which is breath tests. Rifaximin has been shown to be of benefit to these patients.

PURPOSE: The purpose of the study is to discuss the potential mechanism of action of rifaximin, a minimally absorbed antibiotic. In addition, we evaluate the various clinical trials undertaken to study the efficacy and safety profile of rifaximin.

KEYWORDS: Rifaximin, irritable bowel syndrome, small intestinal bowel overgrowth, diarrhoea

Introduction

Irritable bowel syndrome (IBS) is the most prevalent functional gastrointestinal (GI) disorder; it affects up to 15% of the world's population.[1–3] It is diagnosed using Rome III criteria, in which the presence of abdominal pain or discomfort is the cardinal symptom, along with altered bowel habits, such as changes in the consistency and frequency of stools.[4] Other symptoms, such as bloating, a sensation of incomplete evacuation, straining (constipation), and urgency (diarrhoea), are also commonly present, although these symptoms are not necessary for IBS to be diagnosed. Currently, there is no gold standard for the diagnosis of IBS.[5] Diagnosis is difficult because there are no reliable or standardized biomarkers and because the pathology cannot be detected with radiological or endoscopic tests.[6] Patients with IBS are further subtyped using the Bristol Stool Form Scale (BSFS) according to their predominant stool pattern: constipation-predominant (IBS-C) or diarrhoea-predominant (IBS-D), mixed, or unsubtyped/unclassified (ie, insufficient abnormality of stool consistency to meet criteria for the other IBS subtypes).[7] Patients with alarming features should undergo colonoscopy to rule out organic disease, and random biopsies should be obtained to test for microscopic colitis in patients with IBS-D.[8]

Patients with IBS have an average duration of disease of 10 or more years.[9] Irritable bowel syndrome is often undiagnosed or untreated, with as few as 25% of IBS sufferers seeking professional health care.[10] Those seeking care are often frustrated by the lack of results of traditional treatment and management strategies. Thus, IBS can negatively impact an individual's quality of life and result in significant direct and indirect costs.[9] This is in part due to additional medical tests and medical and nonmedical therapies, the value of which is still unproven.[11]

The most common currently used pharmacologic treatments include antispasmodics, antidepressants, antidiarrhoeals, osmotic laxatives, and bulking agents.[12] Alternative treatments include the use of probiotics and peppermint oil. Nonpharmacologic interventions, which may improve symptoms, include exercise, stress reduction, and treating coexisting sleep disorders.[11] Most of the patients with IBS believe that certain food items are important triggers of the GI symptoms and self-address their dietary concerns.[13]

Diarrhoea-predominant IBS is the most common subtypes, occurring in approximately 40% of patients.[14] The most commonly used over-the-counter treatments include prebiotics and antidiarrhoeals, such as loperamide. Probiotics are effective treatments for IBS, although which individual species and strains are the most beneficial remains unclear.[15–17] Loperamide generally improves the symptoms of diarrhoea, such as stool consistency and borborygmi, although it provides no significant

improvement in global IBS symptoms compared with placebo, and it does not improve abdominal pain or distension.[18] Regarding antispasmodics, a recent Cochrane review concluded that although there is weak evidence of the benefit for abdominal pain and global symptom relief, it is unclear whether individual antispasmodic classes are effective.[19] In addition, in higher doses, antispasmodics have anticholinergic-like effects. Another class of drugs being studied for IBS-D are 5HT3 antagonists, such as ondansetron, but the trials performed to date have provided no conclusive evidence that they can alleviate the global symptoms of IBS-D.[20,21] Increased synthesis of bile acid may cause some patients to develop IBS-D, and most of these will respond to bile acid sequestrants.[22] Alosetron was the only Food and Drug Administration (FDA)-approved medication available until recently; at one point, it was withdrawn from the market due to its side effects, but it has since been reintroduced. One meta-analysis showed that alosetron positively affected global symptoms, pain, and discomfort in nonconstipated female patients with IBS.[23] However, 1 in 4 patients treated with alosetron may develop constipation and its more serious complications, such as ischaemic colitis.[24] The efficacy of alosetron is unclear in male patients.[23] Antidepressant therapy, especially tricyclic antidepressants, has generally proven effective to some degree.[25] In terms of psychological treatment options, such as cognitive behavioural therapy, mindfulness, gut-directed hypnotherapy, and psychodynamic therapy, the evidence supporting their use in patients with IBS is strong, but their availability limits their use in clinical practice.[26]

Rifaximin, a minimally absorbed antibiotic, is the latest drug to be approved by the FDA; it was approved in May 2015[27] after it showed promising results in 2 large-scale randomized trials.[28,29] It is an oral, wide-spectrum, long-acting, GI-specific antibiotic that has no clinically relevant bacterial resistance.[30,31] Therefore, rifaximin may be useful in the treatment of GI disorders associated with altered bacterial flora, including IBS and small intestinal bacterial overgrowth (SIBO).

In the following sections, we will evaluate the clinical potential of this drug. This review is based on a systematic search of the articles in CrossRef and PubMed through September 19, 2016.

Rifaximin – Background and Mechanism of Action

Rifaximin is a semisynthetic antibiotic that has an extra pyridoimidazole ring, making it a type of poorly water-soluble and minimally absorbed (<0.4%) rifamycin. It has in vitro activity against enteric gram-negative bacteria, including enteric pathogens.[32] It is most effective against the bacteria in the small intestine due to the higher concentration of bile in this region of the GI tract than in the colon.[33,34] These properties make it effective for the treatment of IBS-D due to its postulated cause of gut bacterial overgrowth.[35,36]

Small intestinal bacterial overgrowth is a mixed syndrome characterized by a change in the quantity or quality (protective vs pathogenic bacteria composition) of bacteria in the small intestine. It is generally defined as the presence of ≥10⁵ bacteria/mL of upper GI aspiration.[37] However, this definition is generally relaxed for the consideration of SIBO in IBS studies.[38] Several studies have shown a definite relationship between IBS and SIBO. According to an article by Ghoshal,[37] in the 11 studies they reviewed, the frequency of SIBO varied from 4% to 78% among patients with IBS and from 1% to 40% among controls. In IBS, it not only increased the number of bacteria in the gut but also the bacterial composition that is implicated in the disease.[39]

Technique used to diagnose SIBO

The role of SIBO in IBS depends on the mode of testing for SIBO. A meta-analysis found that breath tests can be used as a valid measure of SIBO in IBS.[40] As more than 80% of the gut flora cannot be cultured using typical methods,[41] indirect methods are important feasible and straightforward means of testing. The most feasible test involves detecting the gas produced by bacteria. Although the reported range varies, breath testing has been found to be abnormal in patients with IBS.[42,43] In one study, 68 of 93 patients who had a positive breath test were found to have IBS-D (73%).[43] In a meta-analysis of 11 studies, breath testing was found to be abnormal more often among IBS subjects than healthy controls (odds ratio = 4.46).[44] Breath test results normalize in patients with the use of antibiotics.[42] Although the lactose breath test (LBT) or lactose hydrogen breath test (LHBT) is often used, data show that their diagnostic accuracy is inferior to that of glucose breath testing (GBT) (55.1% vs 71.7%), suggesting a need to switch to the more accurate GBT in future clinical trials assessing bacterial overgrowth in patients with IBS.[45]

When duodenal aspirate cultures collected using upper GI endoscopy were studied, it was concluded that SIBO of aerobic bacteria is independently linked with IBS. This was more common in cases of IBS-D (60%) than in other types (27.3%).[46] A recent study disapproved the hypothesis that bacterial overgrowth in patients with IBS was caused using proton pump inhibitors.[47]

The newest method for studying the intestinal microbiota is isolating and analysing the 16S profile of the genetic material (ie, DNA) from the duodenal material of patients with IBS-D and controls.[46] Such studies have confirmed the presence of microbial overgrowth in the small bowel in IBS, with a concomitant reduction in bacterial diversity. Significant variations were found in the quantity of 12 genera of intestinal bacteria.[46] Greater levels of *Escherichia coli* and *Klebsiella* spp were found in all patients with IBS. These factors support the use of a minimally absorbable antibiotic for the treatment of IBS-D.

Pathogenesis of SIBO in IBS

The pathophysiology of IBS includes infection and immune activation, serotonin dysregulation, central dysregulation and dysfunction of the brain-gut interaction, genetic predisposition, and bacterial overgrowth.[12]

Table 1. Significant clinical trials involving rifaximin.

STUDY	PATIENT PARAMETERS	METHODOLOGY	OUTCOMES
Double-blind, randomized, placebo-controlled studies			
Pimental et al[28]	87 patients meeting Rome I criteria for IBS	Patients were randomly assigned to receive 400 mg of rifaximin 3 times daily for 10 d (n = 43) or placebo (n = 44). Weekly questionnaires were administered for 10 wk	Rifaximin recipients had greater improvement in IBS symptoms (*P* = .020) with a lower incidence bloating after treatment, but no changes were seen in constipation, diarrhoea, or abdominal pain
Sharara et al[61]	Patients with >12-week history of bloating (most of the patients met Rome II criteria)	Patients received rifaximin 400 mg twice daily (n = 63) or placebo (n = 61) for 10 d. LHBT was performed at day 0 and day 10	There was a significant difference in global symptom relief with rifaximin vs placebo (41.3% vs 22.9%; *P* = .03)
Lembo et al[62]	Patients with IBS-D (Rome II criteria)	Phase 2 trial in which 191 patients received rifaximin 550 twice daily and 197 patients received placebo for 14 d. Afterwards, both groups were given the placebo for 14 d	Patients receiving rifaximin reported greater improvement in global symptoms (52% vs 44% for placebo; *P* = .03)

Abbreviations: IBS, irritable bowel syndrome; IBS-D, diarrhoea-predominant IBS; LHBT, lactose hydrogen breath test.

A plethora of vital functions are performed by the intestinal bacteria. They are responsible for fermenting carbohydrates in the small intestine and converting them into a gaseous form.[38] Thus, increased concentrations of bacteria may lead to bloating and flatulence.[38] This may cause excessive distention of the intestinal wall, which leads to abdominal pain.[48,49] The gut microbiota, in addition to the bacterial deconjugation of bile salts, produces toxic metabolites that impair the intestinal function.[50] These deconjugated bile salts can cause malabsorption of fats and impaired peristaltic activity. This can cause osmotic diarrhoea.[51,52] Small intestinal bacterial overgrowth is also associated with increased release of interleukin 8.[53] In patients with SIBO, increased mean intraepithelial lymphocytes and reduced mean villus length were found in small bowel biopsies. These changes, which may lead to poor digestion and diarrhoea, were reversible with antibiotics.[54] Gut microbiota can cause the activation of cytokines and immune mediators.[55] Immune-mediated cytokines can have multiple effects, such as altered epithelial secretions, exaggerated nociceptive signalling, and abnormal motility, which may lead to IBS-like symptoms.[55,56]

The gut microbiota also affect GI sensorimotor function, mainly via 3 methods. One such method is immune modulation, which we have discussed elsewhere.[57] In addition, bacterial chemotactic peptides, such as formyl-methionyl-leucyl-phenylalanine, stimulate the enteric nervous system and afferent nerves, whereas endotoxins (lipopolysaccharides) may affect gut motility.[58] Bacteria in the small intestine in patients with SIBO produce short-chain fatty acids (SCFA). Colonic motility is increased due to acidification by SCFA.[59,60] Hence, changes in gut flora may cause altered motility and predispose individuals to develop IBS-like symptoms.

Clinical Profile of Rifaximin

With these causes in mind, the effectiveness of a minimally absorbable antibiotic such as rifaximin was first tested in IBS in a study by Pimentel et al.[28] Since then, several trials have been conducted; these are summarized in Table 1.

A few observations were common to all the studies summarized in Table 1. The improvement in overall IBS symptoms was maintained 10 to 12 weeks after treatment (Sharara et al[61] showed improvement of 28.6% vs 11.5%; *P* = .02). Bloating scores were significantly improved after treatment (46% vs 40% for placebo; *P* = .04 in Lembo et al[62]).

The 2 large, double-blinded, randomized, phase 3 trials that provided the basis for rifaximin obtaining FDA approval were TARGET-1 and TARGET-2.[6] In these, 1258 adult patients with IBS-D were selected. The patients were randomized to receive either rifaximin (550 mg 3 times daily) or placebo for 2 weeks and were monitored for an additional 10-week period after therapy completion. The results obtained were similar to those of previous studies. Significantly more patients in the rifaximin group were relieved of global IBS symptoms than in the placebo group during the first 4 weeks after treatment (40.7% vs 31.7%; *P* < .001, in the 2 studies combined). Similarly, more patients in the rifaximin group than the placebo group were relieved of bloating (40.2% vs 30.3%; *P* < .001, in the 2 studies combined). These findings remained the same for at least 3 months after treatment.

TARGET-3 was undertaken as a phase 3 trial to evaluate the safety and efficacy of repeated treatment with rifaximin.[63] Of 1074 patients who responded to open-label rifaximin, 692 (64.4%) relapsed after some time; of these, 636 were randomly assigned to receive repeat treatment with rifaximin or placebo. There were significantly more responders in the rifaximin group than in the placebo group (38.1% vs 31.5%; *P* = .03). The responders with the cardinal symptom of abdominal pain fared better in the rifaximin group vs placebo (50.6% vs 42.2%; *P* = .018), but stool consistency was not similarly affected (51.8% vs 50.0%; *P* = .42).

Rifaximin has been also shown to have marked effect on abnormal breath test results.[64] Of the 64 patients who had an LBT at week 4 after treatment, 55 (86%) tested negative. Children who responded to rifaximin and had a negative LBT showed greater improvement in global IBS symptoms ($P < .005$). A retrospective study[64] showed that of the 23 patients who returned for visit within 4 to 5 months, 19 (82.6%; $P < .01$) had negative glucose breath test results vs baseline.

A recent retrospective study investigated the association between rifaximin therapy and LHBT changes in nonconstipated patients with IBS who showed normalized LHBT values after treatment.[65] Patients with IBS symptoms and similar LHBT values prior to therapy received rifaximin 1200 mg daily for treatment periods of 4, 8, or 12 weeks. The differences in LHBT values were statistically significant in the 3 treatment groups, with higher values occurring in patients who were treated for longer periods. Symptomatic improvements in response to rifaximin were also demonstrated prior to the normalization of LHBT values and mostly occurred after 4 weeks of treatment. Although this study demonstrated that patients with higher LHBT values required more time for their values to normalize, LHBT gas levels were not associated with global abdominal symptoms, a finding that is contradictory to other studies.

A meta-analysis of 5 randomized trials showed that rifaximin worked better than placebo for global IBS symptom improvement ($P < .001$; number needed to treat = 10.2).[66]

Safety Profile

In large, placebo-controlled trials (TARGET-1), the rates of serious adverse events were similar for rifaximin and placebo (1.6% vs 2.4%, respectively).[6]

In the meta-analysis by Menees et al, adverse events were reported for 4 of the 5 studies that met inclusion criteria. Overall, the incidence of adverse events and the rate of discontinuation due to adverse events were comparable between the placebo and rifaximin groups. The most frequently cited adverse events (up to 6%) included headache, upper respiratory tract infection, nausea, nasopharyngitis, diarrhoea, and abdominal pain.[66]

In the larger study by Lembo et al,[63] a safety analysis of 1258 subjects yielded similar results. Rifaximin is not known to have significant drug interactions; however, it should be used with caution in patients with Child-Pugh class C cirrhosis. Rifaximin is an antibiotic active against *Clostridium difficile* infection; thus, such infections are uncommon among the patients receiving rifaximin therapy.

A recent study compared generic and branded formulations of rifaximin and found significant differences in systemic bioavailability. Plasma drug concentrations were higher after the administration of generic rifaximin compared with a branded formulation that contains the polymorph rifaximin-α, which has limited bioavailability.[67]

Conclusions

Given the high price of rifaximin on the market, many patients will be unwilling to consider the treatment. One way to make rifaximin treatment more effective and efficient is to test for intestinal bacterial overgrowth in the patients with IBS using lactulose breath testing. Because rifaximin has been shown to be more effective and has a sustained response in patients with positive breath test results, this will be a suitable group for treatment.

Irritable bowel syndrome is a very common GI disorder that causes significant suffering for patients and places a huge cost burden on health systems. One of the latest techniques studied for treating the symptoms of IBS-D is the use of drugs that alter the intestinal microbiota. Rifaximin fits the bill perfectly due to its minimal systemic absorption. In addition, rifaximin has proven to be very effective against the cultures obtained from patients with SIBO, affects the inflammatory environment in patients having a multitude of intestinal diseases, and eliminates the toxins produced by bacteria (eg, lipid metabolism end products).[68,69] With these mechanisms backed by the results of a number of credible randomized studies demonstrating its favourable efficacy and safety profile, rifaximin is the latest drug to be approved by FDA for treatment of IBS-D. As it has been observed that the patients do not relapse long after treatment, it is safe to suggest that the pathology of IBS in these patients has been treated. Moreover, treatment with a repeat dose of rifaximin produces similar, significant reductions in IBS symptoms.

Author Contributions

KG contributed to writing of the article, HSG to data collection, and SVH to data analysis.

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