REVIEW

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Update on the Role of Rifaximin in Digestive Diseases

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ABSTRACT

Various environmental factors affecting the human microbiota may lead to gut microbial imbalance and to the development of pathologies. Alterations of gut microbiota have been firmly implicated in digestive diseases such as hepatic encephalopathy, irritable bowel syndrome and diverticular disease. However, while these three conditions may all be related to dysfunction of the gut-liver-brain axis, the precise pathophysiology appears to differ somewhat for each. Herein, current knowledge on the pathophysiology of hepatic encephalopathy, irritable bowel syndrome, and diverticular disease are reviewed, with a special focus on the gut microbiota modulation associated with these disorders during therapy with rifaximin. In general, the evidence for the efficacy of rifaximin in hepatic encephalopathy appears to be well consolidated, although it is less supported for irritable bowel syndrome and diverticular disease. We reviewed current clinical practice for the management of these clinical conditions and underlined the desirability of more real-world studies to fully understand the potential of rifaximin in these clinical situations and obtain even more precise indications for the use of the drug.

Key words: liver cirrhosis – hepatic encephalopathy – irritable bowel syndrome – diverticular disease – gut microbiome – rifaximin-α – symptomatic uncomplicated diverticular disease.

Abbreviations: AGA: American gastroenterological association; ARG: antibiotic resistance gene; BID: twice daily; CCL20: C-C motif chemokine ligand 20; CD: Crohn's disease; CKD: chronic kidney disease; DD: diverticular disease; ED: emergency department; FGIDs: functional gastrointestinal disorders; GI: gastrointestinal; HE: hepatic encephalopathy; IBS: irritable bowel syndrome; IBS-C: constipation-predominant IBS; IBS-D: diarrhea-predominant IBS; IBS-M: IBS with Mixed Bowel habits; IBS-QoL: IBS quality of life; ICU: intensive care unit; LBT: lactulose breath test; MHE: minimal hepatic encephalopathy; MIC: minimum inhibitory concentration; MMSE: mini-mental status examination; NADs: nonabsorbable disaccharides; OB: oxidative burst; OHE: overt hepatic encephalopathy; OR: odds ratio; QALY: quality-adjusted life-year; QoL: quality of life; SIBO: small intestine bacterial overgrowth; SUDD: symptomatic uncomplicated diverticular disease; TID: times/day; TIPS: transjugular intrahepatic portosystemic shunt; UC: ulcerative colitis; VAS: visual analogue score.

INTRODUCTION

Gut microbiota is involved in the development of and communication with a variety of host's systems, such as the immune, endocrine, and nervous systems, forming pivotal functional axis, i.e., the gut-liver-brain axis [1]. Intestinal microbiota appears to regulate levels of gut peptides such as cholecystokinin, ghrelin, leptin, peptide tyrosine tyrosine, glucagon-like peptide-1, and 5-hydroxytryptamine that are secreted by enteroendocrine cells, which thus influence the vagal afferent pathway [2]. It is now becoming clearer that the bidirectional communication between gut microbiota and the brain has a key role in the pathogenesis of hepatic encephalopathy (HE), irritable bowel syndrome (IBS) and diverticular disease (DD), and that gut microbiota modulation has a role in their treatment [3].

Hepatic encephalopathy is defined as brain dysfunction caused by liver insufficiency and/or portal-systemic shunting and is believed to be attributable to gut-derived substances [4]. The disease has a relevant burden for caregivers and health services, being a significant cause of morbidity and hospitalization as well as leading to impaired quality of life and overall functioning [4].

Irritable bowel syndrome is a chronic condition that was historically held to affect 7-21% of the general population,

although more recent studies suggest that the prevalence is about 4% [5]. Given its symptoms, IBS negatively impairs quality of life and work productivity [6] and is often found in association with anxiety and depression, which may be due to a dysregulated gut-brain axis [7]. Moreover, in the era of SARS-CoV-2, COVID-19 has also been reported to be a possible trigger of IBS, also called post-infectious IBS [8, 9].

Patients with DD suffer from several chronic symptoms that include abdominal discomfort, bloating, and altered bowel habit, an entity referred to as symptomatic uncomplicated diverticular disease (SUDD). In addition, considered to be akin to IBS, DD is a common condition in Western countries. It is thought to have a multifactorial etiology that includes both environmental and genetic factors in addition to insufficient dietary fiber intake [10].

In terms of the pathophysiology, alterations in gut microbiota have been firmly implicated in all three disorders [11-15]. However, while these three conditions may all be related to dysfunction of the gut-liver-brain axis, the precise pathophysiology appears to differ somewhat for each. In HE, for example, gut-derived toxins, and in particular the accumulation of ammonia, produced by bacteria in the gut as well as by inflammation, oxidative stress, and impaired liver function, appears to lead to cerebral edema [15, 16]. In IBS, the fecal composition is known to differ from that of healthy controls, which may be associated with altered intestinal permeability and intolerance to some foods, which is further supported by the clinical success of dietary approaches in some patients [17]. Lastly, in DD, it has been hypothesized that alterations in gut microbiota together with chronic inflammation may give rise to the condition [17].

The use of eubiotics, and especially rifaximin, in the treatment of HE, IBS, and DD, has been previously highlighted; rifaximin is largely considered to be a safe and effective treatment option [17]. However, choice of treatment is increasingly important not only in consideration of clinical efficacy, but also in terms of costs and the potential for long-term administration [18]. Herein, we overview the current evidence for use of rifaximin in the treatment of HE, IBS, and DD.

A literature search was performed on PubMed for articles and abstracts. Only articles after 2015 were considered for the present review. Search terms included free text words and combinations of the following terms: "irritable bowel syndrome", "diverticular disease", "hepatic encephalopathy", "gut microbiota", "rifaximin". Papers were selected for inclusion in the present review according to their relevance, as judged by the authors.

RIFAXIMIN: GENERAL PROPERTIES

The eubiotic rifaximin has extensive evidence for its efficacy in the treatment of gastrointestinal conditions [17, 19]. This agent is an oral nonabsorbable antibiotic with a broad spectrum of activity and a good safety profile [20] (Table I). Rifaximin is an analog of rifampin that binds to the β-subunit of bacterial DNA-dependent RNA polymerase to inhibit bacterial RNA synthesis [21]. Because it is nonabsorbable, blood levels remain negligible following oral administration and its activity is thus limited to the gastrointestinal tract (Table I). It is important to emphasize that the property of not being absorbed, and therefore the therapeutic effects observed, have been specifically demonstrated with the alpha polymorph of rifaximin. As a consequence, the therapeutic results obtained with this polymorph should not be simply translated to generic formulations of rifaximin, which can display significant systemic absorption [22].

Table I. General characteristics of rifaximin.

▪ Extensive evidence for efficacy in gastrointestinal diseases
▪ Oral, nonabsorbable
▪ Blood levels negligible
▪ Activity limited to the gastrointestinal tract
▪ Broad spectrum of activity
▪ Good safety profile
▪ Inhibits bacterial RNA synthesis by binding to the β-subunit of bacterial DNA-dependent RNA polymerase

Several studies have shown that rifaximin can modify the gut microbiome. In general, changes in the overall composition of the gut microbiome appear to be relatively modest, even though rifaximin induces changes in bile acid composition and modulates microbiome function [23]. In this regard, the modified gut microbiome leads to increased intestinal permeability, and subsequently lower levels of bile acids may further increase the translocation of gut bacteria [24]. Thus, since rifaximin acts locally given its minimal absorption, it has the potential to modulate the gut-liver axis which are evident in patients with cirrhosis [24]. Moreover, local effects in the gut are held to be responsible for the beneficial effects of rifaximin in liver and digestive diseases [25]. Subsequent studies indicated that rifaximin treatment promotes the growth of beneficial bacteria, such as *Bifidobacteria* and *Lactobacilli* [26]. Recent observations support the hypothesis that rifaximin exerts a beneficial modulation of colonic microflora, namely an "eubiotic" effect [27].

RIFAXIMIN IN HEPATIC ENCEPHALOPATHY

Mechanistic/Translation Evidence

A relatively large number of studies have been carried out in recent years investigating the mechanism of action of rifaximin in HE (Table II). The mechanistic study by Patel et al. randomized 38 patients with cirrhosis and HE to either rifaximin (550 mg BID, twice daily) or placebo for 90 days [28]. The primary outcome was 50% reduction in neutrophil oxidative burst (OB) at 30 days. Compared to placebo, rifaximin improved the grade of HE, but was not associated with a 50% reduction in OB compared to baseline. However, it reduced the levels of mucin-degrading sialidase-rich bacterial species, and favored an intestinal microenvironment that was enriched in tumor necrosis factor (TNF)-α and interleukin (IL)-17E, which may have reduced the risk of infection through repair of the gut barrier. A possible role of rifaximin in reducing intestinal inflammation was also seen in a study investigating levels of 10-7G, a novel biomarker for intestinal inflammation and endoscopic mucosal healing in serum [29].

Table II. Studies assessing rifaximin in hepatic encephalopathy.

Author, year	Type of study	Population	Primary objective(s)	Main results
Mechanistic/translation evidence				
Patel et al., 2022 [28]	Placebo-controlled, double-blind, mechanistic study	38 patients with cirrhosis and HE were randomized to rifaximin-alpha (550 mg BID) or placebo for 90 days	50% reduction in neutrophil oxidative burst (OB) at 30 days	Rifaximin-alpha did not lead to a 50% reduction in spontaneous neutrophil OB at 30 days vs. baseline
Tamai et al., 2021 [29]	Retrospective analysis	30 patients with cirrhosis and HE	Changes in 10-7G as an index of intestinal inflammation	Levels of 10-7G were significantly and progressively decreased over 9 months, implying that rifaximin improves intestinal inflammation
Mangas-Losada et al., 2019 [30]	Open-label study	30 controls without liver disease, 30 cirrhotic patients without MHE and 22 patients with MHE	Assess changes in immunophenotype	In rifaximin responders all alterations in the immune system were normalized (CD14++CD16+ pro-inflammatory monocytes, CD69 in T lymphocytes); in non-responders only normalization of IL-6, C-C motif chemokine ligand 20 (CCL20), and differentiation of T lymphocytes to Th22 was observed
Abdel Moneim et al., 2021 [31].	Open-label parallel, prospective interventional study	100 patients randomized to 400 mg rifaximin 3 times/d plus 30-45 mL lactulose 3 times/d or lactulose alone for 6 months	Difference between MIC of rifaximin between groups	MIC did not differ significantly after treatment exposure vs. baseline either between groups or within the same group
Kaji et al., 2017 [32]	Open-label study	20 patients with decompensated cirrhosis	Investigate the efficacy of rifaximin for HE with the linkage of gut microbiome in decompensated cirrhotic patients	Rifaximin significantly improved cognition and reduced endotoxin activity without significantly affecting the composition of the gut microbiome
Schulz et al., 2019 [33]	Open-label study	5 patients with liver cirrhosis and MHE treated with rifaximin 550 mg bid alone or combined with lactulose 30-60 mL daily for 3 months	Characterize the active bacterial assemblages in duodenum and feces in patients with MHE before, during, and after long-term therapy with rifaximin	All patients had a significant improvement of MHE and no significant changes in the bacterial community profile at any time point
Shamsaddini et al., 2021 [34]	Open-label study	163 patients with cirrhosis and 40 controls	Determine the impact of ARGs in cirrhosis-related gut metagenome on outcomes and disease progression, and study the effect of rifaximin on ARG burden	Cirrhosis is associated with high gut microbial ARG gene burden vs. controls, which worsens with disease progression
Bajaj et al., 2021 [35]	Cross-sectional: controls and cirrhotic outpatients (on rifaximin) were followed for 90-day hospitalizations. Pre/post: compensated cirrhotics underwent stool collection pre/post 8 weeks of rifaximin	40 controls and 163 cirrhotic patients	Understand role of the virome in disease progression	Unlike bacteria, fecal phages are sparsely linked with cirrhosis characteristics and 90-day outcomes. Phage and bacterial linkages centered on urease-producing, ammonia-generating Streptococcus species were affected by disease progression and rifaximin therapy
Prevention				
Zeng et al., 2021 [36]	Multicenter randomized open-label prospective study	200 patients with decompensated cirrhosis randomized to 400 mg rifaximin twice daily for 6 months or to standard care	Explore if low-dose rifaximin can prevent complications and prolong survival in cirrhotic patients	Low-dose rifaximin significantly decreases the rate of overall complications, and is associated with prolonged survival
Tapper et al., 2020 [37]	Retrospective database analysis	49,164 persons with HE among US Medicare enrollees	Describe outcomes after developing HE among contemporary, aging patients	HE is associated with poor outcomes; combination lactulose-rifaximin is associated with improved outcomes
Bureau et al., 2021 [38]	Randomized, double-blind, multicenter, placebo-controlled trial	197 patients with cirrhosis undergoing TIPS randomized to receive rifaximin 600 mg BID or placebo 14 days before and 168 days after the procedure	Determine if rifaximin prevents overt HE after TIPS vs. placebo	An episode of overt HE occurred in 34% (95% CI, 25% to 44%) of patients in the rifaximin group and 53% (CI, 43% to 63%) with placebo during the post-procedure period (OR 0.48)

Table II (continued)

Seifert et al., 2021 [39]	Retrospective analysis	233 patients receiving TIPS	Investigate HE prophylactic regimens after TIPS	In patients with HE prior to TIPS, effective prophylaxis of HE is feasible via combination of lactulose and rifaximin with no additional benefit from L-ornithine-L-aspartate
Kubota et al., 2021 [40]	Randomized trial	83 patients with HE randomized to 1,200 mg/day of rifaximin or 1,500 mg/day L-carnitine and rifaximin 1,200 mg/day	Assess effects of L-carnitine in patients receiving rifaximin for HE	No significant reduction in portal systemic encephalopathy index between groups; hospital admission rates were 30.9% and 9.8% for rifaximin alone or combination treatment, respectively ($p = 0.028$)
Treatment				
Hiramine et al, 2021 [41]	Observational study	76 patients who developed OHE of West Haven grade II or higher	Examine the therapeutic effects of rifaximin for OHE in Japanese patients	Rifaximin was associated with decreased blood ammonia levels, lower incidence of OHE, and fewer hospitalizations in Japanese patients with HE
Suzuki et al., 2019 [42]	Retrospective cohort study	65 patients with HE who initiated rifaximin 1200 mg/day	Investigate effects of long-term treatment with rifaximin on HE and liver function	Blood ammonia levels significantly declined from 157 to 86 mug/dL at 4 weeks after rifaximin ($P < 0.01$), and the effect was prolonged; Child-Pugh score decreased in 51% of patients after 12 weeks of rifaximin
Nishida et al., 2019 [43]	Single-center retrospective observational cohort study,	38 patients who had taken rifaximin 1200 mg/day for more than 24 weeks	Determine clinical effects of long-term rifaximin therapy in decompensated liver cirrhosis patients with overt HE or hyperammonemia	Median serum ammonia before treatment was 104 mug/dL and 85 mug/dL at 2 weeks after treatment ($P = 0.002$); low levels were maintained for up to 124 weeks
Chang et al., 2021 [44]	Real-world single-center retrospective cohort study	12 patients receiving rifaximin add-on to lactulose and 31 patients receiving lactulose	Evaluate one-year efficacy of rifaximin add-on to lactulose for the maintenance of HE remission in Taiwan	Significant improvement seen in maintenance of HE remission, decreased episodes and days of HE-related hospitalizations, serum ammonia levels, MMSE, episodes of hospitalizations with combination therapy vs. lactulose alone
Oey et al., 2019 [45]	Real-world retrospective study	127 patients with OHE	Assess hospital resource use during 6-month episodes before and after rifaximin add-on to lactulose	Addition of rifaximin to lactulose was associated with a significant reduction in the number and length of HE-related hospitalizations for overt HE
Hudson et al., 2017 [46]	Multicenter, retrospective, observational study	207 patients with HE who initiated rifaximin	Compare all-cause and liver-related hospital resource use in the 6 and 12 months pre-rifaximin and post-rifaximin initiation in UK patients with HE	Treatment with rifaximin was associated with significant reductions in hospitalizations, bed days, ED attendances and 30-day readmissions.
Cheng et al., 2021 [47]	Meta-analysis	Six studies with 559 patients	Compare the efficacy of rifaximin and NADs in HE	No significant differences in mental status, blood ammonia level, or drug adverse drug effects between rifaximin and NADs
Han et al., 2021 [48]	Meta-analysis	28 randomized controlled trials with 2979 patients	Compare rifaximin to placebo or other active drugs (NADs, LOLA, probiotics) for patients with OHE, MHE, and recurrent HE	Rifaximin significantly reduced HE grade, improve cognitive impairment, and prevented the risk of recurrent HE episodes compared to other treatments with no difference in mortality; rifaximin treatment was better than other active drugs in improving psychometric indicators and reducing the risk of rehospitalization
Dhiman et al., 2020 [49]	Meta-analysis	25 trials with 1563 patients	Synthesize evidence for most effective treatments for MHE and prevention of OHE in patients with cirrhosis	Rifaximin and lactulose were most effective for reversal of MHE; LOLA and lactulose were most effective for prevention of OHE. Lactulose was the only agent that was effective in reversing minimal HE, preventing OHE, and reducing ammonia
Hospitalizations and costs				
Volk et al., 2021 [50]	Analysis of IBM Marketscan Commercial and Optum's de-identified Clinformatics Data Mart databases	13,515 rifaximin episodes and 9,946 lactulose alone episodes	Assess healthcare costs and hospitalization rates associated with rifaximin versus lactulose alone in patients at risk for HE	Rifaximin was associated with lower costs of $2,417 and $173 lower total mean medical costs and HE-related hospital costs per-patient-per-month, respectively; in a simulated plan of 1 million lives, if 50% of HE patients treated with lactulose alone had rifaximin added on and were adherent, the total cost savings would be $7.5 million per year

Table II (continued)

Jesudian et al., 2020 [51].	Markov model developed with 4 health states (remission, overt HE, liver transplantation, and death)	Clinical inputs and data sources from the published literature	Assess incremental cost-effectiveness of rifaximin +/- lactulose vs. lactulose alone in patients with OHE	Rifaximin +/- lactulose regimen provided added health benefits despite an additional cost versus lactulose monotherapy; model results showed an incremental benefit of $29,161 per QALY gained and $27,762 per life year gained with rifaximin +/- lactulose vs. lactulose monotherapy
Kabeshova et al., 2016 [52]	Markov model used to estimate rifaximin cost-effectiveness	Costs based on current French treatment practices	Estimate long-term cost-effectiveness of rifaximin in combination with lactulose vs. lactulose alone in cirrhotic patients who have experienced at least two prior OHE events	Rifaximin is a cost-effective treatment option with an incremental cost per QALY gained of €19,187 and €18,517 over two different time horizons (2 and 5 years)
de Jong et al., 2021 [53]	Budget impact analysis under Dutch reimbursement conditions	Resource use was based on Dutch real-world data	Evaluate clinical and economic impact of treating all patients eligible with rifaximin as an adjunct to lactulose for prevention of OHE in the Netherlands	Despite increased drug costs, treatment with rifaximin is estimated to result in potential cost savings over a 5-year period of €7.2 million from a Dutch hospital perspective; The budget impact is €397,770 from a payer's perspective
Roggeri et al., 2017 [54]	Data used were from an Italian observational real-world study	Costs associated with patients treated with rifaximin were estimated considering reduction in hospitalizations for HE recurrences	Evaluate the impact on the Italian National Health Service expenditure of treatment with rifaximin 550 mg BID for reduction of OHE recurrences	Treatment with rifaximin is associated with a reduction in hospitalizations for HE recurrences that leads to an overall reduction of total costs estimated to be €30,000 in the first year and reaching €260,000 in the third year

ARG: antibiotic resistance gene; CKD: chronic kidney disease; ED: emergency department; HE: hepatic encephalopathy; MHE: minimal hepatic encephalopathy; MIC: minimum inhibitory concentration; MMSE: mini-mental status examination; NADs: nonabsorbable disaccharides; OHE: overt hepatic encephalopathy; OR: odds ratio; QALY: quality-adjusted life-year; TIPS: transjugular intrahepatic portosystemic shunt.

In this analysis of 30 patients with cirrhosis and HE, levels of 10-7G significantly and progressively decreased over a period of 9 months, further implying that rifaximin improves intestinal inflammation in these subjects. In patients with minimal HE, it has also been reported that in responders to rifaximin all alterations in the immune system were normalized (reduced the proportion of CD14++CD16+ pro-inflammatory monocytes, and reversed the increased expression of CD69 in T lymphocytes), while in non-responders only normalization of IL-6, C-C motif chemokine ligand 20 (CCL20) and differentiation of T lymphocytes to Th22 were observed [30].

Other studies have examined the changes in gut microbiota following treatment with rifaximin. Among these, there was an open-label parallel, prospective interventional study in which 100 patients were randomized to receive rifaximin 400 mg TID (times/day) plus 30-45 mL lactulose TID or lactulose alone for 6 months [31]. The authors considered the difference between minimum inhibitory concentration (MIC) of rifaximin as the primary outcome in the two groups. While rifaximin was associated with a significantly longer time to new episodes of HE, fewer patients developed an overt episode of HE, and a decrease in hospitalizations, there was no difference in the MIC for rifaximin. This demonstrates that rifaximin is associated with limited potential to develop antimicrobial resistance, at least during the study period of 6 months.

In turn, Kaji et al. [32] reported that rifaximin did not significantly affect the composition of the gut microbiome. This was demonstrated in a study involving 20 patients with decompensated cirrhosis and receiving 400 mg rifaximin TID for 4 weeks. In addition to clinical and laboratory parameters, sequencing of the V4 hypervariable region of the bacterial 16S rRNA gene was also performed. While improvements were seen in serum ammonia levels, no difference in the major components of the gut microbiome was seen between baseline and after 4 weeks, although the relative abundances of *Veillonella* and *Streptococcus* were decreased. The finding that rifaximin does not lead to changes in the composition of the bacterial community was also shown by Schulz et al. [33] in a study characterizing active bacterial assemblages in duodenum and feces in 5 patients with cirrhosis and minimal HE prior to, during, and following therapy with rifaximin (550 mg BID with or without lactulose). These authors reported that bacterial colonies were dissimilar in duodenal and fecal samples, and that no significant changes were found in the bacterial profiles at different times following rifaximin therapy.

Shamsaddini et al. [34] examined the effects of rifaximin on antibiotic resistance genes in the gut of patients with cirrhosis. Interestingly, the gut microbial antibiotic resistance gene burden appeared to be higher in patients with cirrhosis than in controls with chronic kidney disease and diabetes. However, the antibiotic resistance gene burden was not affected after treatment with rifaximin, but higher burden was associated with hospitalizations and death in patients with cirrhosis. Bajaj et al. [35] also recently evaluated the bacterial metagenome in patients with cirrhosis and HE. Stool samples were analyzed from 40 controls and 163 patients with compensated cirrhosis who had been treated with either rifaximin or lactulose. It was reported that phage-bacterial correlation network linkages were more complex in control subjects and less complex in patients with cirrhosis and HE receiving lactulose. However, the complexity increased in patients with HE who were receiving rifaximin. There

were also major changes in phage-bacterial correlations that involved *Streptococcus* phages and urease-producing *Streptococcus* in patients who were prospectively administered rifaximin, with no changes in alpha/beta diversity or individual bacterial or phage taxa.

The review carried out by Bajaj et al. [17] with literature search up to 2015 concluded that rifaximin as treatment for HE is supported by consolidated clinical evidence and is a well-established therapy in routine practice. Rifaximin has been shown to significantly improve neuropsychiatric symptoms in HE and decrease the levels of ammonia in blood more effectively than neomycin or other antibiotics. Rifaximin is also associated with a significant decline in mortality compared to lactulose, and it appears to be better tolerated than lactulose. It was hypothesized that rifaximin exerts its therapeutic action through modulation of bacterial function, and not by reducing the overall abundance of bacteria in the gastrointestinal tract, while selecting the beneficial bacterial species. Notwithstanding, it has been noted that additional information is needed from randomized clinical trials on additional clinical endpoints, such as acute-on-chronic liver failure, decompensation of cirrhosis, and death [25].

Prevention

Zeng et al. [36] recently published the results of a multicenter randomized open-label prospective trial in which 200 patients with decompensated cirrhosis were randomly assigned to receive rifaximin 400 mg rifaximin BID for 6 months or to a control group not receiving rifaximin. There were significantly fewer complications overall with rifaximin compared to the control group ($p<0.001$). While there was no difference in the rates of liver transplantation-free survival, rifaximin did prolonged liver transplantation-free survival in the subgroup of patients with Child-Pugh score ≥ 9 ($p=0.007$). Rifaximin also reduced events involving worsening ascites, HE, and gastric variceal bleeding, with a safety profile that was similar to that seen in the control group. In a study involving 49,164 Medicare enrollees, the optimal therapy for HE was estimated to be the combination of lactulose and rifaximin considering gastroenterology consultations and 30-day readmissions to hospital [37].

Bureau et al. [38] published the results of a randomized, double-blind, multicenter, placebo-controlled trial in which 197 patients were randomized to receive rifaximin 400 mg/day or placebo for 14 days prior to receiving a transjugular intrahepatic portosystemic shunt (TIPS). During the postprocedural period, overt HE occurred in 34% of patients receiving rifaximin and in 53% of patients in the placebo group (OR=0.48). The study concluded that rifaximin can be considered for HE prophylaxis following TIPS. This finding was also confirmed in a study including 233 patients with HE receiving TIPS [39]. Effective prophylaxis of HE with a combination of lactulose and rifaximin was considered feasible to prevent recurrence of HE over a period of 1 year following TIPS, with no added benefit of l-ornithine-L-aspartate [39]. Addition of L-carnitine has also been reported to decrease the risk of hospitalization in patients receiving rifaximin. In a randomized study of 80 patients receiving 1,200 mg/day rifaximin or the same dose of rifaximin plus 1,500 mg/day L-carnitine there was no significant difference between groups in the portal systemic encephalopathy index. However, the hospital admission rate was 31% in those receiving rifaximin alone over the 12-week treatment period compared to 10% in those receiving the combination therapy. The effectiveness of combination therapy warrants additional further research [40].

Treatment

Several studies have reported on real-world experience with rifaximin in patients with HE. Several of these trials were carried out in Japanese patients. In the first, involving 74 patients with overt HE, the mean annual number of overt HE episodes was reduced from 2.51 to 0.76 with a significant decrease in HE-related hospitalizations ($HR=0.187$; $p < 0.001$) (41]. The overall efficacy rate after 1 year of rifaximin therapy was calculated to be 65.8%, while serum albumin ≥2.7 g/dl was predictive of efficacy. In a retrospective analysis of 65 Japanese patients being administered rifaximin for a median of 42 weeks, significant and sustained decreases were seen in blood ammonia levels, along with a decrease in the Child-Pugh score in 51% of patients at 12 weeks of treatment [42]. The presence of ascites at baseline was an independent risk factor for HE recurrence ($HR=4.71$). In a smaller real-world analysis of 38 Japanese patients with HE and receiving rifaximin 1200 mg/day for >24 weeks, a significant decrease was seen in serum ammonia that was maintained for at least 24 weeks with no decline in liver function [43]. Chang et al. [44] reported on the outcomes of patients receiving rifaximin plus lactulose or lactulose alone. Compared to lactulose monotherapy, in those receiving combination therapy significantly greater improvement was seen in maintenance of HE remission, number of HE episodes, and HE-related hospitalizations.

Oey et al. [45] reported on the real-world outcomes of 127 patients with HE in the Netherlands over a period of 6 months. Compared to the 6-month period prior to receiving rifaximin, there were significant reductions in HE-related hospital admissions (0.86 to 0.41 admissions/patient) and in mean length of hospital stay (8.85 to 3.79 bed days/admission). However, there were no significant differences in HE-related ICU (Intensive Care Unit) admissions, length of stay in ICU, or emergency department or outpatient visits. In a multicenter, retrospective, observational study in 207 patients in the UK using hospital electronic databases, compared to the 6-month period before receiving rifaximin, treatment with rifaximin reduced the mean number of all-cause hospitalizations (1.9 to 0.9), hospital bed days/patient (25.4 to 10.6), 30-day hospital readmissions/patient (0.8 to 0.4) and emergency department visits/patient (1.0 to 0.5) [46].

Three meta-analyses have been recently carried out to investigate the effects of rifaximin in HE. Cheng et al. [47] compared the efficacy of rifaximin to nonabsorbable disaccharides that involved 6 studies with 559 patients. In this meta-analysis, rifaximin was better than nonabsorbable disaccharides ($RR=1.87$) for resolution of HE, although there were no significant differences in mental status, blood ammonia, or adverse effects between rifaximin and nonabsorbable disaccharides. Han et al. [48] compared rifaximin to other drugs used in the management of HE that

involved 28 randomized controlled trials and 2979 patients. Versus comparators, rifaximin significantly reduced HE grade, improved cognitive impairment, and prevention of recurrent HE episodes, but with no significant difference in mortality. Lastly, Dhiman et al. performed a meta-analysis of different treatments for minimal HE that included 25 trials and 1,563 patients [49]. For reversal of HE, rifaximin was associated with the highest odds ratio (OR=7.53), compared to lactulose (OR=5.39), the combination of probiotics and lactulose (OR=4.66), L-ornithine L-aspartate (OR=4.45), and probiotics (OR=3.89).

Studies assessing rifaximin in hepatic encephalopathy are summarized in Table II.

Hospitalizations and Costs

In recent years, several studies have examined the potential impact of rifaximin on healthcare costs. In analysis of commercially insured patients with HE in the US of 13,515 rifaximin ± lactulose episodes and 9,946 lactulose alone episodes, yearly rates of HE-related and all-cause hospital admissions declined by 33% and 27%, respectively, when treated with rifaximin compared to lactulose, with a similar decrease in HE-related hospital days [50]. According to the authors, savings of $2,417 could be expected in total mean medical costs per-patient-per-month. Considering a simulation of 1 million lives, adding rifaximin to lactulose in the treatment of at least 50% HE patients would lead to a total cost savings of $7.5 million per year. The benefits of a combined rifaximin/lactulose treatment regimen were also confirmed in a Markov model used to predict costs and outcomes of patients with HE during maintenance therapy with rifaximin ± lactulose [51]. Compared to lactulose monotherapy, there was an incremental benefit of $29,161 per quality-adjusted life-year (QALY) gained and $27,762 per life-year gained with rifaximin ± lactulose. This falls within the commonly accepted threshold for incremental cost-effectiveness. A similar Markov model was used to assess cost effectiveness in France in which rifaximin was found to be a cost-effective treatment option with an incremental cost per QALY gained of €19,187 and €18,517 over 2 and 5 years, respectively [52].

In a budget impact analysis from the Netherlands, rifaximin in combination with lactulose saved €4,487 per patient over a 5-year period compared to lactulose monotherapy [53]. In addition, combination therapy could save about 3,000 hospital admissions and 15,000 hospital bed days, with 300 fewer deaths over a 5-year period. From a Dutch hospital perspective, combination therapy would be expected to lead to a cost of 7.2 million euros savings over a 5-year period. In Italy, treatment of patients with rifaximin has been predicted to lead to a total saving of about €3,000,000 within the third year of therapy through reduced costs related to hospitalizations and treatment of recurrences of HE [54].

In a systematic review on the pharmacoeconomic impact of rifaximin in the treatment of HE, it was concluded that rifaximin had a favorable pharmacoeconomic profile compared with lactulose, because it was associated with shorter hospital stays and reduced healthcare costs [55].

RIFAXIMIN IN IRRITABLE BOWEL SYNDROME

Mechanistic/Translational Evidence

Several studies have investigated the mechanism of action of rifaximin in diverse gastrointestinal conditions, including IBS (Table III). Through analysis of gut microbial community profiles, Ponziani et al. [56] reported that among 25 patients with gastrointestinal conditions including ulcerative colitis, Crohn's disease, IBS, and DD, microbial alpha diversity showed a slight increase in patients who responded to rifaximin, and a decrease in clinical non-responders [56]. Moreover, clinical improvement following therapy with rifaximin appeared to be associated with an increase in the abundance of *Faecalibacterium*. Using bacterial 16S rRNA gene-targeted pyrosequencing, in patients with diarrhea-predominant IBS (IBS-D) who had been treated with rifaximin it was documented that fecal microbiota richness, but not diversity, was decreased compared to healthy controls with alterations of fecal microbiota. In particular, *Firmicutes* was significantly decreased and *Bacteroidetes* was increased [57]. DuPont et al. [57] also confirmed that *Staphylococcus* isolates taken from the skin of patients with IBS-D receiving rifaximin for 2 weeks (1,650 mg/day for up to 3 courses) did not demonstrate clinically significant or persistent resistance to rifaximin [58].

In a subanalysis of the TARGET 3 trial, the composition and diversity of gut microbiota were evaluated in a subset of 103 patients using variable 4 hypervariable region 16S ribosomal RNA gene sequencing [59]. Seven taxa including *Peptostreptococcaceae*, *Verrucomicrobiaceae*, and *Enterobacteriaceae* had significantly lower relative abundance after two repeated courses of rifaximin 550 mg TID. In another analysis of patients from TARGET 3, *Bacteroidaceae* (36.7%) and *Enterobacteriaceae* (33.9%) were the most frequent of 1,429 bacterial and yeast isolates [60]. Moreover, *Clostridioides difficile* and *Staphylococcus* isolates were highly susceptible to rifaximin, and rifaximin was not associated with resistance of *Bacteroidaceae*, *Enterobacteriaceae*, and *Enterococcaceae* isolates.

Other studies have reported slight differences in species richness, but not community diversity, which could differentiate IBS patients from healthy controls. In patients with IBS-D, constipation-predominant IBS (IBS-C), and IBS with mixed bowel habits (IBS-M), *Bacteroidetes, Firmicutes, Proteobacteria*, and *Actinobacteria* were constantly present in all samples [61]. However, *Firmicutes* predominated in fecal samples from IBS-C, while *Bacteroidetes* predominated in samples from healthy controls, IBS-D and IBS-M. No significant differences between patients who responded or not to rifaximin in metagenomic nor metabolomic analyses were demonstrated.

In other mechanistic studies, Zhuang et al. [62] reported that in Chinese patients with IBS-D, 2 weeks of treatment with rifaximin led to improvement in gastrointestinal symptoms and quality of life [62]. However, the benefits were not related to successful eradication of small intestinal bacterial overgrowth. Besides the modulation of the microbiota induced by rifaximin, preclinical and animal model studies suggest that rifaximin may also function to normalize visceral hypersensitivity, reduce mucosal inflammation, alter expression of immune modulators, and inhibit gastrointestinal permeability [63, 64].

Table III. Studies assessing rifaximin in irritable bowel syndrome.

Author, year	Type of study	Population	Primary objective(s)	Main results
Mechanistic/translation evidence				
Ponziani et al., 2020 [56]	Observational study	25 patients with UC, CD, IBS, and DD receiving rifaximin (1,200 mg/day for 10 days) treatment for a clinical indication	Investigate the correlation between changes in the gut microbiota composition and symptoms	Clinical improvement consequent to rifaximin treatment is associated with an increase in *Faecalibacterium* abundance
Zhuang et al., 2018 [57]	Observational study	Thirty IBS-D patients and 13 healthy controls	Characterize fecal microbiota of (IBS-D patients and explored the effect of rifaximin on gut microbiota using bacterial 16S rRNA gene-targeted pyrosequencing	Rifaximin was effective in terms of SIBO eradication in IBS-D patients; rifaximin induced alterations of some special bacteria rather than affecting the overall composition of microbiota in IBS-D patients
DuPont et al., 2017 [58]	Observational study	115 patients with IBS-D	Examine antimicrobial susceptibility of Staphylococcus isolates from skin swabs of patient with IBS-D who received multiple courses of rifaximin	Short-term (2-week) exposure to rifaximin (1,650 mg/day for up to 3 courses) did not lead to clinically significant or persistent resistance to rifaximin, rifampin, or other clinically important antibiotics
Fodor et al., 2019 [59]	Subanalysis of TARGET 3, a randomized, double-blind, placebo-controlled, phase 3 study	Patients with IBS-D initially received open-label rifaximin 550 mg TID for 2 weeks; responders who then relapsed were randomized to receive 2 repeat courses of rifaximin 550 mg TID or placebo for 2 weeks	Examine the effects of rifaximin on the gastrointestinal microbial community in patients with IBS-D	The effects of rifaximin were generally short-term, and there was little evidence of significantly different changes in taxa relative abundance at the end of the study (up to 46 weeks) vs. baseline
Pimentel et al., 2017 [60]	Subanalysis of TARGET 3, a randomized, double-blind, placebo-controlled, phase 3 study	Patients with IBS-D initially received open-label rifaximin 550 mg TID for 2 weeks; responders who then relapsed were randomized to receive 2 repeat courses of rifaximin 550 mg TID or placebo for 2 weeks	Determine the rifaximin repeat treatment effect on fecal bacterial antibiotic susceptibility	Short-term repeat treatment with rifaximin has no apparent long-term effect on stool microbial susceptibility to rifaximin, rifampin, and nonrifamycin antibiotics
Zeber-Lubecka et al., 2016 [61]	Stool samples were collected before and after treatment and analyzed	72 patients, including 31 with IBS-D, 11 with IBS-C (constipation), and 30 with IBS-M (mixed constipation and diarrhea) and 30 healthy controls	Investigate the interactions between IBS symptoms and the gut microbiome, including the relation to rifaximin	Species richness, but not community diversity, differentiated all IBS patients from healthy controls; neither metagenomics nor metabolomics analyses identified significant differences between patients with and without improvement after treatment
Zhuang et al., 2020 [62]	Observational study	78 IBS-D patients defined by the Rome IV criteria receiving 400 mg rifaximin BID for 2 weeks and 10-week follow-up	Investigate the effect of rifaximin on gastrointestinal symptoms, and SIBO eradication in Chinese IBS-D patients	A short course (2 weeks) of rifaximin improved gastrointestinal symptoms in independently of SIBO; the efficacy of rifaximin could not be explained by the successful eradication of SIBO
Clinical evidence				
Lembo et al., 2016 [66]	Phase 3, randomized, double-blind, placebo-controlled trial	1074 patients responding to a 2-week course of open-label rifaximin 550 mg 3 times daily, who then relapsed during an observation phase (up to 18 weeks), were randomly assigned to groups given repeat treatments of rifaximin 550 mg or placebo TID for 2 weeks	Evaluate the safety and efficacy of repeat treatment with the nonsystemic antibiotic rifaximin	The percentage of responders was significantly greater with rifaximin than placebo (38.1% vs 31.5%; P = 0.03); the percentage of responders for abdominal pain (50.6% vs 42.2%; P = 0.018) was significantly greater with rifaximin than placebo, but not stool consistency (51.8% vs 50.0%; P = 0.42)
Lembo et al., 2020 [68]	Subanalysis of TARGET 3, a randomized, double-blind, placebo-controlled, phase 3 study	2,438 patients of whom 1,384 (56.8%) had abdominal pain response to open-label rifaximin	Examine abdominal pain response in adults with IBS-D receiving rifaximin	Weekly decrease (improvement) in responders‘ mean abdominal pain score from baseline ranged from -2.6 to -3.3 points during the 18-week follow-up<, after the first double-blind repeat treatment, a significantly higher percentage of rifaximin-treated patients were abdominal pain responders (53.9%) vs placebo (44.4%, P = 0.02), with similar results after the second repeat treatment (52.9% vs 44.7%, respectively, P = 0.047)

Table III (continued)

Cash et al., 2017 [69]	Subanalysis of TARGET 3, a randomized, double-blind, placebo-controlled, phase 3 study	2438 patients receiving open-label rifaximin	Evaluate rifaximin retreatment on IBS-related QoL in patients with IBS-D	Responders to open-label rifaximin (n = 1074 of 2438 evaluable; 44.1%) had significantly greater improvement from baseline in IBS-QOL overall and all eight subdomain scores versus non-responders at 4 weeks posttreatment (n = 1364; p < 0.001 for all comparisons).
Yoon et al., 2018 [70]	Observational study	63 patients treated with rifaximin for FGIDs with bloating or gas-related symptoms	Evaluate the efficacy of rifaximin in reducing bloating associated with functional gastrointestinal disorders	Of the 51 subjects who were followed-up, 30 (58.8%) had adequate relief of global FGID symptoms and 26 (51.0%) experienced improvement of abdominal bloating after rifaximin treatment
Ford et al., 2018 [71]	Meta-analysis	53 randomized trials of probiotics involving 5545 patients	Examine the efficacy of prebiotics, probiotics, synbiotics and antibiotics in IBS	Which particular combination, species or strains of probiotics are effective for IBS remains, for the most part, unclear; rifaximin has modest efficacy in improving symptoms in non-constipated IBS
Predictors of response				
Lee et al., 2019 [72]	Retrospective chart review	198 patients presenting with gastrointestinal complaints consistent with Rome III criteria for IBS	Investigate changes in fecal calprotectin and intestinal symptoms following treatment with rifaximin in patients with nonconstipated IBS and elevated fecal calprotectin	Fecal calprotectin might be a useful biomarker to measure the effect of rifaximin in nonconstipated IBS patients with elevated fecal calprotectin
Safwat et al., 2020 [73]	Single-center prospective study	96 patients with chronic diarrhea who fulfilled Rome IV criteria for IBS-D	Evaluate the role of fecal calprotectin as a follow-up marker of IBS-D after short-course rifaximin	FC levels normalized in 66 (84.6%) patients, including 60 and 6 patients treated for 2 and 4 weeks, respectively.
Rezaie et al., 2019 [74]	Prospective study	93 patients with IBS-D receiving open-label rifaximin 550 mg TID for 2 weeks, followed by a 4-week posttreatment assessment period	Examine the utility of lactulose breath test in predicting response to rifaximin	Overall, 48.4% of patients responded to rifaximin; of these, 59.7% had a positive baseline lactulose breath test vs 25.8% with a negative test (P = 0.002; OR 4.3); positive baseline test result predicted a higher likelihood of response to rifaximin in IBS-D
Li et al., 2020 [76]	Fecal and rectal mucosal bacterial data were obtained via 16S rRNA sequencing, and fecal fungal data were obtained via ITS2 sequencing	19 healthy controls and 30 IBS-D patients	Explore which component of gut microbiota can predict the efficacy of rifaximin in IBS-D	Rectal mucosal bacteria and fecal fungi were not significantly altered in any patient after rifaximin intervention, but rifaximin enhanced the connections among fecal bacteria, mucosal bacteria and fecal fungi in patients whose fecal bacterial composition were different from healthy controls
Costs				
Shah et al., 2019 [77]	A decision analytic model was used	The analysis was performed from a payer perspective with a 1-year time horizon	Assessed cost effectiveness of rifaximin in management of patients with IBS-D	At current drug prices, unrestricted or formulary-restricted coverage would cost an additional $1,207,136 or $171,850/QALY gained, compared to complete non-coverage; a 12% to 62% price reduction ($18.46 to $26.34/pill) for formulary-restricted access and 84% to 88% price reduction ($3.53 to $4.71/pill) for unrestricted access would be needed for rifaximin to be a cost-effective treatment strategy
Shah et al., 2021 [78]	Multilevel modeling analysis	Costs and outcomes among 10 million hypothetical moderate-to-severe patients with IBS was developed to model all possible algorithms including common global IBS treatments and prescription drugs treating IBS-D or IBS-C over 1 year	Determine if routine and algorithmic coverage restrictions are cost-effective from a commercial insurer perspective	Routinely using global IBS treatments before US FDA-approved drug therapies resulted in per-patient cost savings of $9,034.59 for IBS-D and $2,972.83 for IBS-C over 1 year to insurers, compared with patients starting with on-label drug therapy

CD: Crohn's disease; DD: diverticular disease; FGIDs: functional gastrointestinal disorders; IBS: irritable bowel syndrome; IBS-C: constipation-predominant IBS; IBS-D: diarrhea-predominant IBS; QALY: quality-adjusted life-year; QoL: quality of life; SIBO: small intestine bacterial overgrowth; UC: ulcerative colitis.

Clinical Evidence

Rifaximin has been well studied in IBS, especially in the Phase 3 TARGET clinical trials. TARGET 1 and TARGET 2 showed that in patients who had IBS without constipation, treatment with rifaximin for 2 weeks was associated with significant relief of IBS symptoms, bloating, abdominal pain, and loose or watery stools [65]. A meta-analysis of five randomized, placebo-controlled trials (N=1,803 subjects with IBS/IBS-D) that included TARGET 1 and TARGET 2 data, reported that 42.2% of patients treated with rifaximin vs. 32.4% of those receiving placebo achieved global improvement of IBS symptoms (OR=1.57) [67]. In IBS treatment, rifaximin is also considered to be safe and well tolerated [17]. Considering its mechanism of action in therapy of IBS, it has been hypothesized that rifaximin acts by altering the composition of gut microbiota with reduction of mucosal inflammation, and improved barrier function of the small intestine [17].

TARGET 3 demonstrated that repeat rifaximin treatment was effective and well tolerated in patients with relapsing symptoms of IBS [66]. A sub-analysis of TARGET 3 also showed that of 2,438 patients, 56.8% had abdominal pain response to rifaximin (≥30% improvement from baseline in mean weekly abdominal pain score during ≥2 of the first 4 weeks following treatment) [68]. Moreover, following the first repeat treatment, significantly more patients treated with rifaximin were abdominal pain responders (53.9%) compared to placebo (44.4%), with similar results after the second repeat treatment (52.9% vs 44.7%, respectively).

Following TARGET 3, another trial in 2,579 patients with IBS extended those findings by showing that repeated treatment with rifaximin (550 mg BID for 2 weeks) improved IBS-related quality of life [69]. In the open-label phase, 54.9% of patients referred improvement in the Irritable Bowel Syndrome Quality of Life (IBS-QOL) overall score. Among 636 patients with relapse of IBS, the minimally clinically important difference in the overall IBS-QOL score (≥14-point improvement from baseline) was reached by significantly more patients on rifaximin (38.6%) compared to placebo (29.6%). In a small study of 63 patients with IBS receiving rifaximin (800 mg/day and 1,200 mg/day for 5 to 14 days), it was reported that 58.8% had adequate relief of global functional gastrointestinal disorder symptoms and 51.0% experienced improvement of abdominal bloating [70].

Lastly, a drug safety evaluation of rifaximin reported that, considering the data from retrospective and prospective studies, there were no significant differences in the incidence of adverse events between rifaximin and the comparator [26]. Overall, only around 6% of the reported adverse events were severe, and among these 1.6% were serious but only 0.1% were rifaximin-related.

In 2018, Ford et al. [71] carried out a meta-analysis of the efficacy of various classes of agents for IBS. The analysis identified five trials with similar design that evaluated rifaximin in non-constipated patients with IBS; rifaximin was found to be more effective than placebo for persistent symptoms (RR=0.84) and was thus considered to have modest efficacy in improving symptoms in non-constipated IBS. Adverse events were not more frequent with either probiotics or antibiotics vs. placebo.

Predictors of Response

Since not all patients with IBS respond to rifaximin, it is of interest to find markers that may help to predict response to therapy. While not strictly predictive, two studies have found that levels of fecal calprotectin normalize following therapy with rifaximin. In the study by Lee et al. [72], of 198 patients with IBS, 162 achieved normalized fecal calprotectin values after receiving rifaximin for 4-12 weeks. Among these, the majority of patients who received rifaximin for 8 or 12 weeks showed a significant improvement in gastrointestinal symptoms by the fourth week of treatment. Fecal calprotectin levels decreased together with concomitant improvement of clinical symptoms. In 78 patients with IBS-D, it was similarly reported that a cutoff of 148.5 μg/g for fecal calprotectin could predict non-responders with 100% sensitivity and 50% specificity, and therefore might be considered as a marker for follow-up [73].

Lactulose breath test (LBT) has been reported to predict the response to rifaximin in patients with IBS. In particular, in 93 patients with IBS-D Rezaie et al. [74] found that 48.4% of patients responded to rifaximin (550 mg TID for 2 weeks); of these, baseline LBT was positive in 59.7% and negative in 25.8% of patients [74]. Patients with a positive result had significantly greater improvement from baseline in 6 of 7 symptoms related to IBS. The results of LBT after rifaximin treatment did not correlate with clinical response, although patients whose LBT normalized following rifaximin had the highest response rate (76.5%). However, these results are considered to be controversial given the ambiguity in classification of patients and definition of LBT used in that study [75].

Lastly, Li et al. [76] classified patients with IBS-D into two groups based on fecal bacterial composition, those with a composition similar to or different from healthy controls. In patients with a composition different from healthy controls, rifaximin increased fecal *Bifidobacterium* and decreased both *E. coli* and *Enterobacter*. It was further found that compared to those with a fecal composition similar to healthy controls, rifaximin improved abdominal symptoms to a greater extent than those with a different bacterial composition. Accordingly, fecal bacterial composition might be considered as a potential predictor of response to rifaximin in patients with IBS-D.

Costs

Only a limited number of studies have been published regarding analysis of costs in patients with IBS. Shah et al. [77] analyzed common payer coverage restrictions to determine the maximum price at which rifaximin would be cost effective in the US for patients with IBS-D. It was found that a price reduction of 12-62% for formulary-restricted access and of 84-88% for unrestricted access would be needed for rifaximin to be considered cost-effective. Thus, in this model, payer coverage for rifaximin for patients with IBS-D exceeds accepted cost-effectiveness thresholds at current drug prices. However, in another analysis by the same group, routine use of other non-prescription FDA-approved therapies could lead to cost savings of $9,034 per patient for IBS-D compared to on-label drug therapies [78]. Nonetheless, the most cost-saving and cost-effective treatment algorithm for IBS-D initiated with rifaximin.

Recommendations

The American College of Gastroenterology has recently developed the first clinical guideline for IBS using GRADE methodology [79]. Among the guidance for therapy, a limited trial of a low fermentable oligosaccharides, disaccharides, monosaccharides, polyols (FODMAP) diet was recommended in patients with IBS to improve global symptoms. In IBS with constipation symptoms, chloride channel activators (strong recommendation; moderate quality of evidence) and guanylate cyclase activators (strong recommendation; high quality of evidence) were recommended, while for global IBS with diarrhea symptoms the guidelines recommend the use of rifaximin (strong recommendation; moderate level of evidence). More recently, the American Gastroenterological Association (AGA) guidelines for the treatment of IBS-D have suggested the use of rifaximin (conditional recommendation, moderate certainty) [80]. In addition, in patients with an initial response to rifaximin who develop recurrent symptoms, the AGA suggests retreatment with rifaximin (conditional recommendation, moderate certainty) [80]. Similarly, clinical guidelines of the United European Gastroenterology and European Society for Neurogastroenterology and Motility recommend the use of rifaximin in patients with IBS-D, although the therapeutic gain over placebo may be limited (level of evidence high, strong recommendation, consensus 96%) [81].

RIFAXIMIN IN DIVERTICULAR DISEASE

Mechanistic/Translational Evidence

In addition to the study by Ponziani et al. [56] described in the section on IBS, De Vincentis et al. investigated changes in gut microbiota and electronic multisensorial assessment of stools and breath in patients with DD undergoing treatment with rifaximin (Table IV) [82]. The study evaluated 43 patients, of whom 47% reported clinical improvement after rifaximin therapy. While alpha and beta diversity of stool microbiota showed no significant changes after therapy, significant variation of several taxa was found, including *Citrobacter, Coprococcus, Anaerotruncus, Blautia, Eggerthella lenta, Dehalobacterium, SMB53,* and *Haemophilus parainfluenzae*. In addition, the electronic multisensorial system was able to predict clinical improvement after rifaximin with accuracies ranging from 0.81 to 0.98. In the authors' opinion, an electronic-tongue and electronic-nose has the potential to serve as an easy and inexpensive tool to predict which patients with SUDD are more likely to benefit from therapy with rifaximin.

In the review by Bajaj et al. [17] published in 2018, it was noted that data for the use of rifaximin was limited. However, an analysis of the available evidence showed that rifaximin appears to reduce symptoms, such as abdominal pain and bloating, as well as the frequency and severity of DD flares. In a meta-analysis of 31 studies, rifaximin was superior to comparators (mainly fibers) as therapy for SUDD [83]. Since that time, a number of additional studies have investigated the efficacy of rifaximin alone or in combination with other agents in DD, along with mechanistic and real-world studies.

Clinical Evidence

In 2017, Banasiewicz et al. [84] carried out a retrospective analysis of 248 patients with DD, comparing a group of 145 controls to 103 patients who received rifaximin prophylaxis. The diverticulitis rate was similar in both groups during the 6 months before the study and during 6 months of treatment. Between months 6 and 12 of treatment, a significantly lower frequency of diverticulitis was observed in those receiving rifaximin compared to the control group. Patients administered rifaximin also reported a higher quality of life after 12 months compared to the control group. Festa et al. [85] retrospectively compared 72 patients treated with rifaximin to 52 patients with DD treated with mesalazine. Among the 21 episodes of acute diverticulitis observed, 7 occurred in those receiving rifaximin and 14 occurred in those taking mesalazine. Multivariate analysis showed that recurrence of acute diverticulitis was significantly associated with therapy (rifaximin vs. mesalazine, adjusted HR=0.27).

In a retrospective observational study of 267 patients with SUDD and cyclically treated with rifaximin 400 mg BID for 7 days per month, after 6 months there was a significant reduction in the total severity score (from 1.8 to 0.2) and total symptom score (from 9.4 to 1.4) [86]. The authors concluded that in patients who respond to initial treatment, cyclic rifaximin therapy may be warranted to maintain remission.

A retrospective analysis has been carried out on the long-term benefits of rifaximin in SUDD over 8 years of follow-up [87]. The study compared 346 patients with SUDD treated with rifaximin 800 mg/day for 7 days every month to 470 patients with SUDD who took any other treatment on demand. Median VAS (Visual Analogue Score) score for pain at baseline was 6 in both groups; at 8-year follow-up it was 3 and 6, respectively, in those receiving rifaximin and any other therapy, respectively. Both bloating and daily bowel movements were also significantly reduced in the group of patients taking rifaximin. Cyclical rifaximin was thus considered to be effective in relieving symptoms in patients with SUDD over the long-term.

A real-life retrospective study analyzed 142 patients with DD and mild diverticulitis who underwent three cycles of rifaximin 400 mg BID for 7 days over 3 consecutive months [88]. After the first cycle of therapy, significant reduction in abdominal pain, abdominal tenderness, bloating, disturbances in bowel habit were seen, with a reduction in mean intensity of symptoms from 1.7 to 0.8. After three cycles of treatment, the severity of symptoms decreased further to a mean of 0.3, and up to 75% of patients reported no abdominal pain compared to 4% pre-treatment. A significant decrease in white blood cell count, C-reactive protein, and erythrocyte sedimentation rate was also observed.

In a retrospective, observational study investigating rifaximin 400 mg BID for 5, 7, or 10 days monthly for up to 3 months in 286 patients with SUDD a significant reduction of the VAS score for symptoms was observed in almost all symptoms evaluated [89]. In particular, 47.2% patients reported no abdominal pain and 8.1% reported no symptoms. Acute diverticulitis occurred in 9 patients, but only two cases required surgery due to complicated diverticulitis.

Table IV. Studies assessing rifaximin in diverticular disease.

Author, year	Type of study	Population	Primary objective(s)	Main results
Mechanistic/translation evidence				
De Vincentis et al., 2021 [82]	Prospective longitudinal study	43 patients with SUDD	Determine how rifaximin treatment affects gut microbiota and whether electronic multisensorial assessment of stools and breath can detect these changes	Rifaximin administration is associated with significant variation of selected taxa; while inaccurate in predicting gut microbiota changes, an electronic multisensorial system (e-tongue and e-nose) was able to predict clinical improvement
Banasiewicz et al., 2017 [84]	Retrospective analysis	248 patients with diverticulosis: 145 controls and 103 receiving rifaximin prophylaxis	Analyze the efficacy of rifaximin in preventing diverticulitis in patients visiting proctology clinics	Between the 6th and 12th month of treatment, a significantly lower rate of diverticulitis was seen in patients receiving rifaximin vs. controls; rifaximin was associated with higher QoL vs. controls after 12 months
Festa et al., 2017 [85]	Retrospective analysis	72 patients with SUDD treated with rifaximin and 52 with mesalazine	Assess the impact of long-term treatment with rifaximin or mesalazine in a 10-day schedule for prevention of recurrent diverticulitis	Multivariate Cox regression analysis showed that acute diverticulitis recurrence was significantly associated with therapy (rifaximin vs. mesalazine, adjusted HR 0.27; 95% CI: 0.10 to 0.72), age and gender
Pietrzak et al., 2019 [86]	Retrospective observational study	294 patients with SUDD	Assess effectiveness of rifaximin for recurrent SUDD symptoms and exacerbations in patients who responded to initial treatment	After 6 months of rifaximin treatment there was significant reduction in the total severity score (from 1.8 to 0.2) and total symptom score (from 9.4 to 1.4)
Di Mario et al., 2019 [87]	Retrospective analysis	346 patients with SUDD treated with rifaximin 800 mg/day for 7 days every month and 470 patients with SUDD who took any other treatment on demand	Assessed outcomes of patients with SUDD treated with rifaximin over 8-years of follow-up	No side effects were recorded during the study period; rifaximin is effective in relieving symptoms and reducing the risk of disease-related complications in patients with SUDD
Moniuszko et al., 2017 [88]	Real-life retrospective study	142 patients with SUDD and mild diverticulitis who underwent three cycles of rifaximin 400 mg BID for 7 days over 3 consecutive months	Assess the effect of rifaximin on the symptoms of UDD and mild diverticulitis in patients undergoing routine treatment in gastroenterology outpatient clinics in Poland	After just one cycle of therapy, significant reduction in disease symptoms was observed (abdominal pain, abdominal tenderness, bloating, disturbances in bowel habit); after three cycles, the severity of symptoms decreased markedly, and as many as 75% of patients reported no abdominal pain
De Bastiani et al., 2021 [89]	Retrospective, observational study	286 patients with SUDD receiving rifaximin 400 mg BID for 5, 7, or 10 days monthly for up to 3 months	Assess the efficacy of the treatment of SUDD with rifaximin in a primary care setting by GPs	After three months, a significant reduction of VAS score was observed in almost all symptoms assessed: 47.2% patients reported no abdominal pain ($p<0.001$) and 8.1% reported no symptom; rifaximin treatment is effective in reducing the severity of symptoms in all groups except for constipation in the 5-day group
Tursi et al., 2016 [90]	Survey of symposium participants	115 surveys from 8 European Countries were filled out	Investigate the current opinion of participants of the 2nd International Symposium on Diverticular Disease, on real-life management of patients with DD of the colon	Rifaximin, probiotics, and mesalazine were the most frequent prescribed drugs in symptomatic patients (28.1, 14.9%, and 11.4%, respectively) and to prevent recurrence of disease (42.5%, 12.4%, and 28.2%, respectively); rifaximin, probiotics, and mesalazine were the most frequent prescribed drugs to prevent recurrence of disease (32.2%, 13.2%, and 11.4%, respectively)
De Bastiani et al., 2016 [91]	Survey of general practitioners	245 Italian general practitioners	Investigate opinion of general practitioners on management of patients with DD of the colon	Rifaximin, probiotics, and mesalazine were the most frequently prescribed drugs in SUDD (82.8, 59.5%, and 36.3%, respectively); rifaximin, probiotics, and mesalazine were the most frequently prescribed drugs to prevent recurrence of disease (42.5%, 28.2%, and 12.4%, respectively)
Combination therapy with rifaximin				
Campanini et al, 2016 [92]	Prospective study	63 patients with SUDD receiving rifaximin, 43 rifaximin+fiber+probiotics, 23 mesalamine, and 31 mesalamine+fiber	Assess the role of a fiber-rich diet and probiotic implementation in SUDD in addition to mesalamine or rifaximin in primary-care	Supplementation of fiber and/or probiotics is associated with a significant improvement in the clinical symptoms in patients with DD in a primary care setting.

Table IV (continued)

Banasiewicz et al., 2019 [93]	Observational study	58 patients receiving prophylaxis with rifaximin and 63 receiving rifaximin the addition of arabinogalactan (5 g) and lactoferrin (50 mg) (1 sachet per day for 3 months)	Assess the effects of additional supplementation with a prebiotic consisting of soluble fiber arabinogalactan and lactofferin in patients with DD receiving cyclic treatment with rifaximin (2x400 mg for 7 days once a month)	Significant reduction of pain and improvement of the quality of life was observed in both groups; significant improvement of bowel movement frequency and stool consistency was observed with combination therapy
Pietrzak et al., 2020 [94]	Observational study	281 patients with SUDD and previous recurrences treated with cyclic rifaximin (at least 400 mg BID/7 days/ every month) and continuous arabinogalactan-lactoferrin supplementation (1 sachet daily)	Assess the effectiveness of combined therapy with rifaximin and arabinogalactan-lactoferrin in symptom reduction and normalization of bowel movements	Combination therapy with cyclic rifaximin and continuous arabinogalactan combined with lactoferrin are effective in SUDD in terms of symptom resolution, bowel movement normalization, and prevention of recurrences

DD: diverticular disease; QoL: quality of life; SUDD: symptomatic uncomplicated diverticular disease.

Considering the different treatment times, rifaximin was effective in reducing the severity of symptoms in all groups except for constipation in the 5-day group. The authors considered this as evidence that rifaximin can be effectively prescribed by general practitioners in routine practice.

In 2016, Tursi et al. [90] carried out a survey of 115 participants of the 2nd International Symposium on Diverticular Disease regarding diagnosis, treatment, and management for diverticulosis and symptomatic DD [90]. Probiotics were the most frequently prescribed drug (25%). Rifaximin, probiotics, and mesalazine were prescribed by 28.1, 14.9%, and 11.4% of responders, respectively, for symptomatic patients and by 42.5%, 12.4%, and 28.2%, respectively, to prevent disease recurrence.

In a web-based survey of 245 Italian general practitioners, rifaximin (26%) and probiotics (25%) were most frequently prescribed drugs in patients with DD overall [91]. Rifaximin, probiotics, and mesalazine were prescribed in patients with SUDD by 82.8%, 59.5%, and 36.3% of participants, respectively. Rifaximin, probiotics, and mesalazine were prescribed by 42.5%, 28.2%, and 12.4% of participants, respectively, to prevent disease recurrence.

Combination Therapy with Rifaximin

In a prospective analysis of 178 patients with SUDD, Campanini et al. [92] assigned 63 patients to rifaximin, 43 to rifaximin+fiber+probiotics, 23 to mesalamine, and 31 to mesalamine+fiber for 3 months [92]. The groups receiving fiber and/or probiotics were reported to have a higher number of bowel movements per week. In a retrospective analysis, patients treated with rifaximin receiving concomitant *Bifidobacterium longum* W11 (n=23) had better clinical outcomes than those treated first with rifaximin and then with strain W11 (n=22). Concomitant use of strain *Bifidobacterium longum* W11 also improved stool consistency in most patients.

Two studies have reported on the concomitant use of arabinogalactan plus lactoferrin in combination with rifaximin. Banasiewicz et al. [93] compared 58 patients with SUDD receiving rifaximin 400 mg BID for 7 days in a cyclic regimen to 63 patients receiving rifaximin plus a prebiotic containing arabinogalactan (5 g) with lactoferrin (50 mg) at a dose of 1 sachet per day for 3 months [93]. Significant reduction of pain and improvement of quality of life was observed in both study groups, while significant improvement in normalization of bowel movement frequency and stool consistency was observed in those also receiving the combination treatment. The increase in the quality of life was also significantly greater in those receiving combination therapy compared to rifaximin alone. The same combination of rifaximin with arabinogalactan and lactoferrin was later reported to be effective in a retrospective survey of physicians treating a total of 281 patients with SUDD [94]. After 6 months of combined therapy, significant reduction in the total severity score and improvement in each symptom score was seen. Stool frequency was also normalized and 31.7% of patients had complete symptom resolution independent of diarrhea or constipation before treatment.

Recommendations

In 2017, the Italian Society of Gastroenterology published a position paper on the use of rifaximin in DD [95]. It was noted that there is a lack of rationale for use of rifaximin as primary prevention of diverticulitis, and accordingly its use should be avoided. On the other hand, cyclic use of rifaximin in combination with high intake of fiber is considered safe and beneficial as therapy for SUDD. The authors of the position paper also pointed out that use of rifaximin in prevention of disease recurrence appears to be promising, but additional studies are warranted.

The American Society of Colon and Rectal Surgeons has recently issued treatment guidelines for treatment of left-sided colonic diverticulitis [96]. With regards to recommendations for use of rifaximin, it was noted that mesalamine, rifaximin, and probiotics are not typically recommended to reduce the risk of diverticulitis recurrence, but that they may be effective in reducing chronic symptoms (grade of recommendation, weak based on moderate-quality evidence, 2B). In general, studies evaluating the use of mesalamine, rifaximin, or probiotics are heterogeneous, and the routine use of these agents following an attack of diverticulitis is typically not recommended.

DISCUSSION

At present, in many countries, rifaximin is approved for prevention of recurrent HE in patients with cirrhosis. However, rifaximin leads to complex modulation of the gut microbiome that affects the gut-liver axis, and as such is potentially effective in prevention or management of other digestive diseases.

In recent years, many studies have been carried out on HE. Evidence has been provided for the utility of rifaximin in prevention of HE, and importantly, a real-world study appears to show that in routine clinical use rifaximin is associated with significant reductions in HE-related hospital admissions [45] and all-cause hospitalizations [46]. Meta-analyses have also reported that rifaximin is also beneficial for some of the parameters evaluated, and especially cognitive impairment, but not mortality [48]. A number of mechanistic studies have been carried out, but further effort is needed to understand the reasons for the sometimes-heterogeneous results. Regarding costs, rifaximin also appears to be cost saving in treatment of HE. In addition, other aspects still require further study in HE, also in consideration of the fact that non-responders generally have no other treatments available except for liver transplant. Thus, it would be of interest to identify predictors of response and to understand how patient compliance to therapy affects the efficacy of rifaximin therapy. It is also clear that HE is an often-overlooked condition for which greater physician awareness is needed.

In IBS, a number of mechanistic studies have been carried out, but, similar to HE, the effect of rifaximin in gut microbial composition should be further investigated. It is of definite interest in knowing that progress has been made in identifying predictors of response, and especially fecal calprotectin and LBT. These may help to identify responders to rifaximin in patients with IBS and could also help explain why slight results are seen in pooled populations of patients. Rifaximin appears to be cost saving in patients with IBS, although there is only limited evidence available to date. Lastly, the American College of Gastroenterology guidelines now recommend the use of rifaximin in patients with global IBS and diarrhea symptoms [79], as do the the AGA guidelines for treatment of IBS-D [80] and those from the United European Gastroenterology and European Society for Neurogastroenterology and Motility [81].

In DD, importantly, rifaximin has been shown to have long term benefit in reducing recurrent events [87]. Of interest, cyclic rifaximin therapy appears to maintain remission in these patients [86]. In this regard, additional mechanistic studies in DD are warranted, also with the aim of better understanding the alteration in gut microbiota that occur over the very long-term. However, guidelines do not generally recommend the use of rifaximin in DD, even if it may help to reduce chronic symptoms. Short-term repeat treatment with rifaximin has no apparent long-term effect on stool microbial susceptibility to rifaximin, rifampin, and non-rifamycin antibiotics, based on results of prospective study studied by Pimentel in 2017 [60]. Rifaximin exposure was also not associated with long-term cross-resistance of *Bacteroidaceae, Enterobacteriaceae*, and *Enterococcaceae* to rifampin or non-rifamycin antibiotics.

CONCLUSIONS

Thus, while the evidence for the efficacy of rifaximin in HE appears to be well consolidated, it is less supported for IBS and DD. Accordingly, additional randomized double-blinded studies are needed with rifaximin as monotherapy or in combination with other agents, and especially on larger populations. In addition, for all three diseases, more real-world studies are needed. Comprehensive efficacy assessment through meta-analyses and systematic reviews of rifaximin may however be limited by some results in relatively small clinical trials in IBS and DD. This could explain why, to date, the possibility of providing precise recommendations for the use of rifaximin in these last clinical situations are still precluded by the need for further evidence.

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