Therapeutic Effects and Mechanisms of Action of Rifaximin in Gastrointestinal Diseases

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Abstract

Emerging preclinical and clinic evidence described herein suggests that the mechanism of action of rifaximin is not restricted to direct antibacterial effects within the gastrointestinal tract. Data from this study were derived from general and clinical trial-specific PubMed searches of English-language articles on rifaximin available through December 3, 2014. Search terms included rifaximin alone and in combination (using the Boolean operation “AND”) with travelers’ diarrhea, hepatic encephalopathy, liver cirrhosis, irritable bowel syndrome, inflammatory bowel disease, and Crohn’s disease. Rifaximin appears to reduce bacterial virulence and pathogenicity by inhibiting bacterial translocation across the gastrointestinal epithelial lining. Rifaximin was shown to decrease bacterial adherence to epithelial cells and subsequent internalization in a bacteria- and cell type-specific manner, without an alteration in bacterial counts, but with a down-regulation in epithelial proinflammatory cytokine expression. Rifaximin also appears to modulate gut-immune signaling. In animal models of inflammatory bowel disease, rifaximin produced therapeutic effects by activating the pregnane X receptor and thereby reducing levels of the proinflammatory transcription factor nuclear factor kB. Therefore, for a given disease state, rifaximin may act through several mechanisms of action to exert its therapeutic effects. Clinically, rifaximin 600 mg/d significantly reduced symptoms of travelers’ diarrhea (eg, time to last unformed stool vs placebo [32.0 hours vs 65.5 hours, respectively; P=.001]). For the prevention of hepatic encephalopathy recurrence, data indicate that treating 4 patients with rifaximin 1100 mg/d for 6 months would prevent 1 episode of hepatic encephalopathy. For diarrhea-predominant irritable bowel syndrome, a significantly greater percentage (40.7%) of patients treated with rifaximin 1650 mg/d for 2 weeks experienced adequate global irritable bowel syndrome symptom relief vs placebo (31.7%; P<.001). Rifaximin may be best described as a gut microenvironment modulator with cytoprotection properties, and further studies are needed to determine whether these putative mechanisms of action play a direct role in clinical outcomes.

Rifaximin has been available for nearly 30 years and is currently approved in at least 41 countries around the world. Rifaximin (C₄₃H₅₁N₃O₁₁) is a nonsystemic structural analogue of rifampin that inhibits the synthesis of bacterial RNA by binding to the β subunit of bacterial DNA-dependent RNA polymerase (Figure 1).¹⁻³ Thus, it has been traditionally identified as an antibiotic, with support coming from its apparent modulation of the gut microbiota. Rifaximin is indicated for the treatment of travelers’ diarrhea caused by noninvasive Escherichia coli strains and also for reducing the risk of recurrence of overt hepatic encephalopathy.² This review provides a brief narrative overview of the disease states for which rifaximin is indicated or has potential therapeutic efficacy, followed by a discussion of the putative mechanisms of action of rifaximin.

DATA SOURCES AND SEARCHES

A PubMed search was conducted for English-language articles on rifaximin available through December 3, 2014. The search terms included rifaximin alone and in combination (using the Boolean operator “AND”) with each of the following terms: travelers’ diarrhea, hepatic encephalopathy, liver cirrhosis, irritable bowel syndrome, inflammatory bowel disease, and Crohn’s disease. A general search was conducted, followed by a search of clinical trials only. Articles were selected with 2 aims: (1)
to identify articles that provided epidemiological data and/or a comprehensive overview of travelers’ diarrhea, hepatic encephalopathy and other cirrhosis-related complications, diarrhea-predominant irritable bowel syndrome, and Crohn disease; and (2) to identify articles that reported clinical trial results or any other relevant findings. An additional search included the terms rifaximin AND mechanism of action, rifaximin AND pharmacodynamics, rifaximin AND pharmacokinetics, rifaximin AND (immune system OR immune function OR immune signaling), rifaximin AND bacteria, rifaximin AND (antibiotic OR antimicrobial), and rifaximin AND (gut microbiota OR gut mucosa). Articles were selected from this search with the aim of identifying those reporting data related to the mechanism of action of rifaximin.

TRAVELERS’ DIARRHEA

Travelers’ diarrhea is common among international travelers, affecting up to 50% of all travelers.4-6 Symptoms of travelers’ diarrhea typically occur suddenly and include diarrhea, abdominal cramping, nausea, vomiting, and general malaise.4,7 Travelers’ diarrhea is caused primarily by exposure to a bacterial enteric pathogen; enterotoxigenic E coli and enteropathogenic E coli are the most common causative pathogens.4,6 Most cases of travelers’ diarrhea are mild in intensity, and symptoms are generally self-limited; about 90% of cases resolve within 1 week, and 98% resolve within 1 month of symptom onset.4-7 Antibiotics are typically prescribed for moderate to severe cases of travelers’ diarrhea.4,7 Although considered an acute illness, evidence suggests that travelers’ diarrhea can lead to chronic disease, including reactive arthritis and postinfectious IBS.8

Data from randomized clinical trials support the efficacy and tolerability of rifaximin in the treatment of travelers’ diarrhea.9-11 In a randomized double-blind study, adults who visited a travel health clinic in Mexico, Guatemala, India, or Peru were treated for acute diarrhea with rifaximin 200 mg thrice daily (n=197), placebo thrice daily (n=101), or standard of care (ciprofloxacin 500 mg twice daily plus placebo once daily [n=101]).11 The primary end point was time to last unformed stool; secondary end points were clinical well-being (lack of watery stools and soft stools in 24 hours, with no clinical symptoms besides mild gas or flatulence, or no unformed stools in 48 hours in the absence of fever, with or without clinical symptoms) and treatment failure (defined as clinical deterioration or symptom worsening despite treatment lasting at least 24 hours or continuation of symptoms

FIGURE 1. Chemical structure of rifaximin (C43H51N3O11). Reprinted from Xifaxan (rifaximin) tablets [package insert],1 with permission from Salix Pharmaceuticals, Ltd.
after treatment with the study drug for at least 5 days (120 hours) or at least 24 hours of therapy).

Rifaximin significantly reduced the time to last uniformed stool than did placebo (32.0 hours vs 65.5 hours, respectively; \( P=0.001 \)). \(^{11} \) Rifaximin was as efficacious as ciprofloxacin in reducing the time to last uniformed stool (32.0 hours vs 28.8 hours, respectively; \( P=0.35 \)). The percentage of patients who reported improvement in clinical wellness was significantly greater with rifaximin (76.6%) than with placebo (61.4%) (\( P=0.004 \)) and similar to that with ciprofloxacin (78.2%; \( P=0.74 \)). The percentage of patients who experienced treatment failure was lower with rifaximin than with placebo (14.7% vs 26.7%, respectively; \( P=0.01 \)). However, the rate of treatment failure was lower with ciprofloxacin than with rifaximin (6.9% vs 14.7%, respectively; \( P=0.05 \)). The incidence of adverse events (AEs) was similar in treatment groups, and the most common AEs with rifaximin were headache (8.0% vs 9.0% with placebo) and constipation (4.0% vs 5.0% with placebo).

Rifaximin may also have utility as travelers’ diarrhea prophylaxis for travelers to high-risk regions, \(^{12,13} \) although it is not clear which patient groups should be encouraged to use chemoprophylaxis. Travelers’ diarrhea prophylaxis could have important clinical implications, such as preventing associated long-term complications of travelers’ diarrhea (eg, postinfectious IBS). \(^{8} \)

**COMPPLICATIONS OF LIVER CIRRHOSIS**

Hepatic encephalopathy, a potentially reversible complication of cirrhosis, is associated with neuromuscular dysfunction and various neuropsychiatric symptoms. \(^{14} \) Hepatic encephalopathy is classified into several grades, from minimal (covert) to overt, according to symptom severity. \(^{15} \) Patients with minimal hepatic encephalopathy show mild cognitive impairment that is often clinically undetectable, except through specific psychometric testing. Patients with overt hepatic encephalopathy exhibit clinical symptoms, with pronounced and various degrees of alteration or impairment in cognition, behavior, personality, mood, psychomotor function, sleep patterns, and consciousness.

The pathophysiology of hepatic encephalopathy is uncertain but is believed to be multifactorial. Combined action of the accumulation of gut-derived microbial toxins, inflammation, and oxidative stress is hypothesized to cause brain alterations such as cerebral edema, which underlie the pathogenesis of hepatic encephalopathy. \(^{15-17} \) As liver disease progresses, portosystemic shunting occurs, and the liver becomes less capable of removing neurotoxins from the bloodstream, resulting in increased levels of systemic gut-derived neurotoxins, particularly ammonia. \(^{15-17} \) Treatment of hepatic encephalopathy typically involves medical stabilization of the patient and possible hospitalization in the intensive care unit, elimination of potential precipitating factors (eg, dehydration and hypokalemia), correction of glucose and electrolyte levels, and reduction in systemic levels of gut-derived neurotoxins. \(^{18,19} \)

Multiple randomized clinical trials have evaluated rifaximin for the management or prevention of hepatic encephalopathy. \(^{20} \) In a randomized, double-blind, placebo-controlled clinical trial of rifaximin, Bass et al \(^{21} \) studied adults with cirrhosis and a history of 2 or more episodes of hepatic encephalopathy in the previous 6 months who were in remission at the time of enrollment (Conn score, 0 or 1). Patients were randomized to receive rifaximin 550 mg (\( n=140 \)) or placebo (\( n=159 \)) twice daily for 6 months. \(^{21} \) The primary end point was time to the first breakthrough episode of hepatic encephalopathy (defined as an increase in Corin score to \( \geq 2 \) or, if the baseline Corin score was 0, a Corin score of 1 plus a 1-unit increase in asterixis grade).

Rifaximin 1100 mg/d significantly reduced the risk of recurrence of hepatic encephalopathy, with 31 patients (22.1%) in the rifaximin group and 73 patients (45.9%) in the placebo group experiencing a breakthrough episode of hepatic encephalopathy during the 6-month trial (hazard ratio, 0.42; 95% CI, 0.28-0.64; \( P<0.001 \)). \(^{21} \) Treating 4 patients with rifaximin for 6 months would prevent 1 episode of hepatic encephalopathy (ie, number needed to treat, \( n=4 \)). Rifaximin also decreased the risk of hepatic encephalopathy—related hospitalization than did with placebo, achieving a 50% relative risk reduction (\( P=0.01 \)); treating 9 patients with rifaximin for 6 months would prevent 1 hepatic encephalopathy—related hospitalization (ie, number needed to treat, \( n=9 \)).
9). Rates of AEs were similar between the rifaximin and placebo groups; the most common AEs reported during rifaximin treatment were peripheral edema, nausea, dizziness, and fatigue. The long-term safety of rifaximin 1100 mg/d has been supported by a 24-month open-label maintenance of hepatic encephalopathy remission study, in which AE rates did not increase in comparison with rates reported during the 6-month randomized trial.22

Rifaximin may also influence the long-term prognosis of patients with cirrhosis. In a small European case-control study, rifaximin 1200 mg/d significantly increased overall survival and the 5-year cumulative probability of remaining free of hepatic encephalopathy in patients with alcohol-related compensated cirrhosis and ascites.23

DIARRHEA-PREDOMINANT IBS

Approximately 30 to 45 million adults (~10%-15%) in North America have IBS.24,25 Although IBS may occur at any age, most adults with IBS (67.3%) are 25 to 54 years of age.26 Irritable bowel syndrome is commonly associated with abdominal pain or discomfort (eg, bloating) and altered bowel function, and symptoms may be either chronic or episodic.27,28 Altered bowel function in IBS is typically categorized as diarrhea predominant (IBS-D), constipation predominant, or mixed.27,28 The etiology of IBS is multifactorial and likely involves genetic factors and alterations in immune, motor, and sensory responses to various stimuli.8,29 Therapies for the treatment of IBS-D have historically been limited, and patients may use multiple avenues of treatment including dietary modification, psychological interventions (eg, behavior modification), over-the-counter medications, and prescription therapies.30,31

In May 2015, rifaximin was approved for the treatment of IBS-D in adults, and several studies support the efficacy and safety of rifaximin in the treatment of IBS-D.32-37 In 2 identically designed, randomized, double-blind, placebo-controlled clinical trials (TARGET 1 and 2; N=1260), adults with a diagnosis and current symptoms of IBS without constipation were randomized to receive either rifaximin 550 mg thrice daily or placebo for 14 days.33 The primary end point was adequate relief from global IBS symptoms (based on yes/no response to question for the previous 7-day period) during 2 weeks or more of the first 4 weeks posttreatment; the key secondary end point was adequate relief from IBS-related bloating (based on yes/no response to question for the previous 7-day period) during 2 weeks or more of the first 4 weeks posttreatment.

A significantly greater percentage of patients receiving rifaximin reported that their global IBS symptoms (40.7% vs 31.7% for placebo; \(P<.001\)) and IBS-associated bloating (40.2% vs 30.3% for placebo; \(P<.001\)) had been adequately relieved during the first 4 weeks posttreatment in the pooled TARGET 1 and 2 studies.35 In terms of durability of response, a significantly greater percentage of patients in the rifaximin group vs the placebo group reported adequate relief from global IBS symptoms over a 12-week period (2 weeks of treatment plus 10 weeks of posttreatment follow-up; \(P<.001\), pooled studies). During this 12-week period, a greater percentage of patients receiving rifaximin than those receiving placebo reported adequate relief from IBS-related bloating, although the difference was significant only in the TARGET 2 study (\(P=.003\)). The incidence of AEs was similar in the 2 treatment groups, with headache, upper respiratory tract infection, and abdominal pain being the most common AEs in the rifaximin group.

CROHN DISEASE

Crohn disease is a lifelong relapsing-remitting condition that is associated with chronic inflammation of 1 or more regions of the intestinal tract.38-40 Crohn disease is typically diagnosed before the age of 30 years, and symptoms include chronic diarrhea, abdominal cramping and pain, loss of appetite, weight loss, and fever.38,39 The incidence and prevalence of Crohn disease have increased during the past several decades,38-39 and the condition can lead to serious complications, including intestinal blockage, abdominal abscesses, fistulas, and anal fissures.38-40 Various pharmacologic therapies are included in the management algorithm for Crohn disease, such as anti-inflammatory, immunomodulatory, and antidiarrheal agents, as well as antibiotics.39 Surgery is commonly required in patients who develop complications.39

Although rifaximin is not approved for the treatment of Crohn disease, emerging evidence suggests that rifaximin\(^{41,42}\) or the investigational formulation of rifaximin-extended intestinal
release (EIR) may be efficacious in the treatment of Crohn disease. A randomized, double-blind, placebo-controlled clinical trial evaluated the efficacy and tolerability of rifaximin-EIR 400 mg (n=104), 800 mg (n=98), or 1200 mg (n=99) twice daily vs placebo (n=101) for 12 weeks in adults with active Crohn disease.

The primary end point was disease remission (Crohn’s Disease Activity Index [CDAI] score of <150 points at week 12); the secondary end points were clinical response (maintenance of clinical remission at weeks 14 and 24) and treatment failure (failure to reduce the CDAI score by ≥70 points from baseline after treatment for 1 month or an increase of >100 points in the CDAI score from baseline at any time).

Twelve weeks after treatment initiation, patients treated with rifaximin-EIR 800 mg twice daily were significantly more likely to achieve clinical remission of Crohn disease than patients receiving placebo (62.2% vs 42.6%; P=.005). Patients treated with rifaximin-EIR 400 or 1200 mg twice daily also reported higher rates of remission than did those treated with placebo, although the differences were not statistically significant. Patients treated with rifaximin-EIR 800 mg twice daily also reported a higher clinical response rate than did those treated with placebo (72.0% vs 56.0%; P=.02) and a lower treatment failure rate (25.5% vs 44.6%; P=.005) at the 12-week follow-up visit. Although not statistically significant compared with placebo, higher clinical response rates were also noted with rifaximin-EIR 400 and 1200 mg twice daily. Adverse events occurred at a similar rate in treatment groups, with the most common drug-related AEs being headache, symptoms of Crohn disease, and nausea.

**ONE DRUG, MULTIPLE THERAPEUTIC DOMAINS—RIFAXIMIN AS A GUT MICROENVIRONMENT MODULATOR**

Given the multiple established and potential therapeutic indications for rifaximin, it is relevant to question the possible mechanism(s) of action by which it exerts these diverse therapeutic effects. It is well established that rifaximin acts within the gastrointestinal tract, given its nonsystemic absorption. Rifaximin is also known to exert direct bactericidal and bacteriostatic effects through the inhibition of bacterial RNA synthesis. In a randomized, double-blind clinical trial of rifaximin vs ciprofloxacin for the treatment of travelers’ diarrhea, stool samples were collected for an in vitro assessment of the antimicrobial activity of rifaximin against bacterial enteropathogenic isolates (Table). Forty-four bacterial isolates were obtained from the rifaximin group, representing 3 pathogens (enterotoxigenic Escherichia coli, Salmonella, and Shigella). All 3 pathogens were susceptible to rifaximin in vitro, with minimum inhibitory concentrations of 256 μg/mL or less and an overall minimal inhibitory concentration required to inhibit growth of 90% of organisms ranging from 0.25 to 32 μg/mL, which is substantially lower than fecal concentrations reported with rifaximin (4000-8000 μg/g).

The direct antimicrobial activities of rifaximin appear to be centered on certain regions within the gastrointestinal tract. For example, in an animal model, rifaximin exposure resulted in a sustained reduction in duodenal bacterial levels but had no effect on colonic bacterial levels (Figure 2). In vitro studies suggest that the relative lack of drug effect in the colon may be related to the lower solubility of rifaximin in aqueous environments, such as that found in the colon as compared with the higher solubility of rifaximin in aqueous environments, such as those found in the small intestine.

Patients with cirrhosis have a relatively low concentration of bile acids within the small intestine; this is believed to contribute to gastrointestinal dysbiosis and chronic inflammation due to an overgrowth of pathogenic bacteria, increased endotoxin levels, and secondary stimulation of a potent inflammatory response. The low concentration of bile acids within the small intestine of patients with cirrhosis theoretically would reduce the solubility of rifaximin and thus reduce...
its direct antimicrobial effects in the small intestine. The results of several studies, however, suggest additional mechanisms of action of rifaximin that may not depend on bile acids in the small intestine. In a 2013 study of 20 patients with cirrhosis and minimal hepatic encephalopathy, open-label administration of rifaximin 550 mg twice daily for 8 weeks produced an improvement in cognitive function that was associated with a reduction in endotoxemia and a substantial increase in the relative serum levels of carbohydrate metabolites and long-chain fatty acids (which promote brain function), without any major alterations in the microbial composition of the stool. This effect may be related to a shift toward carbohydrate-using Lactobacilli in the small intestine; a recent study found that the ability of rifaximin to prevent the development of stress-induced mucosal inflammation in an animal model was associated with a relative increase in Lactobacilli in the small intestine. In an animal model of colitis, the therapeutic effect of rifaximin was associated with the inhibition of bacterial translocation across the mucosal epithelia, and this effect theoretically would inhibit the translocation of urease-producing bacteria and reduce systemic neurotoxic levels of ammonia. Collectively, these findings suggest that the clinical effects of rifaximin in hepatic encephalopathy may be exerted, in part, through a mechanism that is distinct from the direct antibacterial effects in the small intestine and might involve alterations in bacterial translocation and the release and/or absorption of endotoxin, ammonia, carbohydrate intermediates, and long-chain fatty acids.

Patients with IBS may have localized gastrointestinal factors that play a role in clinical symptoms, such as gut microbiota dysbiosis, comorbid small intestinal bacterial overgrowth, increased intestinal permeability, and/or chronic mucosal inflammation. In an animal model of inflammatory bowel disease, rifaximin produced therapeutic effects by activating the pregnane X receptor and thereby reducing levels of the proinflammatory transcription factor nuclear factor κB. Of note, allelic variants in the pregnane X receptor gene and alterations in the expression of its target genes have been associated with inflammatory bowel disease in humans. As noted above, the therapeutic effect of rifaximin in an animal model of colitis was associated with the inhibition of bacterial translocation across the mucosal epithelia. In vitro studies suggest that the inhibition of bacterial translocation is related to a reduction in bacterial attachment and internalization in epithelial cells. Indeed, rifaximin was shown to decrease bacterial adherence to epithelial cells and subsequent internalization in a bacteria- and cell type—specific manner, without an alteration in bacterial counts, but with a down-regulation in epithelial proinflammatory cytokine

![Graph showing bacterial counts in different regions of the intestine](image-url)
Thus, rifaximin may have interrelated effects on bacterial translocation and immune function that are distinct from its direct antibacterial effects and are beneficial in the treatment of IBS.

As in patients with cirrhosis and IBS, patients with Crohn disease present with gut microbiota dysbiosis and chronic mucosal inflammation, and they exhibit dysfunction of innate immunity, including immune-mediated bacterial killing. Allelic variants in genes for numerous inflammatory mediators and mediators of the innate immune response have been linked to Crohn disease and associated immune dysfunction. A double-blind, placebo-controlled clinical trial found that among patients with Crohn disease, those who had high levels of C-reactive protein (an immune mediator produced primarily in the liver and considered a marker of inflammation) were more likely to achieve disease remission after treatment with rifaximin 1600 mg/d than with placebo over 12 weeks (odds ratio, 6.0; 95% CI, 1.2-31.2; \( P < .002 \)). These findings suggest that the mechanism of action of rifaximin in the treatment of Crohn disease is not restricted to direct antimicrobial effects in the small intestine but may involve modulation of innate immunity and the inflammatory response in the gastrointestinal tract. Overall, data continue to accumulate, supporting that rifaximin has a multifaceted mechanism of action with efficacy in various gastrointestinal disorders (Figure 4).
CONCLUSION
Mechanistic data continue to emerge to help explain the efficacy of rifaximin in various gastrointestinal disorders, including travelers’ diarrhea, hepatic encephalopathy, and other complications of cirrhosis, IBS-D, and Crohn disease. First, rifaximin clearly has direct antimicrobial effects that are exerted primarily within the small intestine. Second, rifaximin may reduce bacterial virulence and pathogenicity by inhibiting bacterial translocation across the gut mucosal epithelia, which may then reduce the release and/or absorption of endotoxin and bacterial metabolites, stabilize the gut mucosa, and render the mucosa resistant to bacterial inflammation. Third, rifaximin may modulate gut-immune signaling, perhaps via alterations in gene transcription that reduce or reverse levels of proinflammatory immune mediators and the chronic proinflammatory response associated with many gastrointestinal diseases. For a given disease state, rifaximin may act through 1 or more of these mechanisms of action to exert its therapeutic effects, and therefore rifaximin may be best described as a gut microenvironment modulator with cytoprotection properties. However, further research is needed to determine whether these various proposed mechanisms of action play a direct role in observed clinical outcomes.

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Abbreviations and Acronyms: AE = adverse event; CDAI = Crohn’s Disease Activity Index; EIR = extended intestinal release; IBS = irritable bowel syndrome; IBS-D = diarrhea-predominant irritable bowel syndrome

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