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REVIEW

Use of rifaximin in gastrointestinal and liver diseases

Rani H Shayto, Rachel Abou Mrad, Ala I Sharara

Rani H Shayto, Rachel Abou Mrad, Ala I Sharara, Division of Gastroenterology, Department of Internal Medicine, American University of Beirut Medical Center, Beirut 11-0236, Lebanon

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Correspondence to: Ala I Sharara, MD, FACG, AGAF, Professor, Head, Division of Gastroenterology, Department of Internal Medicine, American University of Beirut Medical Center, Cairo Street, Beirut 11-0236, Lebanon. ala.sharara@aub.edu.lb
Telephone: +961-1-350000-5351
Fax: +961-1-366098

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Abstract

Rifaximin is a broad spectrum oral antibiotic with antimicrobial activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria. It is poorly absorbed and thus has a highly favorable safety profile. Rifaximin has been shown to be effective in the treatment of traveler's diarrhea, functional bloating and irritable bowel syndrome, small bowel bacterial overgrowth and in the prevention of recurrent overt hepatic encephalopathy. In addition, there is emerging evidence for a possible beneficial effect of rifaximin in the treatment of uncomplicated diverticular disease and in the prevention of recurrent diverticulitis. The use of rifaximin is associated with a low incidence of development, or persistence of spontaneous bacterial mutants. Moreover, the development of important drug resistance among extra-intestinal flora during rifaximin therapy is unlikely because of minimal systemic absorption and limited cross-resistance of rifaximin with other antimicrobials. This review addresses the current and emerging role of rifaximin in the treatment of gastrointestinal and liver disorders.

Key words: Irritable bowel syndrome; Inflammatory bowel disease; Hepatic encephalopathy; Bacterial overgrowth; Diverticular disease

Core tip: Rifaximin is a poorly absorbed oral antibiotic with highly favorable safety profile. Rifaximin is effective in the treatment of traveler's diarrhea, functional bloating and irritable bowel syndrome, small bowel bacterial overgrowth and in the prevention of recurrent overt hepatic encephalopathy. There is emerging evidence for a possible beneficial effect of rifaximin in the treatment of other disorders including uncomplicated diverticular disease and in the prevention of recurrent diverticulitis. The use of rifaximin is associated with a low incidence of development of spontaneous bacterial mutants or drug resistance among extra-intestinal flora.

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INTRODUCTION

Rifaximin is a poorly-absorbed broad spectrum oral antibiotic, first approved in Italy in 1987 and in the United States in 2004, and now approved in many European, African, and Asian countries for several indications[1,2]. Rifaximin is a rifamycin antimicrobial agent, a rifampin structural analog[3], that inhibits RNA synthesis by binding to the β-subunit of bacterial DNA-dependent RNA polymerase[4]. The addition of a pyridoimidazole ring to the rifampin molecule (Figure 1) makes rifaximin a largely water-insoluble, poorly-absorbable antibiotic[2] (< 0.4%)[5] and hence associated with few systemic adverse events and with a safety profile that is comparable to placebo[6].

Although its poor gastrointestinal (GI) absorbability leads to low systemic blood levels, fecal concentrations remain elevated with unchanged drug[3,7]. Rifaximin does not cause drug-drug interaction and does not alter intestinal or hepatic cytochrome P3A activity[8].

Rifaximin has *in vitro* antimicrobial activity against Gram-positive and Gram-negative, aerobic and anaerobic flora[9]. The increased solubility of rifaximin in bile (an estimated 70- to 120-fold increase in solubility *in vitro* compared to aqueous solution)[3] leads to higher luminal concentrations and enhanced antimicrobial effects[10] against enteric bacteria, with possibly larger effects in the small intestine compared with the more aqueous colon[3] as well as low microbial resistance[11] with minimal effect on colonic microflora. In addition to its direct bactericidal effect, rifaximin has been shown to reduce bacterial virulence factors and morphology[12], the inflammatory response expected from virulent strains of enteroaggregative *Escherichia coli* (*E. coli*) (EAEC) and Shigella, bacterial epithelial attachment and plasmid transfer from donor to recipient strains by > 99% for bacteria resistant or susceptible to rifaximin[12], and to provide cytoprotection through altering cytokine expression and mucosal inflammation by activation of pregnane X receptor involved in detoxification and elimination of foreign chemicals and toxins in the gut in disease states[12,13].

CLINICAL EFFICACY

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a gastrointestinal syndrome characterized by chronic abdominal pain and altered bowel habits without any underlying organic pathology, diagnosed according to the revised ROME criteria[14]. IBS occurs in 5% of the general population[15] and is associated with a high socioeconomic burden

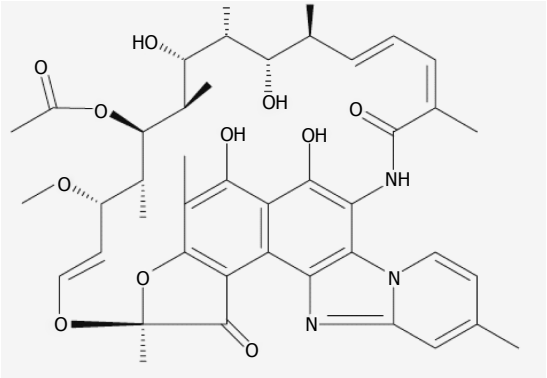

Figure 1 Chemical structure of rifaximin.

by decreasing quality of life, work productivity[16-18], and increasing heath resource utilization[19,20]. Patients with IBS are subdivided on the basis of their bowel symptoms into 4 subgroups: IBS with constipation, IBS with diarrhea (IBS-D), alternating or mixed IBS, and un-subtyped IBS, with up to 40% suffering from the IBS-D form[21]. Though the pathophysiology of this entity remains incompletely defined, multiple factors including abnormal gastrointestinal motility[22-27], visceral hypersensitivity[28-40], food sensitivity[41-56], genetic[57-61] and psychosocial factors[62-70], intestinal inflammation[71-78], post infectious[79-83] and bacterial overgrowth are postulated to contribute to the disease. Furthermore, emerging data suggest that the fecal microbiota in individuals with IBS differ from healthy controls and varies with the predominant symptom[84-89].

IBS management has been primarily focused on symptomatic treatment until data revealed that patients suffering from IBS might have alterations in their gastrointestinal flora, manifested by excessive bacteria in the small bowel, known as bacterial overgrowth. As a result, the use of rifaximin as a potential therapeutic agent for the treatment of IBS has been increasingly investigated. In a randomized double-blind placebo-controlled trial by Sharara *et al*[90] in 124 patients with functional bloating, rifaximin 800 mg/d was found to be superior to placebo in providing global symptomatic relief (41.3% *vs* 22.9% respectively, $P = 0.03$). None of the study patients had an abnormal lactulose hydrogen breath test (LHBT) at baseline. However, hydrogen breath excretion dropped significantly among rifaximin responders and correlated with improvement in bloating and overall symptom scores. Another randomized placebo-controlled study evaluated the effect of rifaximin 1200 mg/d or placebo for 10 d in 87 patients with IBS[91]. By the end of the follow-up period of 10 wk, patients treated with rifaximin reported significantly greater global improvement compared with the placebo group ($P = 0.02$), with an average improvement of 36.4% in the rifaximin group compared to 21.0% in the placebo group[91]. In addition, there was a significant improvement in bloating with rifaximin

while abdominal pain, diarrhea and constipation did not significantly change compared to placebo. The TARGET study group presented data from two identically designed Phase Ⅲ double-blind, placebo-controlled clinical trials (TARGET 1 and TARGET 2) in non-constipated IBS patients showing that rifaximin 550 mg three times daily for 14 d relieved global IBS symptoms and bloating for at least two of the first four weeks of treatment, and improved daily assessments of IBS symptoms, bloating, abdominal pain, and stool consistency compared with placebo[92]. A recent phase 3 trial (TARGET 3) investigating treatment of symptom recurrence in patients with diarrhea predominant IBS (D-IBS) who had previously taken rifaximin demonstrated a significantly higher success rate of recurrence treatment when compared to placebo (33% *vs* 25%, $P = 0.02$)[93]. Rifaximin has since received recent FDA approval for use in adults with IBS-D.

Meyrat *et al*[94] investigated the prevalence of abnormal LHBT and the efficacy of rifaximin in patients suffering from IBS. Of the 150 patients enrolled, 71% had positive LHBT results and were treated with rifaximin 800 mg daily for two weeks. All symptoms under investigation (bloating, flatulence, diarrhea, and abdominal pain) as well as reduced overall well-being, significantly improved upon re-assessment after 1 mo and 3 mo of therapy initiation. A meta-analysis and systematic review by Menees *et al*[95] found that rifaximin is more effective than placebo for global IBS symptom improvement (OR = 1.57; 95%CI: 1.22-2.01) with a number needed to treat (NNT) of 10.2[95]. Rifaximin was also significantly more likely to improve bloating than placebo (OR = 1.55; 95%CI: 1.23-1.96). Although LHBT normalization has been correlated with clinical improvement[96], there are limited data investigating the changes in LHBT during and after treatment of IBS with rifaximin. A recent retrospective study investigated the association of rifaximin therapy and LHBT changes in non-constipated IBS patients who had normalized their LHBT values after treatment. Patients suffering from IBS symptoms had similar LHBT values prior to therapy and had received rifaximin 1200 mg daily for treatment periods of 4 wk, 8 wk or 12 wk. LHBT values were statistically significant in the three treatment groups, with higher values occurring in patients who received longer treatment periods. Symptomatic improvement to rifaximin was also demonstrated to occur prior to normalization of LHBT values and mostly occurring after 4 wk of treatment[97]. Although this study demonstrated that patients with higher LHBT values take longer time to normalize their values, LHBT gas levels were not associated global abdominal symptoms, findings that are contradictory to other studies[98-100]. In view of increasing evidence of the relationship of small intestinal bacterial overgrowth (SIBO) and IBS pathophysiology, identifying SIBO in IBS patients may prove beneficial for optimal treatment options. While LHBT is often used, data show that its diagnostic accuracy is inferior to glucose breath testing (GBT) (55.1% *vs* 71.7%), suggesting a need to switch to the more accurate GBT in future clinical trials assessing for bacterial overgrowth in IBS patients[101].

Traveler's diarrhea

Traveler's diarrhea (TD) is a common illness among travelers from resource-rich to resource-poor regions of the world. Diarrhea can be caused by a variety of bacterial, viral, and parasitic organisms, which are most often transmitted by contaminated food and water. Bacteria cause more than 90% of TD cases in most geographic areas, the most common organism being enterotoxigenic *E. coli* (ETEC)[102-104] accounting for 40% of cases, followed by enteroadhesive *E. coli* in 10%-20% of cases.

Rifaximin was tested in randomized controlled trials as treatment of TD and found to shorten the duration of the illness[105,106]. In a randomized controlled trial comparing 3 d of ciprofloxacin to rifaximin for TD, there was no significant difference in the 2 groups with respect to clinical improvement during the first 24 h, failure to respond to treatment, or microbiological cure. Compared to placebo, rifaximin resulted in significant reduction in the median time to last unformed stool over placebo (32.0 h *vs* 65.5 h respectively ($P < 0.001$) with no associated adverse events[107]. Rifaximin is routinely given for TD as 400mg twice a day for three days, and may be used as a self-treatment for TD as stated by the International Society of Travel Medicine[108]. With a lesser degree of efficacy, rifaximin can also be used for the prevention of TD[109]. Several trials have assessed the efficacy of rifaximin in preventing traveler's diarrhea in different geographical areas using different dosing regimens. In a randomized-double blinded placebo controlled trial aimed at assessing the efficacy of TD prevention in a United States military airbase in Turkey, Armstrong *et al*[110] concluded that rifaximin 1100 mg once daily for two weeks was not different from placebo although the *P* value of 0.07 neared statistical significance. An estimated protective efficacy of 67% was demonstrated[110]. In 2011, Flores *et al*[111] similarly showed the lack of a statistically significant reduction in TD when 550 mg rifaximin was administered once daily for two weeks in Mexico. However, a noticeable reduction in mild diarrhea during the first week of therapy and comparable side effect profiles to 200 mg taken twice daily were demonstrated[111]. A placebo-controlled trial by Martinez-Sandoval *et al*[112] in United States travelers to Mexico found that rifaximin provided a 58% protection rate over placebo against TD. Fewer individuals on rifaximin developed all-cause TD compared to placebo (20% *vs* 48%, respectively; $P < 0.0001$) or required antibiotic therapy for TD (14% *vs* 32%, respectively; $P = 0.003$). Adverse events in the rifaximin group were fewer than placebo. A study by Zanger *et al*[109] in 2003 investigating the preventive

efficacy of TD in individuals travelling to South and Southeast Asia showed that travelers consuming rifaximin 200 mg twice daily for a travel duration of 28 d had a reduced risk of TD during and post travel period when compared to placebo. A 48% protection was noted, lowering the incidence of TD from 1.99 (1.5-2.64) per 100 person-days to 1.04 (0.72-1.48) (incidence rate ratio of 0.52, 95%CI: 0.32-0.84 P = 0.005). However, similar incidences of TD between the rifaximin and placebo arms were noted 1 wk after return from travel[109]. Although this study demonstrated some degree of protective efficacy, it is speculated that the low 48% protective efficacy may be due to the low incidence of enteroinvasive pathogens and a 2-4 time higher *Caympylobacter spp* incidence causing TD in the South and Southeast Asia area[109].

Small intestinal bacterial overgrowth

Small intestinal bacterial overgrowth (SIBO) is characterized by an increase of overall bacterial burden and emergence of different species of enterobacteria, *bacteroides*, *clostridia*, and *fusobacteria* in the small intestine. Rifaximin has been shown to normalize the hydrogen breath test and improve symptoms of SIBO[113-115]. High doses of rifaximin (1200 or 1600 mg/d) lead to a significant improvement in terms of therapeutic efficacy and SIBO eradication without increasing the incidence of side effects[116,117]. A recent study by Zhang *et al*[118] on cirrhotic patients showed that rifaximin 200 mg TID for a week was effective in reducing SIBO events in parallel with minimal hepatic encephalopathy. Patient blood ammonium levels were also significantly reduced (56.1 to 39.1 μmol/L, P < 0.01) along with psychometric tests. A recent small open-label study on SIBO subjects with no IBS showed LHBT normalization in only 42.1% of participants and concluded that rifaximin was not effective in normalizing LHBT in that patient category[119].

Hepatic encephalopathy

Hepatic encephalopathy (HE) is a reversible syndrome of impaired brain function occurring in patients with advanced liver failure. Patients with overt hepatic encephalopathy have clinically apparent impairments in cognitive and neuromuscular function. The pathophysiology of HE is multifactorial but ammonia is the most implicated and best characterized neurotoxin that may precipitate HE. The gastrointestinal flora, mainly the urease-producing species, is an important source of ammonia, which enters the circulation via the portal vein. Normally, the liver clears most of the ammonia but in liver cirrhosis the impaired liver function leads to accumulation of ammonia in the circulation, which is also worsened by shunting of blood around the liver via dilated collaterals. Furthermore, muscle wasting may also contribute since muscle is an important site of extrahepatic ammonia removal.

Current AASLD/EASL guidelines continue to recommend lactulose as the first line therapy for OHE (Grade II-1, B1) and only suggest rifaximin as an add-on therapy for the prevention of OHE recurrence (Grade I-A, 1)[120] (see below). Data is insufficient regarding the use of rifaximin as a first line therapy for the treatment of OHE, and there are no recommendations regarding rifaximin use as a standalone therapeutic agent for the treatment of OHE[120]. Rifaximin may be used in combination with lactulose in patients with overt HE as the combined effect leads to reversal of the condition in 76% of patients *vs* 50.4% in those on lactulose alone[121]. Similar results were reached in another study[122].

Prevention of overt HE

A randomized, double blinded, placebo controlled trial in 299 patients with chronic liver disease in remission from recurrent HE compared 550 mg rifaximin twice daily to placebo over a period of 6 mo. Rifaximin significantly reduced the risk of OHE compared to placebo with a hazard ratio of 0.42 (95%CI:, 0.28-0.64, P < 0.001) and a relative risk reduction of 58% of breakthrough HE (22.1% in rifaximin users *vs* 45.9% in the placebo arm) with a NNT over 6 mo of 4. There was also a reduction in HE associated hospitalizations (13.6% *vs* 22.6% placebo) with a HR of 0.50 (95%CI:, 0.29-0.87, P = 0.01). It is important to note that more than 90% of patients in this study received concomitant lactulose, thus providing evidence of the superiority of rifaximin and lactulose *vs* lactulose monotherapy[123]. Rifaximin significantly improved health related quality of life (HRQOL) in patients with cirrhosis and recurrent HE[123,124].

The previous trial was followed by a 24 mo phase 3, open-label maintenance (OLM) study to assess the safety and rate of hospitalization with long-term rifaximin use[125]. Data were analyzed according to all patients who had received rifaximin in both studies (all-rifaximin arm n = 392), to patients who received placebo in the RCT (n = 82), patients who had been treated with rifaximin in the RCT (n = 70) and to patients who only participated in the OLM (n = 170). Patients receiving rifaximin demonstrated a lower rate of all-cause hospitalizations [0.45 events per person-exposure years [PYE)] compared to the placebo arm in the RCT (1.31 PYE). In addition, HE related hospitalizations in the all-rifaximin arm (0.21 PYE), OLM only-rifaximin arm (0.23 PYE) and RCT rifaximin arm (0.30 PYE) were similar and lower than the RCT placebo arm (0.72 PYE, P < 0.0001) Long-term rifaximin use (≥ 24 mo) was associated with a significant reduction in rates of hospitalization for any cause (0.45 events PYE with rifaximin *vs* 1.31 with placebo; P < 0.0001) and rates of HE-related hospitalizations (0.21 *vs* 0.72, P < 0.0001). All-rifaximin group had a lower AE rate (0.71 *vs* 2.76), lower drug-related AE rate (0.11 *vs* 0.74), lower

severe AE rate (0.48 *vs* 1.37), and lower rate of discontinuations caused by AEs (0.25 *vs* 0.98) when compared to the RCT's placebo arm. The all-rifaximin group was not associated with increased mortality rates (0.15) compared to RCT's placebo group (0.24)[125]. Again, concomitant lactulose use was standard with 89.8% of the all-rifaximin group receiving lactulose and only 10.2% receiving only rifaximin. A recent analysis of the above placebo group (n = 82) was done to better clarify the impact of crossing over from placebo to rifaximin 550 mg twice daily on breakthrough HE and hospitalization rates[126]. Significantly lower rates of HE were noted in the first 6 mo of rifaximin use compared to placebo with an estimated 79% reduction in the risk of breakthrough HE episodes and a NNT of 3[126]. However, no statistically significant reduction was observed between the two groups in HE related or all-cause hospitalization. Most common adverse events (AE), severe AEs and infection-related AEs were also similar[126].

Minimal hepatic encephalopathy

Minimal hepatic encephalopathy is a subtle subclinical form of HE with only mild cognitive and psychomotor impairment[127] without disorientation, asterixis, or other signs and symptoms of overt hepatic encephalopathy[120]. Minimal hepatic encephalopathy (MHE) occurs in up to 50% of patients with chronic liver disease and may predict the future development of OHE[120]. There are no current gold standards for diagnosing MHE and data concerning the role of rifaximin in the treatment or prevention of MHE are limited. Current AASLD/EASL guidelines do not routinely recommend treatment of MHE or Covert Hepatic Encephalopathy (CHE) with exceptions made on a case by case basis using approved treatments for OHE (Grade II-2, B,1)[120]. A RCT by Sharma *et al*[127] investigated the prevalence of MHE and the effect of rifaximin along with other routinely used drugs in reversing MHE compared to placebo. One hundred twenty four patients were enrolled, 31 of which received rifaximin 400 mg three times daily for 2 mo and were compared to participants receiving L-ornithine-L-aspartate (LOLA), Cap Velgut, and placebo. Critical Flicker Frequency (CFF) improved significantly with rifaximin, LOLA, and Cap Velgut compared to placebo with no significant difference in the improvement effect between the 3 drugs. This study suggests a beneficial role of drug therapy, including rifaximin, for the improvement of MHE as measured by CCF and neuropsychometric tests; however more studies with larger sample sizes are required to corroborate these results[127]. The RiMINI trial is a recently initiated RCT aimed at investigating the efficacy of standalone rifaximin (550 mg twice daily) *vs* rifaximin + lactulose (30-60 mL) for 3 mo on the improvement of MHE through neuropsychometric and neurophysiological changes in 60 patients suffering from liver cirrhosis and MHE[128].

Diverticular disease

Diverticular disease of the colon is very common in Western countries and contributes significantly to healthcare costs. Its prevalence is age-dependent, increasing from less than 20% at age 40 to 60% by age 60[129,130]. Most patients remain asymptomatic during their whole life. Diverticulitis, defined as inflammation/infection of the colonic diverticula, occurs in around 10% to 25% of people with diverticula[131] although this number has been more recently challenged by retrospective and prospective studies suggesting an incidence closer to 4%-5%[132,133].

The pathophysiology of colonic diverticulosis and the mechanism(s) leading to diverticulitis is(are) not clearly defined. It has been suggested that colonic diverticular disease may be related in part to a colonic microflora disorder[134]. This is supported by limited data showing differences in microflora composition between high and low risk populations[135,136]. Few randomized controlled trials have assessed the efficacy of rifaximin in the treatment of symptomatic uncomplicated diverticular disease and in the prevention of recurrence of diverticulitis. A meta-analysis by Bianchi *et al*[137] examined 4 prospective randomized trials involving 1660 patients that examined the long-term efficacy administration of rifaximin plus fiber supplementation *vs* fiber supplementation alone on symptoms and complications in patients with symptomatic uncomplicated diverticular disease. The pooled rate difference for symptom relief was 29.0% (rifaximin *vs* control; 95%CI: 24.5%-33.6%; P < 0.0001; NNT = 3) and the pooled rate difference for complications was -1.7% in favor of rifaximin (95%CI: -3.2% to -0.1%; P = 0.03; NNT = 59). When considering only acute diverticulitis as complication, the pooled rate difference in the rifaximin group was -2% (95%CI: -3.4% to -0.6%; P = 0.0057; NNT = 50).

Recently, Lanas *et al*[138] conducted a multicenter randomized open controlled study in patients with a recent episode of colonic diverticulitis, currently in remission. Patients received 3.5 g of high-fiber supplementation twice daily with or without one week per month of rifaximin (400 mg twice daily) for 12 mo. The primary endpoint was recurrence of diverticulitis. The study was underpowered and was interrupted after enrolling 165 patients because of inability to meet the anticipated recruitment target. Recurrences occurred in 10.4% of patients given rifaximin plus fiber *vs* 19.3% of patients receiving fiber alone[138]. Logistic regression adjusted for confounders showed a significant treatment effect (OR = 3.20; 95%CI: 1.16-8.82; P = 0.025). Patients with diverticulitis diagnosed greater than one year before and receiving rifaximin had a lower incidence of recurrences. There is some evidence to suggest that the combination of rifaximin with mesalamine is superior to rifaximin alone

for improving severity of symptoms, bowel habits, and preventing recurrent diverticulitis[139].

Inflammatory bowel disease

The pathogenesis of inflammatory bowel disease (IBD) remains poorly understood. It is hypothesized that the gut microflora plays a role in the initiation and/or perpetuation of the process[140,141]. Antibiotics have a well-established role in the treatment of septic complications of IBD. Their benefit in the primary treatment of IBD is not well elucidated, however they are still commonly used in practice. Several trials have been carried out with metronidazole, ciprofloxacin, clofazimine, and other combinations. They appear to be useful in the treatment of Crohn's disease (CD)[142-144], ulcerative colitis (UC)[145] and pouchitis; however, prolonged use of these antibiotics is associated with various systemic side effects. Based on observational data, rifaximin was associated with some improvement in IBD. Rifaximin reduces development and to promote healing of colitis in mice by reducing bacterial translocation[146]. Rifaximin may improve the existing dysbiosis in patients with CD by modulating colonic microbiota and increasing *Bifidobacteria* and *Faecalbacterium prausnitzii*[147]. Rifaximin may also exert anti-inflammatory activities by increasing expression of pregnane-X-receptor and antagonizing the effects of tumor necrosis factor-alpha (TNF-α) on epithelial cells *in vitro*[148,149].

CD

Due to its antibacterial and anti-inflammatory properties, rifaximin was assessed in the treatment of active CD. In an open-label trial, 29 patients with active CD received 200 mg of rifaximin TID for 16 weeks. Rifaximin reduced the CD activity index (CDAI) score by more than 40% and induced remission in 59% of cases[150]. Rifaximin, as adjunctive therapy for CD, was also shown to induce remission in up to 70% of cases[151]. These observational data were followed by controlled studies to investigate the role rifaximin in IBD. In a multicenter placebo controlled trial, 83 patients with mild-to-moderate CD were randomized to receive rifaximin 800 mg BID or placebo for 12 wk. Rifaximin for 12 wk was superior to placebo and induced clinical remission in 52% of cases compared with 33% in the placebo group[152]. More recently, a multicenter randomized trial compared patients with moderately active CD who received extended intestinal release rifaximin (EIR) to those given placebo. By 12 weeks of treatment, 62% of patients who received 800 mg of rifaximin-EIR were in remission compared to 43% of patients who received placebo (P = 0.005). After the follow-up period of 12 wk, this difference was maintained (45% in the rifaximin-EIR and 29% in the placebo group, P = 0.02)[153]. Despite the above clinical evidence, the role of rifaximin in CD is unclear. It is important to note that most studies did not provide information on inflammatory markers such as CRP or fecal calprotectin, or on endoscopic mucosal healing.

UC

The efficacy of rifaximin was assessed in a small group of patients with mild-to-moderate clinical flare of UC who were intolerant to steroids. Following the addition of rifaximin at a dose of 400 mg twice a day for 4 wk, clinical remission was achieved in two thirds of cases[154]. Gionchetti *et al*[155] randomized 28 patients with steroid refractory UC to rifaximin 400 mg BID or placebo for 10 d. In the treatment group, 64.3% of patients had clinical improvement with significant reduction in stool frequency (P < 0.02), rectal bleeding (P < 0.05) and sigmoidoscopic score (P < 0.05) compared with placebo.

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the preferred surgical treatment for patients with medically refractory UC. The most common long-term complication after this type of surgery is pouchitis characterized by an increased number of loose bowel movements, urgency, and abdominal cramping. Patients often develop an antibiotic-dependent form of pouchitis requiring long-term antibiotic therapy for maintenance of remission. The role of rifaximin for maintenance therapy of antibiotic-dependent pouchitis was assessed in 51 patients after IPAA for ulcerative colitis. Patients received a 2-wk course of various antibiotics for induction of remission. Patients in remission then began maintenance therapy with rifaximin 200 mg/d (to 1800 mg/d) for up to 24 mo. At 3 mo, remission was maintained in 65% of patients; 79% of these patients were still in remission at 6 mo, 58% at 12 mo and 6% at 24 mo[156].

Primary prophylaxis of spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis (SBP) is defined as an ascitic fluid infection without an evident intra-abdominal surgically-treatable source[157]. It is a complication of advanced liver disease occurring in as many as 25% of cirrhotic patients[158]. One of the early steps in the development of SBP is a disturbance in gut flora with overgrowth and translocation of a specific organism, most commonly *E. coli*[159,160]. Cirrhosis predisposes to the development of bacterial overgrowth possibly because of altered small intestinal motility[161] and increased intestinal permeability[162]. Rifaximin could theoretically prevent SBP in patients with liver cirrhosis by reducing gut bacteria. One retrospective study on 404 patients with liver cirrhosis and large ascites classified patients into two groups based on the use of rifaximin. Patients who were on any other antibiotic prophylaxis for SBP and those who had an episode of SBP prior to the use of rifaximin were excluded. The median follow-up time was 4.2 mo. During this time period, 89% of patients on rifaximin remained SBP-free compared with 68% of

those not on rifaximin (P = 0.002)[163]. Similar results were obtained in patients with HE taking rifaximin over a 6-mo period where it resulted in a more effective prophylaxis of SBP compared to norfloxacin[164]. Nonetheless, in a recent prospective study on a heterogeneous population of 152 liver cirrhosis patients, rifaximin pre-treatment did not reduce the chance of occurrence of SBP[165]. Whether rifaximin is appropriate for long-term primary prophylaxis of SBP in cirrhotic patients with ascites remains unclear.

Rifaximin may exert a positive effect on portal hemodynamics in patients with liver cirrhosis and portal hypertension, by correcting bacterial translocation and endotoxemia. Vlachogiannakos *et al*[166] have shown that the use of rifaximin for 4 wk in patients with decompensated alcoholic liver disease (ALD) leads to a significant decrease in hepatic venous pressure gradient (HVPG) correlating with reduction of plasma endotoxin levels. The same group of investigators studied the effect of long-term rifaximin administration in decompensated ALD patients who had shown a hemodynamic response to rifaximin and compared them to matched controls. Patients who received rifaximin had a significant lower risk of developing variceal bleeding (35% *vs* 59.5%, P = 0.01), HE (31.5% *vs* 47%, P = 0.03), SBP (4.5% *vs* 46%, P = 0.03), and hepatorenal syndrome (4.5% *vs* 51%, P = 0.04) than controls[167]. The five-year cumulative probability of survival was significantly higher in patients receiving rifaximin than controls (61% *vs* 13.5%, P = 0.01).

Clostridium difficile infection

Clostridium difficile (*C. difficile*) infection (CDI) is one of the most common healthcare-associated infections and causes significant morbidity and mortality especially among elderly hospitalized patients[168]. *C. difficile* is the causative organism of antibiotic-associated pseudomembranous colitis. Metronidazole and vancomycin are currently the standard of care of CDI; their dose and route of administration depends on the severity of the disease[169]. Small clinical trials have tested rifaximin in the treatment of CDI. One randomized study OF 20 patients who received rifaximin 600 mg/d or vancomycin 1 g/d for 10 d demonstrated that rifaximin is as effective as vancomycin for resolving diarrhea[170]. In another open-label trial, rifaximin 1200 mg/d for 10 d demonstrated a favorable safety profile and was an effective initial therapy for CDI in hospitalized patients. Furthermore, the success rate in this study (86%) was similar to rates reported in studies of vancomycin and metronidazole[171].

Small case series have suggested that sequential therapy with vancomycin followed by rifaximin may be effective for the prevention of recurrence of CDI[172,173]. More recently, one retrospective analysis reviewed 32 cases of recurrent CDI treated with rifaximin, after a course of metronidazole or vancomycin. A 2-wk course of rifaximin (400 mg twice daily) was found to be beneficial for patients with recurrent CDI, with 17 of the 32 patients (53%) responding favorably[174]. Rifaximin may be effective in breaking the cycle of predictable recurrences following other regimens used to treat CDI[172]. It has an excellent safety profile and has not been shown to be associated with the emergence of resistant strains of *C. difficile*[175].

DEVELOPMENT OF RESISTANCE

In a placebo controlled trial evaluating the development of resistant coliform bacterial strains following short term rifaximin use (200 mg three times daily *vs* 600 mg three times daily *vs* placebo) for 3 d, there was no change in the minimum inhibitory concentration required to inhibit growth of 90% of organisms (MIC_{90}) between pre (day 0) and post treatment (day 3 and 5) stool samples, indicating no significant changes in susceptibility in patients treated with rifaximin on a short term basis[176]. As member of the rifamycin family of drugs, chronic use of rifaximin may be associated with selection of highly resistant and stable bacterial mutants in the intestine, primarily due to genetic alteration in bacterial DNA dependent RNA polymerase. Rifaximin shows a lower degree of resistance compared to rifampin possibly because of high gut concentrations and extremely low systemic absorption[12]. High-dose exposure to rifaximin, 8 x the minimum inhibitory concentration (MIC) resulted in low incidence of spontaneous resistant mutations amongst the different strains of aerobic and anaerobic gram positive and gram negative bacteria, ranging from 1×10^{-9} to 1.7×10^{-7}[177].

The effect of intermittent high-dose rifaximin (1800 mg daily in 3 treatment periods of 10 d, each followed by 25 d of washout) on enteric bacteria (enterococci, coliforms, lactobacilli, *bifidobacteria*, *Bacteroides* spp., and *Clostridium perfringens*) was studied in patients with ulcerative colitis[178]. After each washout period, concentrations of the bacteria tested returned to initial values, suggesting that the administration of high doses of rifaximin does not significantly modify the colonic microflora. Rifaximin-resistant isolates were found, mostly in *Bifidobacteria* and have documented rapid disappearance of bacteria resistant to rifaximin from the intestinal tract upon treatment washout[179].

Real life data are also available from studies on susceptibility alterations of bacterial isolates causing TD from different geographic locations and over time[180,181]. Bacterial isolates from individuals with TD while visiting India, Mexico, Jamaica or Kenya in 1997 were challenged against different antimicrobial agents, of which rifaximin demonstrated an intermediate activity with MIC_{50} of 16 μg/mL and MIC_{90} of 32 mg/L[180]. Around 10 years later, reevaluation of susceptibility changes in Mexico, India and Guatemala between 2006 and 2008 demonstrated no change in the MIC of

Table 1 Proposed treatment regimen(s) with rifaximin by indication

Disorder	Evidence of beneficial effect	Recommended regimen	Ref.
IBS	Randomized controlled multicenter studies show improvement in global IBS symptoms	400-550 mg three times daily for 2 wk May require intermittent retreatment	[87,88]
Treatment of TD	Randomized controlled trials show reduced duration of the illness	200 mg three times daily for 3 d	[94,95]
Prevention of TD	Randomized controlled trials in patients traveling to south and southeast Asia; and Mexico	200 mg twice daily or 600 mg daily while in high risk area	[97,98]
SIBO	Rifaximin normalizes the hydrogen breath test and improves symptoms	400 mg three times daily for 2 wk May require retreatment	[99-101]
Hepatic encephalopathy	Randomized controlled trials, proved efficacy and safety	550 mg 2 or 3 times daily chronically	[104-106]
Diverticular disease	Randomized controlled trials showed that rifaximin improves symptoms and prevents recurrence	400 mg twice daily for 7 d every month	[110-115]
IBD and pouchitis	Observational data and small pilot studies	400-800 mg twice daily for 12 wk	[125-129]
SBP prophylaxis	Retrospective study	May require retreatment or intermittent treatment 400 mg three times daily chronically	[136]
Recurrent *Clostridium difficile* infection	Small case series and retrospective studies	400 mg twice daily for 2 wk	[140-142]

IBS: Irritable bowel syndrome; TD: Traveler's diarrhea; SIBO: Small intestinal bacterial overgrowth; IBD: Inflammatory bowel disease; SBP: Spontaneous bacterial peritonitis.

isolates to rifaximin while other antimicrobial agents (*e.g.*, fluoroquinolones, cephalosporins, azithromycin) had a significant increase in their MIC levels compared to bacterial isolates from a decade earlier[181].

Based on the above, rifaximin use appears to be associated with a low incidence of development or persistence of spontaneous bacterial mutants. Moreover, the development of important drug resistance among extra-intestinal flora during rifaximin therapy is unlikely because of minimal systemic absorption and limited cross-resistance of rifaximin with other antimicrobials.

CONCLUSION

Rifaximin is a broad spectrum poorly absorbed oral antibiotic with proven efficacy in a number of gastrointestinal and liver conditions (Table 1). In addition, there is emerging evidence for a possible beneficial role of rifaximin in other conditions such as diverticular disease, decompensated cirrhosis, inflammatory bowel disease and *C. difficile* infection. The extremely low systemic absorption, excellent safety profile, and limited cross-resistance are distinct advantages of this drug. Appropriate dosing for the proper indication is important to improve outcomes and limit potential for abuse and development of resistance.

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