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Mini Review

Long-term Use of Rifaximin in Cirrhotic Patients with Hepatic Encephalopathy: A Mini Review

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Abstract

Hepatic encephalopathy (HE) is a brain disorder secondary to cirrhosis, characterized by cognitive deficits, psychiatric manifestations, and motor impairments. It is associated with frequent hospitalizations, high mortality rates, and poor quality of life in cirrhotic patients. Additionally, ammonia and inflammation are key contributors to the onset of HE. Rifaximin is minimally absorbed in the intestine and is considered a locally acting, semi-synthetic antibiotic with broad-spectrum antibacterial activity. The pharmacological effects of rifaximin include reducing plasma ammonia levels, decreasing proinflammatory cytokine levels, and modulating gut microbiota and their functions. Currently, both Chinese and EASL clinical practice guidelines recommend rifaximin (800–1,200 mg/d) as a first-line treatment for HE for up to six months. However, the efficacy and safety of long-term (≥six months) use of rifaximin for HE remain debated. This review aimed to analyze the long-term (≥six months) use and dose-effect relationships of rifaximin treatment for HE. Long-term, low-dose use of rifaximin (600–800 mg/d) may offer potential benefits in terms of efficacy, safety, and cost-effectiveness.

Introduction

Hepatic encephalopathy (HE) is a neuropsychiatric disorder in patients with liver disease and hyperammonemia.[1,2] Up to 40% of cirrhotic patients exhibit HE, which results in a substantial reduction in median survival time after diagnosis.[3] HE is broadly categorized into overt hepatic encephalopathy (OHE) and covert hepatic encephalopathy (CHE), with the latter encompassing minimal hepatic encephalopathy (MHE), which significantly impairs quality of life.[4] Ammonia toxicity and subsequent oxidative stress are key pathogenic mechanisms in HE,[5] making serum ammonia reduction a primary management strategy.

Rifaximin targets intestinal bacteria with minimal systemic absorption.[6] Studies suggest that rifaximin may treat HE by lowering ammonia levels, reducing inflammation, and rebalancing the gut microbiome.[7–9] Current clinical practice guidelines recommend rifaximin for the treatment and prevention of HE to improve patients' quality of life. Chinese guidelines suggest a treatment course of six months, whereas EASL recommendations do not specify a duration threshold.[10,11] However, evidence regarding the effectiveness, safety, and cost-effectiveness of long-term HE treatment is limited, and the optimal dosage of rifaximin for different stages of HE remains unclear. For the purposes of this review, "long-term" is defined as rifaximin administration lasting ≥six months. The review focuses on analyzing the therapeutic mechanisms of rifaximin in HE, investigating long-term treatment and prevention regimens and their dose effects, and discussing safety and compliance.

Pharmacology and mechanism of Rifaximin in HE

Rifaximin is a semi-synthetic, non-absorbable antibiotic derived from rifamycin, enabling high concentrations within the gastrointestinal tract.[6] Fecal concentrations of rifaximin exceed the minimal inhibitory concentration values against a broad spectrum of pathogens.[12] Moreover, dosage adjustments for hepatic dysfunction are unnecessary due to its minimal oral absorption, even in patients with HE.[13] Rifaximin exhibits polymorphism that influences its pharmacokinetics, with the alpha crystalline rifaximin being the most widely used. It exerts antibacterial properties by inhibiting bacterial RNA synthesis.[14] Moreover, rifaximin exhibits broad-spectrum antibacterial activity against both gram-positive and gram-negative aerobic and anaerobic bacteria.

The gut microbial dysbiosis is linked to complications in cirrhosis, particularly bacterial infections and HE.[15] The prevalence of small intestinal bacterial overgrowth is higher in patients with cirrhosis related to non-alcoholic steatohepatitis compared to those with non-alcoholic fatty liver disease.[16] Moreover, the gut-liver

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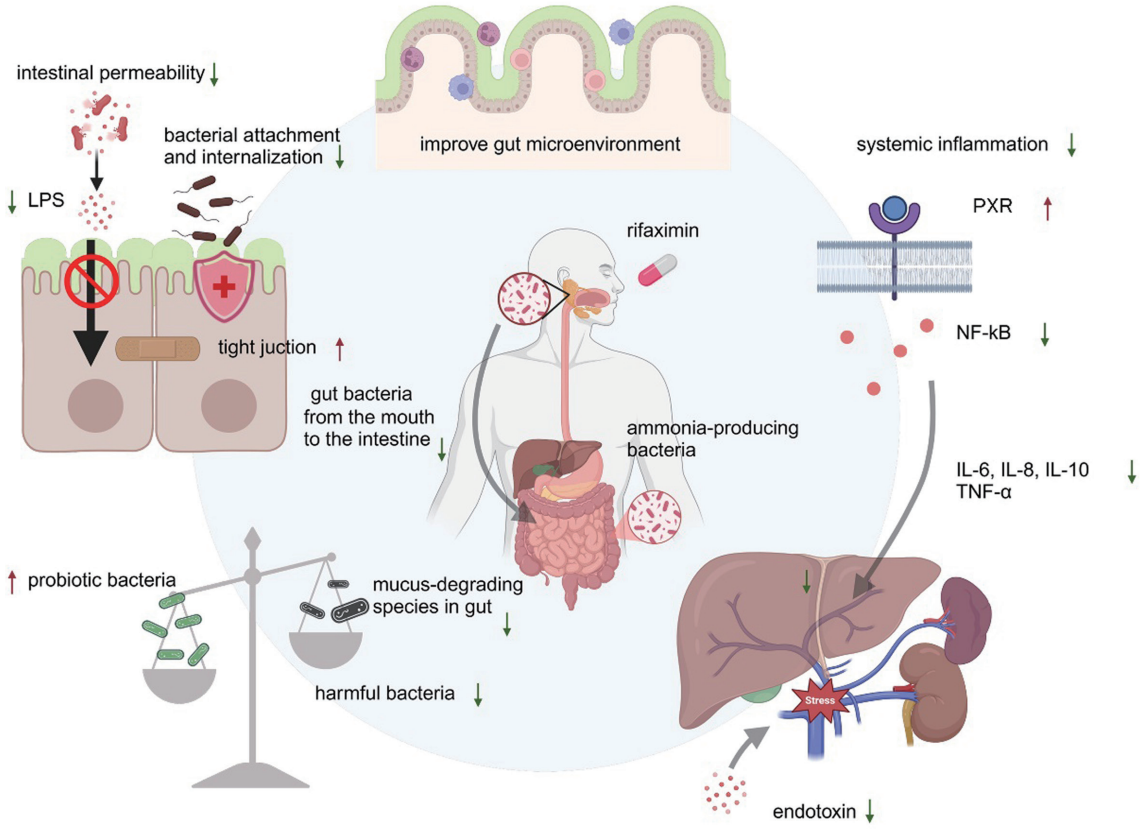

Fig. 1. Mechanisms of rifaximin in treating HE. Rifaximin improves the gut microenvironment by reducing the abundance of harmful bacteria while increasing probiotic bacteria. It inhibits the translocation of bacteria from the mouth to the intestine and decreases the population of mucus-degrading species and ammonia-producing bacteria within the gut. By strengthening epithelial tight junctions, rifaximin reduces intestinal permeability, thereby enhancing resistance to bacterial attachment and internalization. Additionally, it exerts anti-inflammatory effects via the NF-κB signaling pathway and decreases endotoxin levels in the blood. This figure was created with BioRender.com. HE, hepatic encephalopathy; LPS, lipopolysaccharides; PXR, pregnane X receptor; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; TNF-α, tumor necrosis factor-alpha; ↑, increase; ↓, descrease.

axis is altered, with increased intestinal permeability and reduced luminal primary bile acid levels potentially promoting bacterial translocation.[17]

The mechanisms of rifaximin in treating HE are illustrated in Figure 1. Rifaximin regulates gut microbiota by decreasing the abundance of harmful bacteria while increasing probiotic bacteria (Fig. 1).[7] The RIFSYS trial showed that rifaximin inhibited bacteria from translocating from the mouth to the intestine, thereby alleviating HE.[18] It also reduces intestinal permeability by strengthening epithelial tight junctions, thereby diminishing bacterial and endotoxin translocation and reducing inflammation (Fig. 1).[19] Notably, while rifaximin decreases the abundance of *Streptococcus spp*., it does not disrupt overall microbial diversity.[20] Moreover, rifaximin reduces glutaminase-2 expression while enhancing asparagine synthetase and solute carrier 7A11, activating ammonia detoxification.[9] It also exerts anti-inflammatory effects via the NF-κB pathway and protects SH-SY5Y cells from iron overload-induced injury by rectifying iron metabolism disorders.[8,21]

Long-term rifaximin treatment of HE

Although there is limited direct head-to-head evidence comparing rifaximin with lactulose over the long term, some studies suggest that rifaximin, when combined with lactulose, significantly improves efficacy. Specifically, the therapeutic benefits of lactulose are likely attributable to reducing intestinal pH, promoting beneficial microbial communities, and enhancing gut barrier function.[22] In contrast, rifaximin may further reduce bacterial translocation and systemic inflammation, thereby preventing the development of infections.[18] The combination of rifaximin and lactulose might create a synergistic effect, maximizing therapeutic outcomes in HE improvement and reducing HE-related hospitalizations. A randomized controlled trial suggested that six months of rifaximin treatment was more effective than a placebo in maintaining HE remission, reducing breakthrough episodes (*HR*, 0.42; 95% *CI*, 0.28–0.64; $P < 0.001$), and reducing HE-related hospitalization rates (*HR*, 0.50; 95% *CI*, 0.29–0.87; $P = 0.010$). Notably, over 90% of patients received lactulose, with rifaximin-based regimens demonstrating superior efficacy compared to lactulose monotherapy.[23] Real-world studies have revealed that the combination of rifaximin and lactulose reduces serum ammonia levels, maintains HE remission, and decreases HE-related hospitalizations.[24,25] Furthermore, improvements in mini-mental status examination scores and a reduction in variceal bleeding risk were observed at six and twelve months post-rifaximin initiation.[24]

While the rifaximin regimen shows efficacy, drug formulations

and dose optimization remain controversial. Studies have also assessed the effectiveness of different rifaximin treatment regimens. A phase II trial investigated various formulations of rifaximin in outpatients with early decompensated cirrhosis for 24 weeks. No significant differences were found in cirrhosis-related hospitalization or all-cause mortality compared to placebo. However, the immediate-release 40 mg dose improved both time to all-cause hospitalization and reduced mortality risk compared to placebo (15.4% *vs.* 27.7%; $P = 0.03$) in post-hoc analysis (Table 1).[26] Notably, patients using rifaximin for HE were treated later in the disease course, and earlier initiation of rifaximin may enhance quality of life.[26]

In addition to treating HE, lactulose and rifaximin are first-line therapies for preventing HE recurrence.[10,27] A prospective study revealed that adjunctive rifaximin (400 mg, TID) improved prevention of HE recurrence and related hospitalizations (32% *vs.* 75%; $P = 0.005$) compared to lactulose alone in patients with HCV-related cirrhosis.[28] Another real-world study confirmed the effectiveness of rifaximin over six months in preventing HE recurrence (0.79 *vs.* 1.78; $P = 0.013$), while no significant difference was found in acute exacerbations in persistent HE (1.48 *vs.* 1.77; $P = 0.582$).[29] A multicenter randomized study further found that low-dose rifaximin (400 mg, BID) for six months markedly reduced HE incidence compared to the control group (9% *vs.* 11%; $P < 0.001$) in decompensated cirrhosis patients (Table 1).[30] The low dosage not only reduces the medical burden and improves compliance but also potentially decreases the risk of side effects associated with long-term use. Given these benefits, Chinese guidelines recommend a reduced dose of 400–600 mg/d for secondary prevention.[10] However, despite random allocation of patients with decompensated cirrhosis, the distribution of patients with a previous history of HE differed between the two groups. Although the history of HE was adjusted for by logistic regression, the observed differences in HE incidence might be influenced by this uneven distribution.

Overall, rifaximin demonstrates benefits in treating HE, especially when combined with lactulose. Most studies show that rifaximin enhances HE remission, prevents HE recurrence, and reduces hospitalization rates. Additionally, early use may improve quality of life, suggesting its potential role in early intervention strategies. However, there are currently no head-to-head comparisons of low-dose (800 mg/d) and standard-dose (1,200 mg/d) rifaximin in HE. Future research should explore optimal dosages and administration timing for treatment.

Long-term rifaximin treatment of CHE

While OHE management is well-characterized, the subtle domain of CHE requires equal attention. Despite lacking overt clinical symptoms, CHE is common and associated with a worse prognosis and quality of life. Without timely and effective treatment, CHE may progress to OHE.

Given the importance of managing CHE, recent studies have explored rifaximin as a therapeutic option. A cohort study found that rifaximin reduced hyperammonemia, with 41.6% of patients recovering from CHE at 12 weeks.[31] Moreover, another prospective cohort study found that rifaximin therapy normalized the immune system in MHE responders at six months, while non-responders showed only partial normalization, possibly due to irreversible changes in peripheral inflammation.[32] Analyzing these distinctions could help identify predictors for MHE responsiveness to rifaximin. Notably, rifaximin for six months promoted subtle brain function, enhanced executive functions, and normalized pro-inflammatory cytokine levels, rather than directly addressing functional disturbances induced by MHE.[33] Further observational research on treatment regimens revealed that continuous rifaximin therapy in MHE outperformed cyclic use in improving quality of life and HE symptoms, such as cognitive impairments.[34]

Current studies on rifaximin treatment for CHE are predominantly observational, which may introduce selection bias. Patients in different groups may vary in disease severity, prior treatment history, or comorbidities, potentially skewing the results. Additionally, while certain confounders may be partially controlled, unknown confounders could still influence the outcomes. Despite these potential biases, these studies consistently show rifaximin improving brain function, modulating the immune system, and enhancing quality of life in treating CHE. Continuous rifaximin administration appears to be more effective than cyclic regimens. Future randomized controlled studies should explore different treatment regimens for managing CHE patients.

Effectiveness of preventing HE after transjugular intrahepatic portosystemic shunt (TIPS)

Promising results in established HE naturally raise the question of prophylactic applications in high-risk interventions. Rifaximin could be used as prophylaxis for HE prior to non-urgent TIPS placements.[11] A randomized trial found that rifaximin (200 mg, BID) given before and after TIPS prevented OHE compared to placebo (34% vs. 53%), without increasing adverse events (Table 1).[35] Another pooled post-hoc analysis of a phase III randomized, double-blind trial compared rifaximin (550 mg, BID) combined with lactulose to lactulose alone for six months, indicating that the combination effectively decreased OHE recurrence (*HR*, 0.32; 95% *CI*, 0.22–0.47; $P < 0.001$) and subsequent hospitalizations (*HR*, 0.41; 95% *CI*, 0.25–0.67; $P < 0.001$).[36] While a retrospective cohort study found that combined treatment effectively prevented HE recurrence after TIPS in patients with prior HE, it failed to prevent HE in patients without such a history.[37]

However, the retrospective nature of the study and the lack of information on prior prophylaxis suggest that the effectiveness of this regimen may be influenced by other treatment strategies. Future research should focus on determining which patients should receive a prophylactic regimen and establish the ideal timing and duration of prophylactic treatment.

Safety of long-term use of rifaximin

Rifaximin demonstrates a high safety profile and fewer adverse effects (AEs) in HE management, with common side effects like headache, constipation, abdominal pain, and nausea occurring in approximately 1% of patients.[38] Bass *et al*.[23] found no significant differences in the overall incidence of AEs between the rifaximin and placebo groups. Rifaximin therapy has been linked to C. difficile infections, but two affected patients recovered after continued rifaximin and anti-infective treatment.[23] A 24-month maintenance study indicated that rates of AEs, serious AEs, and AEs-related discontinuation were lower than in the initial six-month trial, and gastrointestinal-related AEs were lower in the rifaximin group compared to the rifaximin plus lactulose group (47.5% *vs.* 69.6%; $P < 0.001$).[39] The IMPRESS study documented C. difficile infections in 1.9% of patients with additional risk factors, with no serious AEs reported.[40] A prospective study reported AEs including nausea, arthralgia, and fatigue, which did not require hospitalization.[28]

However, evidence regarding long-term rifaximin use and bacterial resistance remains limited. Abdel *et al*. found that the mini-

Table 1. Summary of studies evaluating the effectiveness of long-term use of rifaximin for treatment or prevention in cirrhotic patients with HE

Reference	Country	Study Design	Study population	Sample size	Rifaximin dosage	Control	Treatment duration	Main outcomes
Bass *et al*.[23] 2010	United States, Canada, and Russia	Randomized, double-blind, placebo-controlled trial	Patients who were in remission from recurrent HE resulting from chronic liver disease	299	550 mg BID	Placebo	Six months	Rifaximin treatment more effectively than placebo in maintaining HE remission, and rifaximin reduced the risk of a breakthrough episode of HE (*HR*, 0.42; 95% *CI*, 0.28–0.64; $P < 0.001$) and hospitalization (*HR*, 0.50; 95% *CI*, 0.29–0.87; $P = 0.010$) related to the condition
Oey *et al*.[25] 2019	Netherlands	Observational study	OHE	127	Not given	Black	Six months	The addition of rifaximin to lactulose treatment for six months was associated with decreasing the frequency (41% *vs.* 86%; $P < 0.001$) and duration of hospitalizations (3.79 d *vs.* 8.85 d; $P < 0.001$) related to OHE
Chang *et al*.[24] 2021	China (Taiwan)	Retrospective cohort study	Liver cirrhosis complicated by HE (at least two episodes during the previous six months)	43	550 mg BID	Lactulose	12 months	Combination treatment reduced serum ammonia levels, maintained HE remission, and decreased the frequency (1 vs. 3; $P < 0.001$) and duration (11 d vs. 37 d; $P = 0.003$) of HE-related hospitalizations
Bajaj *et al*.[26] 2023	United States	Phase II, randomized, double-blind, placebo-controlled trials	Outpatients with early decompensated cirrhosis	516	Immediate-release 40 or 80 mg, sustained extended-release 40 or 80 mg, or immediate-release 80 mg plus sustained extended-release 80 mg, once nightly	Placebo	Six months	No significant differences were found in cirrhosis-related hospitalization or all-cause mortality compared to placebo; however, post hoc analysis indicated that the immediate-release 40 mg dose improved both time to all-cause hospitalization and mortality than placebo (15.4% *vs.* 27.7%; $P = 0.03$)
Nakai *et al*.[31] 2022	Japan	Retrospective cohort study	HE	102	400 mg TID	Black	The median medication period was 227 days	Rifaximin significantly reduced hyperammonemia (−33.3%; $P < 0.01$), and 41.6% of patients recovering from CHE at 12 weeks ($P < 0.01$)
Casanova-Ferrer *et al*.[33] 2024	Spain	Retrospective cohort study	Healthy controls and cirrhotic patients without MHE and patients with MHE	53	400 mg TID	Healthy and cirrhotic patients without MHE	Six months	Rifaximin enhanced executive functions and normalized pro-inflammatory cytokine levels in responsive patients
Bakulin *et al*.[34] 2023	Russia	Retrospective cohort study	MHE	258	1200 mg daily	Rifaximin (cyclic course)	12 months	Continuous rifaximin therapy outperformed cyclic use, exerting a more pronounced impact on patients' quality of life and HE symptoms such as impaired concentration, memory, cognitive function, and reduced performance

(continued)

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Table 1. *(continued)*

Reference	Country	Study Design	Study population	Sample size	Rifaximin dosage	Control	Treatment duration	Main outcomes
Mangas-Losada *et al*.[32] 2019	Spain	Retrospective cohort study	Controls without liver disease, cirrhotic patients without MHE and patients with MHE	52	400 mg TID	Healthy and cirrhotic patients without MHE	Six months	Rifaximin therapy normalized the immune system in MHE responders but only partially in non-responders at six months, with higher pre-treatment CD69 expression in non-responders
Abdel et.al.[28] 2021	Egypt	Open-label parallel, prospective interventional study	Patients with HCV-related cirrhosis	100	400 mg TID	Lactulose	Six months	Adjunctive rifaximin to lactulose showed superior efficacy in preventing HE recurrence and related hospitalizations than lactulose alone (32% *vs*. 75%; *P* = 0.005), with a low risk of microbial resistance upon long-term use
Chautant *et al*.[29] 2020	France	Retrospective cohort study	HE	62	Not given	Black	Six months	The effectiveness of rifaximin was confirmed in the prevention of HE episodes recurrence (0.79 *vs.* 1.78; *P* = 0.013) but was not proved in the prevention of acute exacerbations recurrence on persistent HE (1.48 *vs.* 1.77; *P* = 0.582)
Zeng *et al*.[30] 2021	China	Multicenter randomized open-labelled prospective study	Patients with decompensated cirrhosis	200	400 mg BID	Only conventional therapy	Six months	Low dose rifaximin markedly reduced the incidence of HE in patients with decompensated cirrhosis than control group (9% vs. 11%; *P* < 0.001)
Koretz *et al*.[35] 2021	France	Randomized placebo-controlled trial	Patients with cirrhosis who were scheduled for TIPS placement	197	200 mg BID	Placebo	182 days	Rifaximin prevented OHE compared with placebo (34% *vs.* 53%) without increasing adverse events
Sanyal *et al*.[36] 2024	United States	A pooled post hoc analysis of a phase III randomized, double-blind trial and a phase IV open-label trial	OHE remission patients	381	550 mg BID	Lactulose	Six months	Rifaximin combined lactulose effectively decreased the recurrence of OHE (*HR*, 0.32; 95% *CI*, 0.22–0.47; *P* < 0.001) and the risk of HE-related hospitalizations (*HR*, 0.41; 95% *CI*, 0.25–0.67; *P* < 0.001) in patients who had achieved OHE remission
Seifert *et al*.[37] 2021	Germany	Retrospective cohort study	Cirrhotic patients receiving a TIPS placement	233	550 mg BID	Lactulose	12 months	Although lactulose combined rifaximin could prevent HE recurrence effectively after TIPS in patients with HE prior to TIPS, it failed to prevent HE in patients without such history (HE prior TIPS: one month, *OR*, 0.048; *P* = 0.003; three months, *OR*, 0.042; *P* = 0.003; 12 months, *OR*, 0.056; *P* = 0.006; no HE prior TIPS: one month, *OR*, 0.490; *P* = 0.234; three months, *OR*, 0.647; *P* = 0.483; 12 months, *OR*, 0.450; *P* = 0.121)

HE, hepatic encephalopathy; OHE, overt hepatic encephalopathy; CHE, covert hepatic encephalopathy; MHE, minimal hepatic encephalopathy; TIPS, transjugular intrahepatic portosystemic shunt.

mum inhibitory concentration remained unchanged after rifaximin treatment compared to baseline over six months.[28] However, some studies have found that rifaximin might lead to resistance against daptomycin and demonstrate cross-resistance in staphylococci.[41,42] Given these findings, judicious use of rifaximin is emphasized, especially avoiding its use in institutional settings. Future research should investigate whether long-term rifaximin use drives antibiotic resistance and explore the mechanisms underlying cross-resistance pathways.

Cost-effectiveness and compliance of long-term use of rifaximin in HE

Although rifaximin demonstrates safety and fewer adverse effects, patient compliance remains a challenge in those with HE. A real-world study revealed that only 54.5% of patients maintained rifaximin treatment at 12 months, with only 35% continuing thereafter.[43] In the US, retention rates were 42%, 25%, and 16% at 180, 360, and 540 days, respectively. Moreover, out-of-pocket costs exceeding $150 for a 30-day supply were associated with decreased rifaximin retention.[44] Despite these compliance challenges, studies indicate that long-term use of rifaximin is cost-effective. A cohort study showed a 27% reduction in annual all-cause hospitalizations compared to lactulose alone, projecting annual savings of $7.5 million if 50% of patients using lactulose alone were to switch to rifaximin and adhere to the treatment.[45] Rifaximin as an adjunct to lactulose not only improved therapeutic outcomes but also provided economic benefits.[46] Moreover, rifaximin was associated with a 59% decrease in annual hospitalizations due to OHE, without increasing overall healthcare costs.[47] These economic advantages must be weighed against implementation challenges.

Economic constraints and insufficient awareness are the main barriers to long-term rifaximin use and adherence in HE patients. Therefore, it is essential to enhance education for patients, healthcare providers, and caregivers. Drug formulations, the complexity of the medication regimen, difficulty with dosing schedules, and forgetfulness may also contribute to low treatment retention rates.[48,49] Thus, improving drug formulations and simplifying the dosing regimen could help patients better integrate the medication into their daily routines.

Prospective

The long-term use of rifaximin in cirrhotic patients with HE presents promising outcomes. A randomized controlled study showed that low-dose rifaximin (800 mg/day) reversed CHE and improved health-related quality of life with similar efficacy and safety to high-dose rifaximin (1,200 mg/day) over eight weeks.[50] Lower doses may be a viable option, providing comparable therapeutic outcomes while potentially minimizing side effects. Future studies should explore its long-term efficacy further. Moreover, a multicenter prospective study found that rifaximin (400 mg, TID) for three months reduced serum ammonia levels and improved effective albumin concentration by enhancing circulating albumin structure in cirrhotic patients with hyperammonemia.[51] Notably, a retrospective cohort study revealed that, although the rifaximin-only group had the highest comorbidity burden, it experienced the greatest reduction in the incidence of colon, esophageal, and stomach cancers in cirrhotic patients compared to the lactulose group, with an average treatment duration of 211 days.[52] This warrants further investigation into its potential oncological benefits. Limitations of this mini review include the limited number of research papers on the development of resistance to rifaximin and the reduction of susceptibility to other antibiotics.

Conclusions

Evidence suggests that long-term use of rifaximin significantly reduces the recurrence of HE, decreases re-hospitalization rates, and improves cognitive function and quality of life in cirrhotic patients with HE, particularly when combined with lactulose (Table 1). Meanwhile, rifaximin demonstrates high safety with fewer AEs, and improving patient compliance may lead to certain cost-effectiveness. Future investigations should elucidate the gut microbiota-mediated mechanisms of rifaximin and assess the potential induction of antibiotic resistance with prolonged use. Additionally, head-to-head studies are needed to determine the optimal dosage and treatment duration for cirrhotic patients with HE, ensuring individualized treatment strategies.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Conceptualization (HD, YH, LL), data curation, original draft preparation (YL, KJ, YH), figures and tables (YL, KJ), review, and editing (HD, YH, LL). All authors have made significant contributions to this study and have approved the final manuscript.

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