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The use of Rifaximin in Patients with Cirrhosis.

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Abbreviations: HE, hepatic encephalopathy, ACLF. Acute-on-chronic liver failure, SBP, spontaneous bacterial peritonitis; BDL, bile-duct ligation; TLR-4, toll-like receptor 4; LPS, lipopolysaccharide; PXR, pregnane-X receptor; RCT, randomized controlled trial; QOL, quality of life; CHE, covert hepatic encephalopathy; OHE, overt hepatic encephalopathy.

ABSTRACT

Rifaximin is an oral non-systemic antibiotic, with minimal gastrointestinal absorption and broad-spectrum antibacterial activity covering both grampositive and gramnegative organisms. Rifaximin is currently worldwide used in patients with cirrhosis for preventing recurrent hepatic encephalopathy because its efficacy and safety has been proved by large randomized clinical trials. In the last decade, experimental and clinical evidence suggest that rifaximin could have other beneficial effects on the course of cirrhosis by modulating the gut microbiome and affecting the gut-liver axis, which, in turn, can interfere with major events of the pathophysiological cascade underlying decompensated cirrhosis, such as systemic inflammatory syndrome, portal hypertension, and bacterial infections. However, the use of rifaximin for prevention or treatment of other complications, including spontaneous bacterial peritonitis or other bacterial infections, is not accepted as evidence by clinical trials is still very weak.

The present review deals in the first part with the potential impact of rifaximin on pathogenic mechanisms in liver diseases, whereas, in the second part, its clinical effects are critically discussed. It clearly emerges that, due to its potential activity on multiple pathogenic events, the efficacy of rifaximin in the prevention or management of complications other than hepatic encephalopathy deserves to be investigated extensively. The results of double-blinded, adequately powered randomized clinical trials assessing the effect of rifaximin, alone or in combination with other drugs, on hard clinical endpoints, such as decompensation of cirrhosis, acute-on-chronic liver failure and mortality, are therefore eagerly awaited.

More than four decades ago, an association between hepatic encephalopathy (HE) and abnormalities in ammonia metabolism was observed[1]. The association between circulating unmetabolized ammonia level and HE was weak. However, since production of ammonia is tightly related to the composition of gut microbiota, the idea emerged that oral administration of minimally-absorbed antibiotics effective against ammonia producing bacteria could help treat or prevent HE[2]. Neomycin which is active against urease-producing bacteria has been one of the first minimally-absorbed antibiotics to be used and controlled trials showed similar efficacy as

compared to lactulose[3]. However, since neomycin is slightly absorbed, there were concerns about nephrotoxicity and ototoxicity during long-term treatment. Ten years ago, a seminal controlled trial showed that rifaximin, another minimally-absorbed antibiotic, was superior to placebo to prevent recurrent HE[4]. It rapidly became apparent that beyond HE, rifaximin could have beneficial effects on the course of cirrhosis through interactions with the gut-liver axis[5-7]. This review focuses on rifaximin in the management of HE in cirrhosis but also on other documented or potential targets of rifaximin including systemic inflammatory response syndrome, portal hypertension, and bacterial infections.

PHARMACOLOGICAL CHARACTERISTICS OF RIFAXIMIN

Rifaximin is a semisynthetic, water-insoluble, rifamycin-based non-systemic antibiotic, with very low gastrointestinal absorption and good antibacterial activity[8]. Compared to rifampicin, it contains an extra pyrido-imidazole ring to reduce systemic absorption that is less than 1% after oral administration[8,9] (figure 1). Nevertheless, it is important to note that rifaximin plasma concentrations are not negligible in patients with cirrhosis, particularly in those with moderate-to-severe liver function impairment (Child B or C patients)[10]. There are some published reports on potential muscle toxicity in cirrhosis, in patients receiving rifaximin in combination with simvastatin 40 mg/day[11]. However, the possibility of these systemic muscle effects of rifaximin seems remote, because in studies with large number of patients with cirrhosis no muscle or other systemic adverse events have been reported (see later). The slight increase in systemic exposure to rifaximin in subjects with cirrhosis should be interpreted in the context of its low systemic availability as well as the rifaximin safety data in cirrhosis. Therefore, no dosage adjustment in patients with advanced cirrhosis is recommended.

Both experimental and clinical data show that rifaximin has a broad-spectrum antibacterial action covering grampositive and gramnegative aerobic and anaerobic bacteria[8,12,13]. Rifaximin elicits its antimicrobial properties by binding the beta-subunit of the bacterial DNA-dependent RNA polymerase and thus inhibiting bacterial RNA synthesis. It has the advantage of low microbial resistance and few systemic adverse events and is safe in all patient populations[8,12,13].

Being virtually non-absorbed, bioavailability of rifaximin within the gastrointestinal tract is high with intraluminal and fecal drug concentrations largely exceeding the minimal inhibitory

concentration values observed in vitro against a wide range of pathogenic organisms. The gastrointestinal tract represents, therefore, the primary therapeutic target of rifaximin[8,9,12,13].

Rifaximin has been shown to modify the gut microbiome. However, changes in overall gut microbiome composition have shown to be relatively sparse and the effects on microbiome have been described to be mediated also by rifaximin-induced changes in bile acid composition and modulation of microbiome function (see later)[14,15].

EFFECTS OF RIFAXIMIN ON PATHOGENIC MECHANISMS OF CHRONIC LIVER DISEASES AND CIRRHOSIS

Impact on liver fibrosis and portal hypertension

Antibiotics have been reported to protect against alcohol-related liver disease in rat models[16], whilst others report aggravation of fibrosis in a CCL4/alcohol rat model[17]. In a bile duct ligated (BDL) model, rifaximin attenuated fibrosis and portal hypertension[18] and more recently, rifaximin was shown to prevent alcohol-induced liver injury in a murine obesity model, whereby pathological changes in the intestinal microbiota signature induced by chronic ethanol feeding were partly reversed by rifaximin.[19].

Given rifaximin's ability to selectively target the gut microbiota[20], decreased liver fibrosis in pre-clinical models [18] and a favorable long-term safety profile, it follows that rifaximin may be a useful intervention in reducing fibrogenesis driven by gut microbiota components[21].

From the established relationship between portal pressure and systemic inflammation[22], it follows that rifaximin, through modulation of fibrosis and gut microbiota, could be expected to lower portal pressure. Indeed, in an observational study, Vlachogiannakos et al[23] showed that rifaximin significantly lowered portal pressure at 4 weeks, associated with decreased plasma endotoxin levels. In contrast, another randomized study in stable cirrhosis with ascites (mean MELD 11.7), showed no reduction in portal pressure after 4 weeks of rifaximin, nor improvement in renal function or major effects on inflammatory markers and gut microbiota composition[15,24]. The reason(s) for the different results of these studies is not known, but it is possible that unnoticed active alcohol use, differences in liver disease severity and/or duration of treatment may explain

differences across studies. While the dynamic component of portal hypertension and markers of bacterial translocation can change relatively fast, structural effects such as reduction of fibrosis is slow and treatment duration of at least 12 -24 month is probably necessary to allow histological changes.

Of interest, a controlled study assessing the combination of rifaximin with propranolol showed this to have a greater impact on portal pressure reduction and necessitating a lower mean propranolol dose, compared to propranolol alone[25]. A mechanistic explanation forwarded for the observed beneficial effects on portal pressure and fibrosis is provided by a study in BDL toll-like receptor-4 (TLR4) mutant mice, showing that rifaximin modulates TLR4 activation by LPS, thus resulting downstream in less fibronectin generation from activated stellate cells and endothelial cells[18].

Gut-liver axis and systemic inflammation

Patients with cirrhosis experience alterations in their gut-liver axis: an altered gut microbiome, increased intestinal permeability, and lower gut luminal primary bile acids levels may contribute to increased bacterial translocation[26]. As mentioned before, rifaximin is minimally-absorbed and is thought to act locally in the gut, therefore, rifaximin might exert modulating effects on elements of the gut-liver axis.

In vitro, rifaximin enhances intestinal epithelial layer homeostasis through activation of human Pregnane X Receptor (PXR) leading to inhibition of NFκB-dependent inflammatory pathways including TNFα, IL-6, IL-8 and IL-10 secretion and by induction of biotransformation enzymes phase 1 (e.g., CYP3A4) or phase 2 (e.g., glutathione-S-transferase A1)[27-29]. Bacterial attachment and internalization in enterocytes is also affected by rifaximin. In addition, rifaximin increases transepithelial electrical resistance and viability of human colonic tumor-derived Caco-2 cells[30]. Rifaximin also decreases toxicity PXR-dependently caused by *Clostridium difficile toxin A* via the TLR-4 pathway in Caco-2 cells[30] (figure 2).

Rodent models expressing human PXR were established to investigate PXR-dependent effects of rifaximin *in vivo*, since rifaximin is a human, but not rodent PXR agonist. Induction of biotransformation enzymes by rifaximin was confirmed in these hPXR mice[28,29]. Notably, favourable effects of rifaximin were also observed in mice without hPXR. Serum LPS binding

protein levels were markedly enhanced after BDL in wildtype mice and tended to be normalized after rifaximin treatment, again an effect mediated by TLR-4[18].

Effects of rifaximin on synthesis and metabolism of bile acids and their enterohepatic circulation are yet unclear. A reduction in the secondary/primary faecal bile acids ratio after 8 weeks of rifaximin treatment was observed in 6 patients with cirrhosis[14]. The relevance of this finding, however, is yet unclear as plasma bile acid composition was not affected in another study in 38 patients with cirrhosis after 90 days of rifaximin treatment[31].

The effects of rifaximin on systemic inflammatory markers are not extensively studied in patients with cirrhosis. IL-6, IL-10 and/or TNFα levels in plasma were decreased in patients with NAFLD, alcoholic cirrhosis and cirrhosis with HE, respectively, with treatment periods ranging from 4-12 weeks[31-33]. In contrast, no effects of rifaximin on systemic cytokine levels were observed in patients with cirrhosis and ascites after 4 weeks[15]. In patients with NAFLD, rifaximin also improved insulin resistance, serum glucose, AST, ALT and ϒGT after 6 months[32].

In contrast to patients with cirrhosis or NAFLD, rifaximin showed no effects on IL-6 and IL-10 mRNA levels in peripheral blood mononuclear cells, serum CD14 levels or LPS in 40 patients with common variable immunodeficiency after two weeks[34]. This suggests that the systemic inflammatory status may be regarded as a prerequisite for the beneficial anti-inflammatory effects of rifaximin on patients with cirrhosis or NAFLD.

Given the barely detectable quantities of rifaximin in the systemic circulation, local effects in the gut have to be assumed as the basis for the beneficial effects of rifaximin in patients with liver diseases. The human intestinal epithelium may be regarded as the key player mediating effects of rifaximin in patients with cirrhosis. Experimental studies are underway exploring effects of rifaximin on human enterocyte transport, metabolism and detoxification function. It is yet unclear whether rifaximin exerts its effects exclusively via PXR-dependent mechanisms or also PXR-independently. Further in depth molecular characterization of rifaximin effects on systemic inflammatory activity via its effects on the enterocyte and, thereby, the gut-liver axis in patients with cirrhosis are clearly needed.

Gut microbiome

The human gut microbiome is assumed to play a role in many diseases[35,36]. Since the microbiome constitutes trillions of microbial cells with high metabolic activity, it is likely that induced changes by specific treatments may be complex and prone to bias of interpretation[35,36]. Indeed, the liver is the first organ encountering microbial products that cross the gut epithelial barrier; therefore, it is likely to be affected by the gut microbiome and its changes in many ways[37]. Especially in end-stage cirrhosis, bacterial translocation seems to play a decisive role in different complications including acute-on-chronic liver failure (ACLF)[26,38].

Different studies have demonstrated that the effect of rifaximin on the gut microbiome is limited on phylum, class, order and family level[7,39] and regardless of the part of the gastrointestinal tract the sample was taken from, which is quite unexpected for a minimally-absorbed antibiotic[40]. Interestingly, other antibiotics, such as norfloxacin, recommended as prophylactic therapy in decompensated cirrhosis[41], may have a stronger effect on the microbiome composition than rifaximin at least in experimental cirrhosis[42].

The question that arises is how does rifaximin interact with microbiome to improve HE and, potentially, other complications of cirrhosis. Maybe the very subtle changes of the microbiome composition (Lactobacillus, Streptococcus, Veillonella) are sufficient to reduce hyperammonemia and endotoxemia in cirrhosis[39,43,44]. Those changes were consistent for Veillonella species only in the cohorts cited above. The underlying mechanisms are still under investigation, but older studies have demonstrated that rifaximin changes strongly the metabolism of the host with increased circulating saturated and unsaturated fatty acids, which are associated with altered microbiome linkages with those metabolites[39]. This observation in humans is paralleled by another study in mice, which demonstrates that rifaximin decreased small-intestinal glutaminase, and increased cecal glutamine content and probably thereby decreased ammonia production[45]. Along these lines, a recent study showed that rifaximin can impact phage-Streptococcus linkages, especially those that produce ammonia[46]. Yet the evidence so far is based either on cross-sectional studies or longitudinal smaller studies, with not only diverging results on the host effects but also on the microbiome effects. We therefore, hope the ongoing larger, longitudinal and multicenter studies within the H2020 projects GALAXY, LIVERHOPE and MICROB-PREDICT may lead to better understanding of the mechanisms of action and possible stratification of patients who may or may not benefit from rifaximin treatment.

EFFECTS OF RIFAXIMIN ON PREVENTION AND MANAGEMENT OF COMPLICATIONS OF CIRRHOSIS

Rifaximin in hepatic encephalopathy

Given the alterations in gut-liver-brain axis in HE, gut-focused interventions have been the mainstay of therapy[47]. Lactulose and lactitol are first-line treatments but they can be associated with adverse events that can limit their acceptance[48]. Rifaximin, being an orally available, minimally-absorbed and safe medication has been studied in all aspects of HE.

While rifaximin was used off-label for HE therapy across several European countries, the widespread use and labeling for HE specifically increased after the FDA approval based on the pivotal RCT by Bass et al in 2010[4]. Table 1 shows a summary of the experience with rifaximin in HE and details of prominent trials are provided in supplementary table 1.

Covert HE therapy: CHE is very common and can be associated with poor survival, overt hepatic encephalopathy (OHE) development and psychosocial impact. Double-blind RCTs have shown that rifaximin is better than placebo with respect to improvement in cognition, quality-of-life (QOL) and driving capability[48,49]. While the mechanism is unclear, changes in microbial function and immune features, and enhanced brain activation have been found. The EASL/AASLD guidelines recommend therapy for CHE on a case-by-case basis[44]. However, rifaximin therapy for CHE is not currently cost-effective even to prevent major outcomes such as traffic crashes[50].

Inpatient therapy for HE: The four prongs for the therapy of HE in hospitalized patients include (a) care of the unconscious patient (b) evaluate other causes of altered mental status, (c) identify and treat precipitating factors and (d) start empiric therapy[47]. All these processes need to occur simultaneously. The first-line empiric therapy in most countries remains lactulose. The role of rifaximin in this setting is unclear[47].

Prior smaller-scale trials have shown that rifaximin may be useful in reducing blood ammonia and asterixis compared to selected therapies such as neomycin and non-absorbable disaccharides. One large open-label study evaluated rifaximin compared to lactulose with clinical outcomes centered on survival and mental status recovery[51]. In that study rifaximin therapy was better than lactulose in inpatient outcomes. These results need to be replicated in other centers. Rifaximin also has not been directly compared with L-ornithine L-aspartate therapy, which in some studies has shown improvement in mental status[52].

Until then, there is a trend towards off-label use of rifaximin in inpatients, but it is most likely a continuation of rifaximin that they were already on prior to hospitalization. The use of rifaximin

on discharge of patients with HE is a major quality indicator of therapy since it is associated with a lower risk of HE recurrence(see below).

Prevention of recurrence: The pivotal trial by Bass et al randomized 299 patients with multiple HE episodes into receiving daily rifaximin 550mg BID vs placebo over 6 months[4]. Primary endpoint was breakthrough hospitalizations due to HE and secondary endpoints included prevention of hospitalizations with HE. More than 90% of patients were on lactulose at baseline, which was continued throughout the trial. In those randomized to rifaximin, there was a significant reduction in breakthrough events and hospitalizations over the 6 months. The number needed to treat was 4 and 9 for these outcomes, respectively. However, most participants had MELD score <19 and due to >2 episodes, the initial usage was focused on these patients. This trial followed smaller-scale trials from Europe where long-term cyclical use was studied with good outcomes. However, the newer formulation, ability to use it twice a day and drug agency approval meant that it could be prescribed for patients to prevent HE[53].

"Real-world" use of rifaximin: Open-label experiences and evaluation of placebo-assigned group that was subsequently given rifaximin showed continued reduction in HE-related episodes even outside clinical trial setting[54]. Studies focused on changes in resource utilization before compared to after rifaximin showed that it can lead to reduction in HE episodes and admission and critical care admissions.

Barriers to rifaximin therapy: Cost and lack of awareness remain major issues to rifaximin therapy. Even in tertiary-care centers, 12.5% of patients who were admitted with HE, were subsequently discharged without HE-specific medications, which translated directly into readmissions[55]. Given the expense of hospitalizations, studies have shown that rifaximin is cost-effective for prevention of recurrence, but greater education of providers, patients and caregivers is needed[56].

Given its track record of acceptance by patients and efficacy in prevention of HE, further trials that evaluate the role of rifaximin in CHE and inpatient therapy of HE are needed, especially in combination or head-to-head against other established therapies.

Effects of rifaximin on bacterial infections

Based on its pharmacological characteristics and the putative effects on pathogenetic mechanisms of cirrhosis, rifaximin is considered by many hepatologists the logical alternative to quinolones or other systemic antibiotics for the prophylaxis of spontaneous bacterial peritonitis (SBP) and potentially of non-SBP bacterial infections, with the belief that rifaximin is active on a broader

range of intestinal grampositive and gramnegative bacteria, is safer, and carries a low risk of inducing resistance to antibiotics.

Unfortunately, after more than a decade of clinical research, a conclusive indication on the use of rifaximin in prevention of bacterial infections cannot be currently given. Almost all the published data are related to primary or secondary prophylaxis for SBP. In general, retrospective studies have shown that the use of rifaximin is associated with lower incidence of SBP and other complications of the disease[57,58] Conversely, prospective observational studies have yielded less consistent results[59] Only few RCTs have been performed so far, in Egypt and South Arabia, comparing the efficacy of rifaximin versus norfloxacin: in these studies, an advantage was seen in favor of rifaximin given for primary or secondary SBP[60,61]; in the former study, rifaximin was also given alternated to norfloxacin and compared to norfloxacin alone[60]. However, the strength of these positive results is undermined by some methodological drawbacks.

To overcome the limitations inherent to each single study, several systematic reviews and meta-analysis assessing both the observational cohort studies and the RCTs have been performed. Again, results suggest that only low-quality evidence supports the superiority of rifaximin over norfloxacin or other systemic antibiotics for either primary or secondary SBP prophylaxis[6,62,63]. In all these studies, both the high heterogeneity in terms of patient inclusion criteria, type and modalities of administration of the comparative prophylactic therapies, primary and secondary end-points and the moderate-to-high risk of methodological biases related to randomization, blinding, attrition and intention-to-treat analysis, preclude the possibility to reach solid conclusions[6,62,63].

Effects of rifaximin on other complications of cirrhosis

Several studies have assessed the impact of rifaximin in prevention of complications of cirrhosis other than HE and bacterial infections[64-71] (table 2). Data are not univocal and often burdened by serious methodological issues. Taking this into consideration, it is suggested that, by reducing serum levels of proinflammatory mediators linked to intestinal bacterial translocation, rifaximin may decrease portal hypertension, improve systemic hemodynamics (increasing systemic vascular resistances and mean arterial pressure) and renal function (improving glomerular filtration rate and urinary sodium excretion)[23-25,66,70]. Hence, valuable clinical benefits have been associated with rifaximin, including a reduction in the incidence of decompensation of cirrhosis, of all-cause

hospitalizations and readmissions, of variceal bleeding, and of acute kidney injury (AKI), including hepatorenal syndrome (HRS), with a decreased risk of renal replacement therapy[58,64,65,67-79,72]. A better control of difficult to treat/refractory ascites was also shown when rifaximin was added to treatment[70,71]. A reduction in mortality was suggested in some studies [51,58,65,70,71]. Although promising, these data must be confirmed by well-conducted, large, RCTs.

Side effects

In rifaximin data sheet, dizziness, headache, constipation, abdominal pain, diarrhea, flatulence, nausea, rectal tenesmus, vomiting, and pyrexia are listed as frequent side effects (> 1/100 to <1/10).

When used in HE, rifaximin side effects have been mild and infrequent. In a review article including the pivotal prophylaxis trial, rifaximin was well tolerated and adverse events were similar to placebo group[4,73]. In the pivotal study, there were two cases of infection by *Cl. Difficile* vs none in the control group. In the extension study, the frequency of this infection did not increase, and was reported in 6 patients[74]. All these patients presented predisposing factors for this infection. Post-marketing studies also described cases of *Cl. Difficile* infection[75]. When rifaximin was used in prophylaxis of SBP, few side effects were observed. In a study, no side effects were described[57] and in others they were uncommon, including abdominal pain, flatulence, nausea, dizziness and headache[60,61].

It has been suggested that rifaximin may favor the muscular toxicity of statins in cirrhosis[11]. This possibility seems unlikely, since only 3 cases of rifaximin rhabdomyolysis have been described in a post-marketing data base[75] and it has not been observed in patients with cirrhosis treated with low doses of simvastatin (20 mg/day) together with rifaximin[76].

FUTURE DIRECTIONS

Currently, the only accepted indication for rifaximin in cirrhosis is prevention of recurrent HE[46]. Use of rifaximin for other indications, such as prevention of bacterial infections, including SBP, is not supported by strong evidence; therefore rifaximin should not be used in clinical practice for indications other than HE (table 3). Nonetheless, due to its complex effects in gut-liver axis and modulating gut microbiome, the potential efficacy of rifaximin in prevention or management of complications of cirrhosis other than HE deserves to be investigated extensively. Ideally, studies should be double-blinded, with rifaximin alone or in combination with other drugs, include large

patient populations, and aimed at hard clinical endpoints, particularly prevention of decompensated cirrhosis, bacterial infections, and ACLF. Some of these studies are underway and results are eagerly awaited (table 4).

CONCLUSIONS

In recent years the paradigm on pathophysiology of decompensation of cirrhosis has deeply changed. It is now clear that decompensated cirrhosis is characterized by sustained pro-inflammatory and pro-oxidant milieu resulting from the systemic spread of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) from gut and diseased liver, respectively. The deep alterations in their gut-liver axis favouring translocation of PAMPs as well as viable bacteria have been the rationale for the use of rifaximin in prevention of several complications of cirrhosis. Rather than having bactericidal effect, rifaximin seems to have direct effects on bacterial function and virulence. Such confirming, its use results in very little change in stool microbiome in cirrhosis. In addition, rifaximin does not appear to increase antibiotic resistance rates. Therefore, rifaximin represents an antibiotic strategy that may prevent infections and other complications of cirrhosis without development of multi-drug resistant bacteria. However, beyond the prevention of recurrent HE, there are currently no other recommended indications for its use in cirrhosis. Indeed, several studies have already shown a potential favourable impact of rifaximin on several steps in pathophysiology of decompensation. Accordingly, beneficial effects of rifaximin have been described. Unfortunately, most of these data are not the result of high-quality RCTs but rather of not-controlled *"real world"* studies, meta-analysis or systematic reviews. This can explain why, up to now, the results are not so univocal and consistent as to be translated into recommendations.

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Table 1. Summary of studies reporting the use of Rifaximin for treatment or prevention of hepatic encephalopathy in cirrhosis.

Type of study	**Number of trials and sample size**	**Results**
Short-term therapy studies (5-30 days)		
Rifaximin vs. placebo	1 (93)	Asterixis improved only with rifaximin. PSE index, mental status, and intellectual function improved similarly in both groups
Rifaximin 200 mg vs 400 mg vs 800 mg per day	1 (54)	PSE index improved only in 400-mg and 800-mg groups.

Rifaximin vs other antibiotics	7 (227)	Ammonia improved more with rifaximin than neomycin (1 RCT) or similarly in both (6 RCTs). PSE index improved similarly in both groups (1 RCT). Intellectual function or mental status improved similarly in both groups (5 RCTs). Asterixis improved faster with rifaximin than with neomycin (1 RCT).
Rifaximin vs non-absorbable disaccharides	6 (448)	Higher ammonia improvement with rifaximin (3 RCTs) or similarly in both groups (3 RCTs).
Long-term studies (3-6 months cyclical)		
Rifaximin vs non-absorbable disaccharides	2 (80)	Ammonia and mental status improved with both trials with all strategies compared to baseline. Higher improvement in PSE index, EEG and mental status with rifaximin. In the second study, rifaximin+/-lactitol did better than lactitol alone with mental status.
Rifaximin vs. neomycin	1(60)	Improvement in psychometric/neuro-physiologic tests, mental status and ammonia were similar across both groups.
Inpatient use		
Rifaximin+Lactulose vs Lactulose alone	1 (120)	Higher HE reversal and lower death in group given rifaximin and lactulose compared to lactulose alone.
Prevention of recurrence		
Rifaximin vs. placebo	1 (299)	Reduction in recurrent HE episodes and hospitalization in the rifaximin group with

		significantly higher improvement in neuro-physiological, quality-of-life and ammonia in the rifaximin group. 91% of patients were on lactulose in both groups.
Real world and open-label rifaximin experience		
Open-label extension and pre/post comparison	2 (474)	Open-label extension and addition of new patients on rifaximin was associated with continued reduction in HE-related and all-cause hospitalization and placebo to rifaximin conversion patients reduced HE episodes further.
Evaluation of healthcare systems after rifaximin introduction	5 (760)	Reduction in mean hospitalizations, readmissions and length of stay

Adapted from Bajaj et al 2020 (53)

PSE Index: a composite score for HE Consisting of 100x[mental health status(con score)x3+asterixis grade x 1 +NCT grade x 1 + ammonia grade x 1 + EEG grade x 1 (if available)]; it is not widely used at this time.

Table 2. Summary of studies evaluating the effect of rifaximin on complications of cirrhosis other than hepatic encephalopathy and bacterial infections.

REFERENCE	STUDY DESIGN	PATIENT POPULATION	MAIN OUTCOMES
Assem M. 2016[60]	Prospective randomized, open-label, comparative multicenter study	239 cirrhotic patients with ascites randomized to 3 groups: rifaximin (550 mg BID), norfloxacin or alternating rifaximin/norfloxacin	Primary outcome: incidence of SBP Overall, 10 patients developed HRS (6 patients [7.6%] in the norfloxacin group, 2 [2.4%] in the rifaximin group and 2 [2.5%] in the combined group, $p > 0.05$) HRS was the main cause of mortality
Sharma BC. 2013[51]	RCT	120 patients with overt HE randomized into 2 groups: lactulose + rifaximin (1200 mg/day) vs. lactulose + placebo	Primary outcome: reversal of HE Addition of rifaximin was associated with: - reduced mortality (24% vs. 49%, $p < 0.05$), with no differences in HRS- and GI-bleeding related deaths
Dong T. 2016 [64]	Retrospective study	88 patients on rifaximin (550 mg BID) for ≥90 days vs. 88 matched controls	Primary outcomes: incidence of AKI and HRS Rifaximin reduced: - the incidence rate ratio of AKI (IRR 0.71 [95% CI: 0.54-0.94]) and of HRS (IRR 0.21 [95% CI: 0.06-0.70]) - the requirement of RRT (5.7% vs. 15.9%; OR 0.23 [95% CI: 0.07-0.74])
Vlachogiannakos J. 2013[65]	Prospective, non randomized case-control study	23 patients with known hemodynamic response (HVPG) to short-term rifaximin treated with long-term rifaximin (1200 mg/day) vs. 46 matched controls	Primary outcomes: survival, variceal bleeding, HE, SBP, HRS Rifaximin therapy was: - an independent negative predictor of variceal bleeding (RH 0.246; 95% CI: 0.069-0.870, $p = 0.03$) - the only factor associated with lower probability of HRS (RH 0.110; 95% CI: 0.012-0.973, $p = 0.047$) - predictor of 5-year survival (RH for mortality 0.258; 95% CI: 0.075-0.891, $p = 0.032$)
Kimer N. 2017[24]	Double-blind RCT	54 stable outpatients with cirrhosis and ascites with HVPG ≥10 mmHg randomized to rifaximin 550 mg BID (n=36) or placebo BID (n=18) for 4 weeks	Primary outcomes: hepatic and systemic hemodynamics, renal function No effect of rifaximin on: - HVPG ($p = 0.94$) - PRA ($p = 0.12$) or other vasoactive hormones (p = ns) - GFR ($p = 0.14$)
Kalambokis GN. 2012[66]	Open-label, prospective, single-center, pilot study	13 patients with alcohol-related cirrhosis and ascites treated with rifaximin (1200 mg/day) for 4 weeks	Primary outcomes: systemic hemodynamics and renal function Rifaximin: - increased MAP ($p = 0.05$), in keeping with increased SVR ($p = 0.01$), decreased PRA ($p = 0.02$) and decreased CO ($p = 0.02$)

			- improved renal function, consistently with increase in GFR (p = 0.006) and urinary sodium excretion (p = 0.03) - decreased plasma endotoxin (p = 0.005), IL-6 (p = 0.01) and TNF-α (p = 0.02) levels
Vlachogiannakos J. 2009[23]	Prospective study	30 patients with alcohol-related cirrhosis and ascites treated with rifaximin (1200 mg/day) for 28 days	Primary outcomes: hepatic hemodynamics Rifaximin: - decreased HVPG (p < 0.0001) - increased MAP (p < 0.05) - reduced plasma endotoxin levels both in systemic (p < 0.0001) and splanchnic circulation (p < 0.0001)
Lim YL. 2017[25]	Open-label RCT	73 patients with HVPG ≥12 mmHg randomized to propranolol monotherapy (n=54) or rifaximin (1200 mg/day) + propranolol (n=19) for 3 months	Primary outcome: HVPG response rate The combination therapy achieved: - a significant decline of HVPG (p = 0.016) - higher HVPG response rate than propranolol alone (87% vs. 56%, p = 0.034). - higher rates of reduction of LPS (p = 0.009) and LPS binding protein (p = 0.002) compared to propranolol monotherapy
Salehi S. 2019 [67]	Retrospective cohort study	101 patients with HE: 66 treated with rifaximin vs. 35 naïve	Primary outcome: all-cause emergency hospital admissions Rifaximin therapy achieved: - reduced all-cause admissions (p = 0.037) - reduced admissions for complications of ascites, including HRS (p = 0.008) and variceal bleeding (p = 0.026) - increased time to hospital readmission (p = 0.040)
Kang SH. 2017[58]	Retrospective cohort study	1042 patients with previous HE: 621 patients with HCC (173 receiving rifaximin 1200 mg/day + lactulose, 448 controls receiving lactulose alone) and 421 without HCC (145 rifaximin + lactulose, 276 lactulose alone)	Primary outcome: overall survival Rifaximin was associated with lower risk of variceal bleeding in the: - entire cohort (HR 0.520; 95% CI: 0.349-0.773; p = 0.001) - non-HCC cohort (HR adjusted for Child-Pugh class [aHR], 0.425; 95% CI: 0.220-0.821; p = 0.011) Rifaximin was associated with a non-significant trend towards lower risk of HRS in the: - non-HCC cohort (HR 0.595; 95% CI: 0.334-1.060; p = 0.078) Rifaximin was associated with a lower risk of death in the: - entire cohort (HR 0.702; 95% CI: 0.504-0.978; p = 0.036) - non-HCC cohort (aHR, 0.697; 95% CI: 0.510-0.954; p=0.024)
Flamm SL. 2018[68]	Post-hoc analysis of a placebo-controlled, multicenter RCT	299 patients with cirrhosis and HE in remission, randomized to rifaximin 550 mg BID (n=140) or placebo (n=159) for 6	Primary outcome of RCT: time to a breakthrough episode of overt HE In patients with MELD ≥12 and INR ≥1.2 rifaximin was associated with: - reduced risk of any first complication (HR 0.41, 95% CI:

		months	0.25-0.67; p < 0.001) - non-significant trend for reduction in the overall risk of non-HE complications, including variceal bleeding and AKI/HRS (HR 0.46, 95% CI: 0.18-1.17; p = 0.10) In patients with MELD <12 and INR <1.2 rifaximin was associated with: - non-significant trend for reduction in the risk of any complication (HR 0.26, 95% CI: 0.06-1.20, p = 0.06)
Ibrahim ES. 2017[69]	RCT	80 patients with decompensated cirrhosis randomized to rifaximin 550 mg BID for 12 weeks (n=40) or no treatment (n=40)	Primary outcome: incidence of HRS - Lower incidence of HRS in the rifaximin group [5% vs. 22.5%; p = 0.048]. - Being in the control group was a predictor of HRS at univariate analysis, but not at multivariate analysis (OR 3.01, 95% CI: 0.46-19.52; p = 0.249)
Hanafy AS. 2016[70]	RCT	600 patients with refractory or rapidly recurrent ascites randomized to diuretic therapy + midodrine 5 mg TID + rifaximin 550 mg BID (n=400) or diuretic therapy alone (n=200)	Primary outcomes: control of ascites Rifaximin + midodrine was associated with: - improvement in hemodynamics, as expressed by increase in MAP and reduction in PRA and aldosterone (p < 0.05 for all variables) - improvement in renal function, as assessed by serum creatinine and BUN decrease, serum sodium increase, 24h-urine output and urinary sodium excretion increase (p < 0.05 for all variables) - better control of ascites, as expressed by a reduction in tapping of ascites (p < 0.0001), weight loss (p < 0.0001), higher rates of complete disappearance of ascites (80% vs. 15%, p < 0.0001) - improvement in overall survival (19.6 vs. 11.6 months, p < 0.0001)
Lv XY. 2020[71]	Prospective observational study	75 patients with ascites receiving SMT (n= 25) or SMT + rifaximin 200 mg QID for 3 to 4 weeks (n=50)	Primary outcomes: control of ascites and survival Rifaximin was associated with: - better control of ascites, as shown by enhanced response to diuretic therapy (p = 0.009) and more marked weight loss (p = 0.011) - increased survival (HR=2.53, 95% CI: 1.01-6.38, p = 0.048)

SBP, spontaneous bacterial peritonitis; HRS, hepatorenal syndrome; OR, odds ratio; CI, confidence interval; RCT, randomized controlled trial; HE, hepatic encephalopathy; BID, bis in die (twice a day); AKI, acute kidney injury; IRR, incidence rate ratio; RRT, renal replacement therapy; HVPG, hepatic venous pressure gradient; RH, relative hazard; CO, cardiac output; GFR,

glomerular filtration rate; PRA, plasma renin activity; MAP, mean arterial pressure; SVR, systemic vascular resistances; IL-6, interleukin 6; TNF-α, tumor necrosis factor alfa; LPS, lipopolysaccharide; HCC, hepatocellular carcinoma; HR, hazard ratio; MELD, Model for End-stage Liver Disease; INR, international normalised ratio; TID, ter in die (three times a day); BUN, blood urea nitrogen; SMT, standard medical therapy; QID, quater in die (four times a day)

Table 3. Recommendations for use of rifaximin in the management of complications of cirrhosis in clinical practice

Recommended
Prevention of Recurrence of Hepatic Encephalopathy
Recommended on a case-by-case basis
Covert Hepatic Encephalopathy (treatment not cost-effective)
Needs further research and therefore not recommended currently
Inpatient therapy of Episodes of Overt Hepatic Encephalopathy
Prevention of Spontaneous Bacterial Peritonitis Recurrence
Prevention of other complications of cirrhosis

Table 4. Studies reported in « c*linicaltrials.gov »* investigating the use of rifaximin in cirrhosis.

Endpoints	**Number of studies**
PREVENTION of COMPLICATIONS of CIRRHOSIS	
Spontaneous Bacterial Peritonitis	4
Covert Hepatic Encephalopathy	3
Decompensated Cirrhosis	2
HE in patients with transjugular intrahepatic portosystemic shunts	2
Acute-on-Chronic Liver Failure*	1
Variceal Bleeding	1
Renal Failure	1
Persistent HE	1
OTHER	
Portal Pressure	2
Systemic Inflammation	1
B-Cell Dysregulation	1
Portal Vein Thrombosis	1
Quality of Life	1

*associated with simvastatin, HE, hepatic encephalopathy

LEGENDS OF FIGURES

Figure 1: Molecular structure of rifaximin and rifampicin.

Figure 2. Putative effects of rifaximin on the gut-liver axis.

Rifaximin was shown to increase intestinal epithelial homeostasis by PXR-dependent mechanisms. Among them, inhibition of NFκB, decrease of TNFα, IL-6, IL-8 and IL-10 secretion, and induction of biotransformation phase 1 and 2 enzyme activities (e.g., CYP3A4, GSTA-1) are notable. Subtle changes in intestinal microbiome composition and lowering of virulence factors have also been observed. Effects of rifaximin on bacterial bile acid biotransformation are yet unclear. Rifaximin led to normalization of serum LPS binding protein levels and thereby lowering of the pro-inflammatory state in the liver. Figure created with Biorender.com.

NF-κB: Nuclear Factor kappa B; TNFα: Tumor Necrosis Factor alpha; IL: Interleukin; CYP3A4: Cytochrome P450 3A4; GSTA1: Glutathione S-Transferase Alpha 1; PXR: Pregnane X Receptor; RXR: Retinoid X Receptor; LPS: Lipopolysaccharides.

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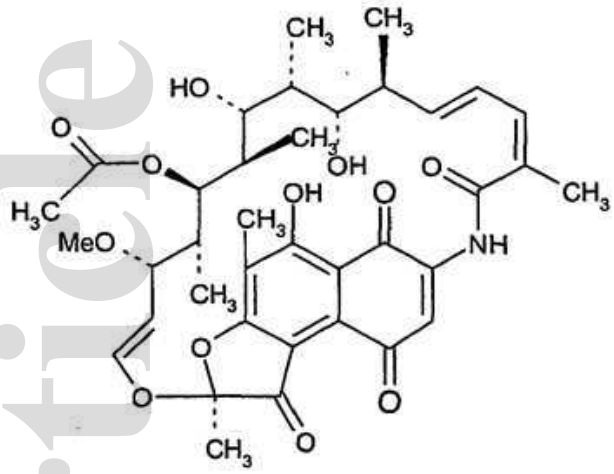

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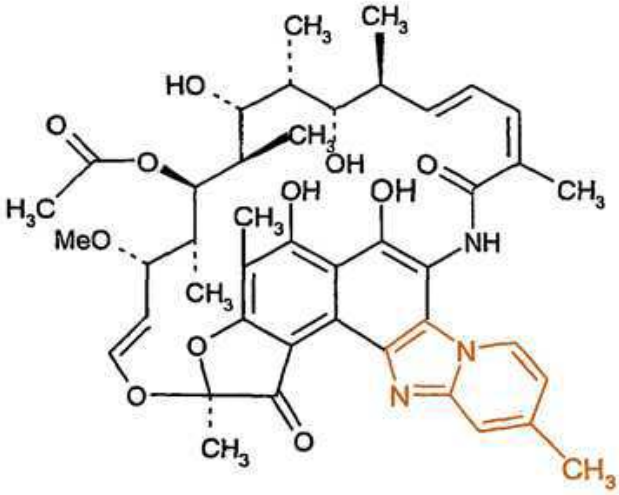

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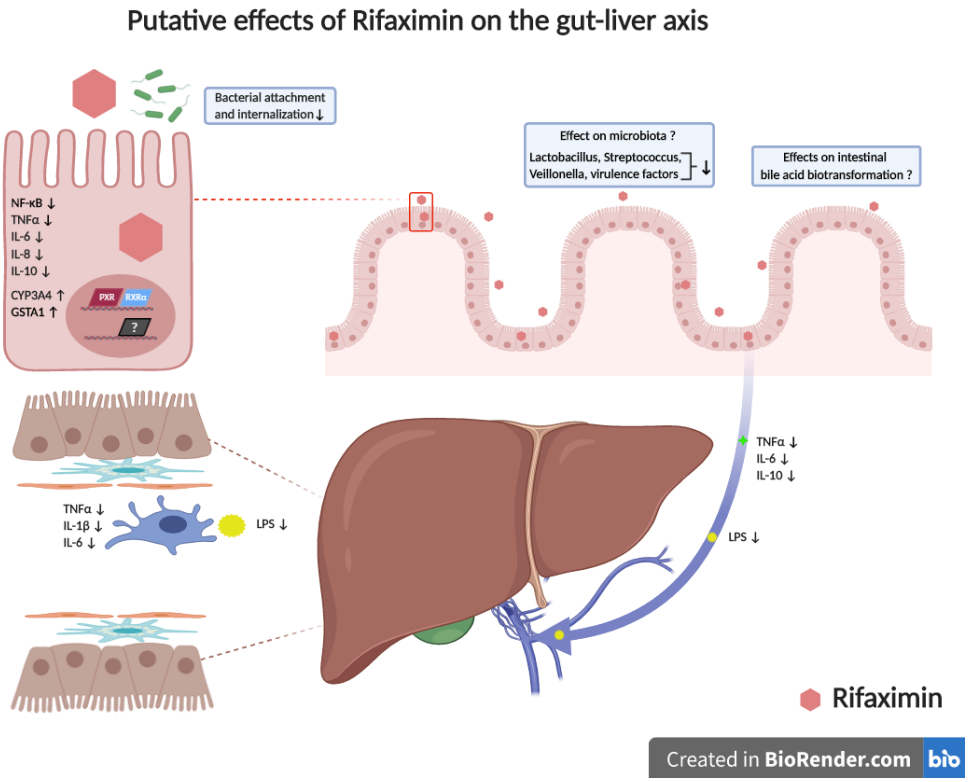

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