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REVIEW ARTICLE

Rifaximin: beyond the traditional antibiotic activity

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Rifaximin is a non-systemic oral antibiotic derived from rifampin and characterized by a broad spectrum of antibacterial activity against Gram-positive and -negative, aerobic and anaerobic bacteria. Rifaximin was first approved in Italy in 1987 and afterwards in many other worldwide countries for the treatment of several gastrointestinal diseases. This review updates the pharmacology and pharmacodynamics of rifaximin highlighting the different actions, beyond its antibacterial activity, such as alteration of virulence, prevention of gut mucosal adherence and bacterial translocation. Moreover, rifaximin exerts some anti-inflammatory effects with only a minimal effect on the overall composition of the gut microbiota. All these properties make rifaximin a good candidate to treat various gastrointestinal diseases.
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INTRODUCTION

Rifaximin ($C_{43}H_{51}N_3O_{11}$, MW = 785.9 Da, Figure 1) is a rifamycin antimicrobial agent and a structural analog of rifampin. Rifaximin is obtained by the reaction between rifamycin O and 2-amino-4-methylpyridine. Rifamycin O is the oxidated form of rifamycin B, fermentation product from the source microorganism *Amycolatopsis mediterranei*.[1]

Rifaximin is an original molecule discovered and patented by Alfa Wassermann in 1980; an implementation of the method of preparation, which made its industrial production feasible, was developed in 1984.[2,3]

Rifaximin, as the other rifamycins, exerts its antibacterial activity by binding to the β-subunit of bacterial DNA-dependent RNA polymerase, thus inhibiting bacterial RNA synthesis.[4,5] Animal and human studies demonstrate that the systemic absorption of rifaximin, after oral administration, is negligible, being less than 0.4% of the administered dose. The discovery of polymorphism of rifaximin in the early 2000s showed that the bioavailability of rifaximin is strictly correlated to its polymorphic form, being the α form (the marketed form) one of the less bioavailable.[6] Rifaximin is a topical antibiotic and, in fact, it exerts its antibacterial activity against microorganisms that cause gastrointestinal infections, but not systemic infections; indeed, rifaximin, released in the gastrointestinal tract, is excreted, primarily, in feces as unchanged drug.[7]

Because of its localized activity, rifaximin has a favorable side-effect profile and a low potential for drug interactions.

Some observations suggested that rifaximin may be more effective in the treatment of infections in the small intestine, because of the higher concentration of bile in this region than in the colon, as bile acids appear to solubilize rifaximin on a dose-dependent manner, increasing the drug's antimicrobial effect.[8]

Rifaximin was first approved in Italy in 1987 and afterwards in several countries for the treatment of various gastrointestinal diseases and, in May 2004, approved by the US Food and Drug Administration for the treatment of traveler's diarrhea caused by noninvasive strains of *Escherichia coli*. Rifaximin obtained, from the Food and Drug Administration and most of the major European countries, in 2010 and 2012, respectively, a new labeling for reduction of the risk of recurrence of overt hepatic encephalopathy in patients with advanced liver disease aged 18 years or older.

Additional indications are still being evaluated. In phase III randomized studies, rifaximin-treated patients were significantly more likely than placebo-treated patients to achieve adequate relief of global inflammatory bowel syndrome symptoms and abdominal bloating, and an additional phase III study is ongoing in inflammatory bowel syndrome. Moreover, rifaximin, in a formulation tailored for an extended intestinal release, is currently under phase III investigation as a potential treatment for Crohn's disease, having provided promising results in inducing remission of Crohn's disease in a phase II multicenter, randomized, double-blind trial, given twice daily to 402 patients with moderately active Crohn's disease for 12 weeks.[9]

Rifaximin exhibits a broad spectrum of *in vitro* and *in vivo* activity,[10] modulates microbial virulence[11,12] and epithelial cell function.[13] The variety of the rifaximin actions, in addition to its antimicrobial effects, may potentially explain the effects of the drug in variety of diseases and syndromes. In fact, although it has been shown to have both bactericidal and bacteriostatic properties that account for some of the antimicrobial effects observed in rifaximin treatment, one of the most intriguing aspects of this drug is that it can shorten the duration of infection, without eradicating enteropathogens and with minimal effects on the colonic bacterial flora.[14,15]

In fact, the most peculiar characteristic of rifaximin, with respect to other antibiotics, is its efficacy without significant changes in gut microbiota composition.[16]

The aim of the present review is to highlight the different actions of rifaximin, in addition to its antibacterial activity.

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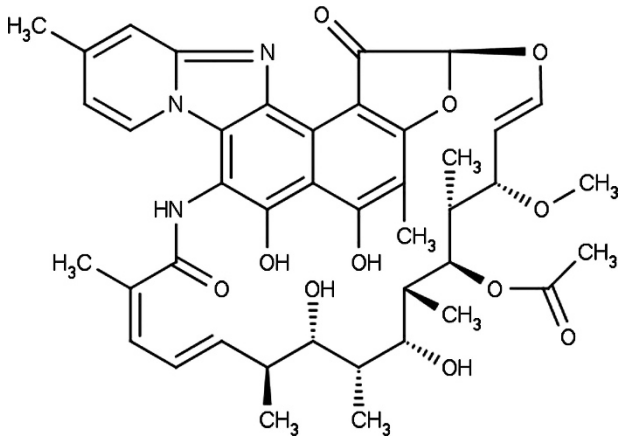

Figure 1 Chemical structure of rifaximin.

ANTIMICROBIAL EFFECTS

Rifaximin is a powerful antimicrobial *in vitro,* with a broad spectrum of antibacterial activity against Gram-positive and -negative, aerobic and anaerobic bacteria, including ammonia-producing species.[17] Traditional MIC breakpoints for rifampin, set by the Clinical and Laboratory Standards Institute, based on drug plasma levels, have no relevance to rifaximin in the treatment of an enteric infection, being a minimally absorbed antibiotic. Based on clinical experience, an arbitrary breakpoint was set at $32\,\mu g\,ml^{-1}$.[18]

MIC_{50} and MIC_{90} values of rifaximin, determined against many different enteropathogens, isolated in different countries, were mainly between 8–64 and 16–$128\,\mu g\,ml^{-1}$, respectively.[7,10,19] Therefore, rifaximin showed an intermediate *in vitro* activity in comparison with other antimicrobial agents as, for example, nalidixic acid and ciprofloxacin. Moreover, rifaximin showed a good *in vitro* activity against several enteropathogens, such as *E. coli*, *Shigella spp* and *Salmonella spp*. This is in accordance with the clinical studies that clearly show the effectiveness of the compound in the treatment of traveler's diarrhea.[14,15] Rifaximin is also effective against *Enterohemorrhagic E. coli* causing diarrhea, bloody diarrhea and hemolytic-uremic syndrome by inhibition of the production and release of Shiga toxin, the major virulence factor of *Enterohemorrhagic E. coli* involved in the pathogenesis of hemolytic-uremic syndrome.[20]

A high antibacterial activity was demonstrated against some enteric bacteria such as *Clostridium difficile*, showing a lower MIC_{50} ($\leqslant 0.25\,\mu g\,ml^{-1}$). Unlike other antibiotics, it does not appear to induce at high rates resistant *Clostridium difficile* strains, during therapy.[21]

Development of resistance against rifaximin is, as for all antibiotics, a potential concern. Resistance to rifamycins mainly results from mutations in the *rpoB* gene that encodes the β-subunit of RNA polymerase, leading to cross-resistance to all rifamycins. However, cases of non-cross-resistance between rifaximin and rifampin have been reported in *C. difficile*. It is also unknown whether these resistance mutations correlate with clinical failures.[22] However, studies investigating rifaximin resistance in traveler's diarrhea-associated *E. coli* have generally found no clinically significant resistance. This was also observed in a very recent study in which the *in vitro* activity of rifaximin in *E. coli* and other enteropathogenic bacteria, isolated from travellers returning to the United Kingdom was determined.[23] Rifaximin showed good *in vitro* activity against diverse *Enterobacteriaceae*, but was largely inactive against *Campylobacter spp*. Moreover, the local concentration of rifaximin in the gut may overwhelm resistance, whereas this is unlikely to be the case for absorbed antibiotics. Rifaximin, similar to rifampin, was also found to have potential to co-select Multi Drug Resistance *E. coli* in the gut flora, albeit at very low frequency. A much stronger association was seen between Extended Spectrum β-lactamase and/or carbapenemase production and resistance to alternative treatments for traveler's diarrhea, notably ciprofloxacin and azithromycin.[23] In addition to the well-characterized mutations in *rpoB,* the activity of Phe-Arg-β-naphthylamide-inhibitable efflux pumps was recently reported to contribute to the development of rifaximin resistance; however, the information on temporal associations and dosing practices, which may promote rifaximin resistance, were lacking.[24,25]

IMPACT ON THE COMPOSITION OF INTESTINAL MICROBIOTA

Rifaximin, in *in vitro* or *ex vivo* models and in humans, does not significantly alter the gut microbiota, leading to a relative abundance of 'health-promoting bacteria' and changing the bacterial metabolites composition in the gut.[16]

In recent studies on hepatic encephalopathy patients, rifaximin was shown to reduce endotoxemia, the levels of secondary bile acids and harmful metabolites, which were positively correlated with *Bacteroidaceae*, *Enterobacteriaceae*, *Porphyromonadaceae*, with only a modest change in stool microbiota composition.[26–28] Bajaj *et al.*[26] did not find a significant change in microbiota at the phylum or order level, before and after rifaximin treatment, but a reduction in the abundance of the taxa *Veillonellaceae* and a trend toward increased *Eubacteriaceae*. The majority of the differentiators were serum long-chain fatty acids that increased after rifaximin therapy, showing that rifaximin has a major effect on the metabolic network.

The local effect of rifaximin may result, also, in a beneficial systemic effect, such as a significant improvement in cognition in hepatic encephalopathy patients, probably related to the gut–liver–brain axis modulation.[29]

Xu *et al.*,[30] in two animal models of visceral hyperalgesia that mimic inflammatory bowel syndrome, demonstrate that rifaximin, after oral administration in rats, while maintaining unchanged the bacterial community composition at the phylum level, induces changes at the family level, leading to a significant relative abundance of *Lactobacillus*. On the contrary, the relative abundance of *Clostridiaceae*, *Erysipelothrichaceae* and *Peptostreptococcaceae* was significantly reduced.

In the same animal model, dramatic changes in bacterial communities, distinct from those observed with rifaximin, were observed after neomycin treatment.

Moreover, in a continuous culture colonic model, colonized by the fecal microbiota of patients affected by colonic active Crohn's disease, rifaximin did not affect the overall composition of the gut microbiota, while causing an increase in the concentration of 'health-promoting bacteria' such as *Bifidobacterium, Atopobium and Faecalibacterium prausnitzii*.[16] A shift in microbial metabolism was also observed, as shown by increases in short-chain fatty acids, propanol, decanol, nonanone and aromatic organic compounds, and decreases in ethanol, methanol and glutamate.

ALTERATION OF VIRULENCE

Rifaximin has, surprisingly, little effect in reducing the bacterial load of both Gram-positive and Gram-negative flora of the colon; in fact, in clinical trials on travellers' diarrhea, rifaximin shows a low rate of pathogen eradication from stool samples, yet it reduces the symptoms of the enteric infection. This clinical efficacy could be due to the

alteration of virulence factors of the enteric bacterial pathogens, without killing them, as observed with sub-therapeutic levels of the drug. Sub-inhibitory concentrations of rifaximin, in fact, altered the virulence of *Enterotoxigenic E. coli* and *Enteroaggregative E. coli*, as well as *Shigella sonnei*. Expression of *Enterotoxigenic E. coli* virulence factors, including heat-stable and heat-lable enterotoxins and surface adhesion intestinal-binding factors, was reduced upon exposure to sub-inhibitory concentrations of rifaximin.[11]

Moreover, rifaximin caused morphological alterations in both susceptible and resistant bacterial strains at concentrations as low as 1/32 of the MIC. Rifaximin reduced plasmid transfer, in different bacteria species by >99% and lowered the viability and virulence of the bacteria, even though they developed resistance, suggesting that exposure of pathogens to sub-MIC concentrations of rifaximin may repress the pathogen virulence expression.[12]

PREVENTION OF BACTERIAL ADHERENCE TO GUT MUCOSA

Rifaximin affects epithelial cell physiology resulting in altered infectivity by enteric pathogens, and baseline inflammation, suggesting that rifaximin conferred cytoprotection against bacterial colonization and infection.[13] In fact, rifaximin pretreatment of *Enteroaggregative E. coli* decreased bacterial adherence to epithelial cells (HEp-2 (laryngeal)) without affecting their viability. The mechanism likely involved direct rifaximin-mediated alterations of the HEp-2 cells, which, in turn, affected bacterial adherence (directly, indirectly or both). Furthermore, the observation that the effects were time- and concentration-dependent suggested that a rifaximin-mediated process was altering cellular parameters important to *Enteroaggregative E. coli* adherence. Reduced mucosal attachment may, at least, partially explain the beneficial effects of rifaximin in gastrointestinal diseases.

PREVENTION OF BACTERIAL TRANSLOCATION

Intestinal bacteria and their byproducts contribute to infectious complications of various clinical diseases like chronic liver disease or inflammatory bowel disease (IBD). It has been shown that bacteria themselves might not need to cross the epithelial intestinal barrier, but translocation of inflammatory compounds, produced at the intestinal wall or toxic products from the gut, might be responsible for the systemic injuries.[31] This thought broadened the definition of bacterial translocation in relation to intestinal permeability, including not only the passage of viable bacteria but also endotoxins, as an activating ligand for hepatic Toll-like receptor 4, an important constituent of the innate immune system, or antigens from the intestinal lumen into the circulation causing systemic inflammation and distant organ injury.

Zhu *et al.*[32] demonstrated that, in a murine model of bile duct ligation-induced liver fibrosis, rifaximin administration leads to less fibrosis, angiogenesis and portal hypertension and that Toll-like receptor 4 pathway is involved in rifaximin-induced attenuation of liver fibrosis and angiogenesis. Furthermore, both aerobic and anaerobic bacteria counts from stool, which increased after bile duct ligation, were significantly reduced in animals receiving rifaximin.

Moreover, Fiorucci *et al.*[33] demonstrated that the presence of the bacterial flora in the colon has a major role in activating colon inflammation in the 2,4,6-trinitrobenzenesulfonic acid model of colitis. Rifaximin administration reduces colitis development by preventing bacterial translocation and exerts immunomodulatory functions, by reducing the colonic bacterial load.

ANTI-INFLAMMATORY EFFECT

Rifaximin is an intestine-specific human Pregnane X Receptor (PXR) agonist. Recent studies in mice have provided insight into a novel function for PXR in IBD. The mechanism of the protective effect of PXR activation on IBD is not fully elucidated, but is due in part to the attenuation of nuclear factor (NF)-κB signaling that results in lower expression of proinflammatory cytokines as interleukin (IL)-10, IL-1β, tumor necrosis factor-α. Thus, PXR may be a novel target for IBD therapy and rifaximin potential therapeutic value in IBD may be in part due to its PXR activation properties.[34]

Rifaximin efficacy, in reducing NF-κB signaling in a PXR-dependent manner, was demonstrated in primary human colon epithelial cells as well as in human colon biopsies.[35] The preventive and therapeutic role of rifaximin, in experimental models of IBD (dextran sodium sulfate and 2,4,6-trinitrobenzene sulfonic acid mouse models), were also demonstrated in PXR-humanized mice, where rifaximin not only prevented IBD before an inflammatory insult, but also decreased symptoms after the onset of colitis.[36]

Chemically induced IBD destroys the structure and function of normal epithelial cells and represses expression of drug metabolism enzymes. This may be, in part, due to activation of NF-κB and increased proinflammatory cytokines (IL-6, IL-10, IL-1β, tumor necrosis factor-α, interferon (INF) α), followed by an imbalance of the epithelial barrier and mucosal immune system and an increase of intestinal permeability. Upon rifaximin-induced PXR activation in epithelial cells, the NF-κB signaling cascade is repressed, cytokine (IL-6, IL-10, IL-1β, tumor necrosis factor-α, INFα) production is inhibited and intestinal permeability reduced. This restores the balance between the epithelial barrier and mucosal immune system, resulting in the reconstruction of cell structure and function.[36] Moreover, Terc *et al.*[37] provided evidence that PXR agonists can enhance wound healing in intestinal epithelial cell monolayers through the activation of p38 MAP kinase-dependent cell migration. Wound healing triggered by PXR agonists occurs in the absence of increased cell proliferation.

In rat models of chronic stress, Xu *et al.*[32] showed that oral administration of rifaximin not only modulated gut bacterial communities, as already explained, but also prevented mucosal inflammation, barrier impairment and visceral hyperalgesia. In particular, rifaximin treatment led to a dominance of lactobacilli and normalization of IL-6 and TNF-α mRNA levels in the distal ileum of stressed rats. Inflammatory cell infiltration in the lamina propria was also reduced, an effect likely mediated by *Lactobacillus*, considering the reported *Lactobacillus*-induced downregulation of proinflammatory cytokines IL-6 and TNF-α in Crohn's disease. This might further explain the benefits of rifaximin in the treatment of various functional gastrointestinal disorders.

CONCLUSIONS

Rifaximin, polymorph α, has a broad-spectrum antibacterial activity *in vitro* against enteric pathogens, characterized by a gut-localized action and minimal systemic absorption. Consequently, rifaximin was developed for a variety of enteric conditions that involve a pathogenic role of bacteria. In addition to its antibacterial activity, there is some evidence that rifaximin may have other activities, including anti-inflammatory activity, alteration of bacterial virulence and prevention of bacterial translocation.

Although the rifamycins were discovered by Sensi in 1957, their derivatives such as rifaximin still show new perspectives of development.

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