**Rifaximin for the treatment of irritable bowel syndrome – a drug safety evaluation**

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**ABSTRACT**

**Introduction:** Irritable bowel syndrome is a functional gastrointestinal disorder with a multifactorial etiology. Alterations of intestinal motility and immunity, gut-brain interactions, as well as gut microbiota dysbiosis contribute to the development of irritable bowel syndrome. Therefore, gut microbiota modulation by non-absorbable antibiotics is a therapeutic option in patients with IBS.

**Areas covered:** Published articles including patients with irritable bowel syndrome reporting data about rifaximin activity and safety have been searched throughout the literature and selected.

**Expert opinion:** The optimal antibiotic molecule should be local-acting, long-acting and safe-acting. Rifaximin is a non-absorbable antibiotic with additional anti-inflammatory and gut microbiota-modulating activity. It is effective in inducing symptoms relief in patients with IBS, even after repeated treatment courses. Rifaximin-related side effects in patients with IBS are reported to be mild and infrequent; microbial resistance is rare and transient, due to the high local concentration of the drug and to the absence of horizontal transmission. Clostridium difficile infection is not usual in patients receiving rifaximin in absence of predisposing conditions such as hospitalization and immunosuppression, which are uncommon in patients affected by irritable bowel syndrome. Nevertheless rifaximin is an antibiotic active against Clostridium difficile infection. Rifaximin has limited metabolic interactions and is not expected to interfere with drug metabolism in patients with normal hepatic function. These properties make rifaximin a safe antibiotic for gut microbiota modulation in patients with IBS.

1. Introduction

Irritable bowel syndrome (IBS) is a relapsing gastrointestinal functional condition characterized, according to the Rome III Criteria, by recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months, which improves with defecation or is associated with a change in frequency or form of stools.[1] These symptoms clearly impact quality of life with important social costs. IBS prevalence in the general population ranges from 5% to 15%, being one of the most common gastrointestinal functional disorders.[2] Overall, more females than males are affected by IBS. It can be classified in diarrhea predominant (IBS-D), constipation predominant (IBS-C), mixed subtype (IBS-M), or unclassified (IBS-U) on the basis of prevalent bowel habit. Its diagnosis is based on clinical assessment, since there are no specific abnormal radiological or endoscopic findings or reliable biomarker tests. The pathophysiology of IBS is still not clear. However, many factors have been implicated, such as low-grade immune activation, increased mucosal intestinal permeability, visceral hypersensitivity,[3] and gut microbiota deregulation.[4] The clinical efficacy of dietary approaches and pharmacological agents able to modulate the gut microbiota further supports the hypothesis of a role of dysbiosis in IBS pathogenesis.[5]
gel electrophoresis fingerprint profiles [15]; furthermore, the composition of mucosa-adherent microbiota is different between IBS patients and healthy controls, being *Eubacterium rectale* and *Clostridium coccoides* the predominant bacterial species, accounting for 48% of the total adherent bacteria in IBS compared to 32% of healthy controls. Finally, the density of bacterial biofilm (a layer of micro-organisms that form a coat on the surface of the intestine) is significantly larger in IBS patients.[16] More recent data have reinforced these observations, showing that the gut microbiota of IBS patients also differs from that of healthy controls in other bacterial species, including *Coprococcus* spp., *Collinsella* spp., and *Coprobacillus* spp.[17] A higher prevalence of *Escherichia coli*, *Enterococcus* spp., and *Klebsiella pneumoniae* has also been reported in some clusters of IBS patients,[18] with significantly higher levels of pathogens in those with SIBO than in those without. Another study described a marked over-representation of *Escherichia/Shigella* and *Aeromonas* spp. in IBS-D subjects, while there was an underrepresentation of *Lactococcus*, *Acinetobacter* and *Citrobacter*.[19] Finally, Kerckhoffs et al.[23] found that *Bifidobacterium catenulatum* levels were significantly lower in patients with IBS than healthy controls.

IBS can also develop in 10% of cases after an acute infectious episode of the gastrointestinal tract, and more than half of subjects may remain symptomatic for bowel dysfunction even 6 years after the acute event.[20,21] In these patients, specific and permanent alterations of the gut microbiota have been described.[22] It can be assumed that the increasing availability of new microbiological techniques will result in increasing knowledge, which may ultimately explain the efficacy of the old therapeutic approaches and help to identify new ones.

These findings provide further evidence that changes in small bowel microbial composition may underlie the pathogenesis of IBS for some patients.[23] However, not only gut microbiota alteration but also other different mechanisms underlie IBS pathophysiology and this should not be ignored. Likely, microbiota changes could be crucial only in some subsets of patients, while could reflect the immediate consequence of different primary triggers in others.

**3. Rifaximin treatment for IBS: is there a role for an antibiotic in a non-infectious disease?**

Based on the role of the gut microbiota in the pathogenesis of IBS, non-absorbable antibiotics should be one of the treatment options for this disease. The ideal antibiotic molecule for this clinical setting should have a local effect, should be able to improve symptoms producing negligible side effects, and should have a broad-spectrum antimicrobial activity and a low resistance profile.

Rifaximin is the non-absorbable antibiotic approved for the use in patients with IBS, since 2015. Its efficacy in patients with IBS is due to direct bactericidal properties as well as due to indirect effects on the gut microbiota additional to the primary antibiotic activity (Box 1).

**In vitro** studies demonstrated that rifaximin is able to modulate bacterial virulence in enterotoxigenic *E. coli* isolates,[24] and that pretreatment of epithelial cells (HEp-2 laryngeal cells, HCT-8 ileocecal cells, A549 epithelial lung cells, and HeLa cervical cells) with rifaximin significantly reduces the adherence of enteroaggregative *E. coli* compared to rifampin, acetone, and doxycycline.[25] In the same study, rifaximin also inhibited *Bacillus anthracis* and *Shigella sonnei* internalization into A549 and HeLa cells more effectively than control antibiotics. Moreover, rifaximin can reduce gut microbiota-driven inflammation by modulating nuclear factor kappa-light-chain-enhancer of activated B cells activation via the pregnane X receptor [26–28] and can inhibit bacterial translocation.[28]

Interestingly, the administration of rifaximin has been associated with a positive modulation of the gut microbiota characterized by the increase in beneficial bacterial strains. Studies based on standard microbiological analyses and others based on continuous cultures [29,30] demonstrated that while rifaximin does not affect the overall composition of the gut microbiota, it increases the abundance of *Bifidobacterium*, *Atopobium* and *Faecalibacterium prausnitzii*, which are important modulators of intestinal health.[31–33] More recent studies in mice models of hyperalgesia [34] highlighted that treatment with rifaximin may increase the abundance of Lactobacilli, which are known to improve gut barrier function, to reduce stress-induced visceral pain and to downregulate pro-inflammatory cytokines.[35–39] Finally, pyrosequencing of 16S ribosomal RNA obtained from fecal samples of patients affected by different gastrointestinal diseases including IBS, confirmed an increase in *Lactobacillus* and *Faecalibacterium* abundance following administration of rifaximin.[40,41]

Taking together all the evidences about the additional properties of the antibiotic rifaximin, it is reasonable to argue that the resulting favorable ‘eubiotic’ modulation of the gut microbiota may contribute to its success in the clinical setting.

One of the first evidences about the efficacy of rifaximin in patients with IBS came from Pimentel’s group (Table 1). [42] Eighty-seven patients who met the Rome I criteria were randomized to receive either rifaximin 1200 mg daily or placebo for 10 days; rifaximin arm obtained a higher rate of global symptoms improvement compared to the placebo one, and this result was maintained for the whole study duration (10 weeks). Another randomized controlled trial including 124 patients affected by IBS reported the amelioration of bloating and flatulence in 40.5% of cases following the administration of rifaximin 800 mg for 10 days, compared to an improvement of only 18.2% in the placebo group, without any reported adverse event (AE).[43]
<table>
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<tr>
<th>Study</th>
<th>Design</th>
<th>No. of pts</th>
<th>Rifaximin dose</th>
<th>Efficacy</th>
<th>Follow-up</th>
<th>AEs</th>
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<tr>
<td>Cuoco et al. [45]</td>
<td>Retrospective</td>
<td>96 pts</td>
<td>1200 mg/daily for 14 days</td>
<td>Significant improvement of IBS symptoms after rifaximin treatment</td>
<td>4–5 Months</td>
<td>None</td>
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<tr>
<td>Pimentel et al.</td>
<td>Double-blind, randomized, placebo-controlled</td>
<td>43 rifaximin / 44 placebo</td>
<td>400 mg tid for 10 days</td>
<td>Average improvement: 36.4% rifaximin group vs. 21% placebo ($p = 0.020$); VAS scores significantly better in the rifaximin group for bloating ($p = 0.010$) but not for abdominal pain ($p = 0.32$), diarrhea ($p = 0.67$), and constipation ($p = 0.069$)</td>
<td>10 Weeks; global improvement and VAS scores improvement for bloating were maintained during follow-up</td>
<td>Placebo vs. rifaximin: abdominal pain 3 vs. 4, constipation 2 vs. 1, nausea 2 vs. 0, vomiting 1 vs. 0, bad taste 0 vs. 2, fatigue 1 vs. 1, straining 0 vs. 1, urgency 0 vs. 1, headache 1 vs. 0, hemorrhoid 1 vs. 0, rash 1 vs. 0, gas 1 vs. 0, fever 1 vs. 0. No statistical difference between groups</td>
</tr>
<tr>
<td>Sharara et al. [44]</td>
<td>Randomized double-blind placebo-controlled</td>
<td>37 rifaximin / 33 placebo</td>
<td>400 mg bid for 10 days</td>
<td>Symptoms relief: 15/37 (40.5%) rifaximin group vs. 6/33 (18.2%) placebo group ($p = 0.04$)</td>
<td>After 10 days follow-up: symptomatic improvement 10/37 (27%) rifaximin group vs. 3/33 (9.1%) placebo group ($p = 0.05$)</td>
<td>None</td>
</tr>
<tr>
<td>Scarpellini et al.</td>
<td>Prospective, parallel-group, randomized</td>
<td>80 pts, 63 with IBS (all subtypes)</td>
<td>1600 mg daily for 7 days</td>
<td>Symptoms improvement: 58 (69%)</td>
<td>–</td>
<td>14 AEs all of mild intensity; the most frequent were constipation (2 in the group 1 and 3 in the group 2), dyspepsia (2 in the group 1 and 1 in the group 2)</td>
</tr>
<tr>
<td>Yang et al. [47]</td>
<td>Retrospective</td>
<td>84 pts</td>
<td>400 mg tid for 10 days</td>
<td>Clinical response: 58 (69%)</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Lembo et al. [48]</td>
<td>Phase II, double-blind, placebo-controlled</td>
<td>191 rifaximin / 197 placebo</td>
<td>550 mg twice daily for an additional 14 days of placebo in both groups</td>
<td>At the end of treatment: global IBS symptoms improvement: 53% rifaximin vs. 43% placebo ($p = 0.03$); bloating improvement: 50% rifaximin vs. 42% placebo ($p = 0.04$)</td>
<td>At the end of 12 weeks follow-up: global IBS symptoms improvement: 62% rifaximin vs. 49% placebo ($p &lt; 0.05$); bloating improvement: 59% rifaximin vs. 51% placebo ($p &lt; 0.05$)</td>
<td>Similar to placebo</td>
</tr>
<tr>
<td>Peralta et al. [49]</td>
<td>Observational</td>
<td>97 pts</td>
<td>1200 mg/daily for 7 days</td>
<td>Symptoms score improved from 2.3 ± 0.6 to 0.9 ± 0.8 ($p = 0.003$) only in patients with BT normalization</td>
<td>3 Weeks</td>
<td>–</td>
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<tr>
<th>Study</th>
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<th>AEs</th>
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<tr>
<td>Pimentel et al. [50]</td>
<td>TARGET 1 phase 3, double-blind, placebo-controlled</td>
<td>309 rifaximin vs. 314 placebo</td>
<td>550 mg tid for 14 days</td>
<td>Global symptoms relief: 126/309 (40.8%) rifaximin vs. 98/314 (31.2%) placebo ( p = 0.01 )</td>
<td>10 Weeks</td>
<td>Rifaximin vs. placebo (pooled data): headache 38 (6.1%) vs. 42 (6.6%), upper respiratory tract infection 35 (5.6%) vs. 39 (6.2%), abdominal pain 29 (4.6%) vs. 35 (5.5%), nausea 27 (4.3%) vs. 24 (3.8%), diarrhea 27 (4.3%) vs. 22 (3.5%), nasopharyngitis 19 (3%) vs. 34 (5.4%), sinusitis 17 (2.7%) vs. 16 (2.5%), vomiting 15 (2.4%) vs. 9 (1.4%), bronchitis 13 (2.1%) vs. 17 (2.7%), cough 13 (2.1%) vs. 9 (1.4%), flatulence 10 (1.6%) vs. 14 (2.2%), back pain 10 (1.6%) vs. 15 (2.4%), pharyngolaryngeal pain 9 (1.4%) vs. 15 (2.4%), chest pain 1 (0.2%) vs. 2 (0.3%), breast cancer 1 (0.2%) vs. 1 (0.2%), cholecystitis or acute cholecystitis 0 vs. 2 (0.3%), upper respiratory tract infection 35 (5.6%) vs. 39 (6.2%), viral gastroenteritis 7 (1.1%) vs. 8 (1.3%), gastroenteritis 6 (1%) vs. 3 (0.5%), cellulitis 3 (0.5%) vs. 1 (0.2%), pneumonia 1 (0.2%) vs. 5 (0.8%), viral infection 1 (0.2%) vs. 4 (0.6%)</td>
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<tr>
<td>Pimentel et al. [50]</td>
<td>TARGET 2 phase 3, double-blind, placebo-controlled</td>
<td>315 rifaximin vs. 320 placebo</td>
<td>550 mg tid for 14 days</td>
<td>Global symptoms relief: 128/315 (40.6%) rifaximin vs. 103/320 (32.2%) placebo ( p = (0.03) )</td>
<td>10 Weeks</td>
<td>–</td>
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<tr>
<td>Di Stefano et al. [51]</td>
<td>Double-blind, randomized, cross-over</td>
<td>24 pts IBS-C</td>
<td>400 mg bid for 7 days</td>
<td>Reduction of cumulative breath H2 excretion, and of bloating, abdominal distention, abdominal pain, flatulence, borborygmi severity only after rifaximin administration in patients normosensitive to colonic fermentation</td>
<td>–</td>
<td>Mild worsening of constipation during rifaximin treatment in 1 pt, headache during placebo in 1 pt</td>
</tr>
<tr>
<td>Meyrat et al. [52]</td>
<td>Phase IV, prospective</td>
<td>106</td>
<td>200 mg quid for 14 days</td>
<td>Symptoms improvement: 5.5 ± 2.6 vs. 4.8 ± 2.7 for flatulence ( p = 0.008 ), 2.9 ± 2.4 vs. 2.7 ± 1.8 for diarrhea ( p = 0.008 ), 5.0 ± 2.7 vs. 4.1 ± 2.2 for flatulence ( p = 0.001 ), 3.9 ± 2.4 vs. 2.4 ± 2.0 for reduced overall well-being ( p &lt; 0.001 )</td>
<td>4 Weeks</td>
<td>Headache 3/106 (3%), dry skin 1/106 (1%), nausea without vomiting 1/106 (1%)</td>
</tr>
<tr>
<td>Pimentel et al. [53]</td>
<td>Double-blind, randomized, placebo-controlled</td>
<td>31 pts (16 neomycin and placebo, 15 neomycin and rifaximin) with C-IBS and methane level &gt;3 ppm on a single breath sample</td>
<td>Neomycin 500 mg bid or neomycin 500 mg bid + rifaximin 550 mg tid and placebo for 14 days</td>
<td>VAS score for constipation (combined vs. neomycin): 28.6 ± 30.8 vs. 61.2 ± 24.1 ( p = 0.0020 )</td>
<td>4 Weeks</td>
<td>Neomycin vs. neomycin/rifaximin: nausea 10 (63%) vs. 7 (47%), bloating and distention 9 (56%) vs. 7 (47%), abdominal pain 6 (38%) vs. 3 (20%), constipation 2 (13%) vs. 2 (13%), diarrhea 2 (13%) vs. 0 (0%) vs. 1 (1%), urgency 0 (0%) vs. 1 (1%), upper respiratory tract infection 0 vs. 1 (1%), malaise 1 (1%) vs. 0 (0%)</td>
</tr>
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</table>

Abbreviations: pt, patient; AEs, adverse events; IBS-C, constipation IBS; VAS, visual analog scale.
Following these favorable experiences, two randomized controlled trials including patients with non-constipation IBS (TARGET-1 and TARGET-2), were published in 2011; these two studies demonstrated that rifaximin 550 mg three times daily for 2 weeks improved symptoms, bloating, abdominal pain, and stools consistency over the whole study period of 10 weeks.[49] A recently published meta-analysis [53] concluded that rifaximin produces a therapeutic gain comparable to other treatment options in patients with IBS and is superior to placebo in inducing global symptoms and bloating improvement, but with a similar safety profile. However, the therapeutic amelioration is small. Only 10% more than placebo and a number needed to treat (NNT) of 10.

Finally, two studies with a small sample size explored the effects of rifaximin on functional symptoms in patients with C-IBS and increased colonic fermentation, demonstrated by methane excretion at lactulose breath test.[50,52] Alone or associated with neomycin, rifaximin improved symptoms severity, especially constipation, straining, bloating, abdominal distention and pain, especially when visceral sensitivity was not altered.

Rifaximin may also be useful in the eradication of SIBO, which may play a role in the development of symptoms in patients with IBS. Rifaximin has demonstrated efficacy in reducing bacterial abundance in the duodenum and in the ileum in mice models of visceral hyperalgesia,[34,54] and has bactericidal effect on duodenal isolates of patients affected by SIBO.[55] The activity of rifaximin in specific tracts of the intestine may be explained by the high bile acids-dependent solubility of the molecule.[56] Although clinical data seem to confirm the beneficial activity of rifaximin in eradicating SIBO in patients with IBS, producing symptoms amelioration,[44–46,48,51] these data derive from uncontrolled studies, in which SIBO diagnosis was not always achieved by glucose breath test. Another study based on jejunal cultures failed to confirm a significant difference in SIBO prevalence between IBS patients and controls.[57]

4. Rifaximin safety in IBS

The debate about rifaximin safety is focused on two main concerns: AEs occurring during treatment, which may be or not drug-related, and, as like as other antibiotic molecules, the risk of infections sustained by resistant microorganisms and the development of *Clostridium difficile* colitis.[58] The issue of infective complications has been particularly stressed in IBS, since use of rifaximin in this setting often requires prolonged or repeated therapeutic attempts.

Consistent data about rifaximin safety come from studies including patients with liver disease, Crohn’s disease, and subjects with traveler’s diarrhea. The most common reported AEs were ascites, headache, nausea, dizziness, dyspepsia, abdominal discomfort, abdominal distension, diarrhea, constipation, and flatulence.[59–67] Although cellulitis, peritonitis, pneumonia, sepsis/septic shock, urinary tract/kidney infection, nasopharyngitis, fever and respiratory tract infections have been reported, data about the occurrence of infections in cirrhotic patients undergoing treatment with rifaximin are contrasting.[65,67,68]

As regards *Clostridium difficile* colitis, two cases have been reported in patients with cirrhosis and hepatic encephalopathy in the registrative trial,[68] while four cases were diagnosed in patients evaluated during the long-term maintenance period.[65] One case of *Clostridium difficile* infection was also reported in patients with Crohn’s disease undergoing treatment with rifaximin.[63]

However, it should be noted that the incidence of *Clostridium difficile* infection mainly depends on the severity of the underlying disease, the immune system function and the rate of hospitalization, conditions that are infrequent in patients with IBS, who are usually in good general conditions and do not require hospitalization. Furthermore, rifaximin has a strong activity against *Clostridium difficile* strains, being therefore uncommon the emergence of infections in absence of predisposing conditions.[69]

4.1. Rifaximin safety in patients with IBS

Data from prospective and retrospective published studies have been encouraging regarding rifaximin safety in IBS. Headache, nausea, abdominal pain, and constipation have been the most shared AEs among rifaximin-treatment arms, but, notably, there was no significant difference in AEs incidence in respect to the group of comparison (Table 1).[45,50–52]

In two studies no AEs were recorded,[43,44] and only one episode of infectious complications (upper respiratory tract infection) was observed in one patient receiving rifaximin in association with neomycin.[52]

Phase II and III trials and the registrative study have drawn a more detailed picture of safety and tolerability of rifaximin.[47,49,70] In both treatment phases and during the post-treatment follow-up, the incidence of AEs was similar to placebo and involved 52.5% of patients being classified as treatment-related in only 12.1% of cases.[71] Headache was the most common symptom, while nausea, abdominal pain, diarrhea, and vomiting were the most common gastrointestinal AEs. The incidence of constipation or diarrhea were lower than 2%. Infections were also reported, in particular upper respiratory tract infections, urinary tract infections, nasopharyngitis and sinusitis, but none of the patients on active treatment developed *Clostridium difficile* infection. Overall, data pooling demonstrated that only about 6% of the AEs were severe, among which 1.6% were serious and in only 0.1% were drug-related. AEs caused drug discontinuation in 2% of patients, even if in only 0.8% of cases there was a clear relationship with rifaximin assumption. A similar safety profile was recorded in the registrative study.[71]

4.2. Rifaximin retreatment and bacterial resistance

IBS is a chronic condition characterized by frequent re-actuation of symptoms. Retreatment is therefore very common, and may represent a serious issue when antibiotic therapy is chosen, since efficacy is usually decreased by the development of microbial resistance. Lack of clinical efficacy has been reported
in more than 70% of cases when antibiotics, such as neomycin have been used for IBS treatment.[46]

A recent study [55] analyzed the *in vitro* bacteriostatic and bactericidal activity of rifaximin on duodenal isolates from 117 patients affected by SIBO, 68 also diagnosed with IBS. At the breakpoint of 32 mcg/mL, 85.4% of *E. coli*, 43.6% of *Klebsiella* spp., 34.8% of *Enterobacter* spp., 54.5% of other Enterobacteriaceae, 82.6% of non-Enterobacteriaceae Gram negatives, 100% of *E. faecalis*, 100% of *E. faecium* and 100% of *S. aureus* were inhibited. Moreover, bactericidal effects were detected on nine bacterial isolates after 24 h of exposure to rifaximin 500 mcg/mL. Taking into account that rifaximin can reach fecal concentrations as high as 8000 mcg/g,[72] with a consequent very high tissue concentration per minimal inhibitory concentrations for tested isolates, this could explain the high efficacy of rifaximin even in the case of retreatment.

Nevertheless, rifaximin resistance requires chromosomal mutation and is almost rare,[73] with resistant bacterial strains disappearing within 12 weeks after treatment discontinuation. [74] While some studies failed to demonstrate the emergence of bacterial resistance following administration of rifaximin [75] in patients with inflammatory bowel diseases resistant *E. coli* strains have been isolated,[76] as well as rifampin-resistant skin Staphylococci have emerged in a small number of healthy volunteers following rifaximin intake.[77] Rifaximin-resistant organism have nevertheless been isolated after 800-mg daily treatment for 5 days; resistance was developed by 30–90% of fecal bacterial strains, including Enterobacteriaceae, *Enterococcus*, *Bacteroides*, *Clostridium*, and anaerobic coccidi, but it was not sustained since disappeared within months after therapy.[73]

These data may justify the persistence of efficacy observed even when multiple subsequent administrations of rifaximin are performed. A retrospective analysis explored the efficacy of rifaximin-repeated treatment among 71 patients with non-constipated IBS; 48 of them received a second-, 22 a third-, 7 a fourth-, and 4 a fifth-repeat treatment. Rifaximin-treatment attempts were successful in more than 75% of cases initially non-responders to the first course. The median time between treatments was similar, further confirming that duration of rifaximin effects did not decrease after the first treatment.[78] In the TARGET-3,[70] the open label study required for rifaximin-treatment approval for IBS, 636 patients with recurrent symptoms following administration of rifaximin were randomized to receive a first retreatment with rifaximin 550-mg tid or placebo for 2 weeks, followed by a 4-week treatment-free period. The rate of symptoms improvement was significantly higher in the rifaximin group compared to placebo (33% vs. 25%), and this was also true in case of a second retreatment (37% vs. 29%). The rate of recurrence prevention and of response duration was superior in the rifaximin group (13.2% vs. 7.1% and 17.1% vs. 11.7%). Rifaximin retreatment was neither associated with the emergence of resistant bacterial strains nor with opportunistic infections.

Another study demonstrated that rifaximin re-challenge at double dose after initial 1200-mg daily treatment further increased by 53% the rate of symptoms improvement independently of IBS type.[78]

Therefore, rifaximin-repeated treatment or re-challenge at higher dose represent an alternative option in unresponsive patients or in case of symptoms recurrence. The infrequent occurrence of clinical resistance is supported by the rapid loss of mechanisms of resistance among bacterial strains, or it could be in some cases overcome by the high concentrations reached by the drug.

Nevertheless, the acquisition of resistant phenotype may sometimes result as an advantage. Indeed, members of *Bacteroides* spp., *Lactobacillus* spp., *Clostridium/Eubacterium* spp., *Bifidobacterium* spp. and *Atopobium/Collinsella* spp., may become resistant after rifaximin exposure, being able to grow at rifaximin concentrations higher than 1024 mcg/L.[79] Thus, the growth of resistant beneficial bacterial may be another mechanism contributing to rifaximin-positive modulation of the gut microbiota, being part of the ‘eubiotic’ effects of this peculiar antibiotic.

### 4.3. Considerations about pharmacokinetics

Although derived from rifamycin, a cytochrome P450 (CYP450) enzyme system inducer, rifaximin is not expected to interfere with drug metabolism in patients with normal hepatic function. This has been confirmed by two studies including healthy individuals on treatment with CYP450 substrates.[80,81] In particular, in women receiving estrogen-progestin treatment (ethinyl estradiol 0.07 mg daily and norgestimate 0.5 mg daily), rifaximin 800-mg daily administration did not alter estradiol pharmacokinetics, and similar results were obtained with the same rifaximin dose in subjects taking midazolam. However, doses recommended for IBS treatment are higher compared to that used in these two studies; furthermore, liver impairment may heavily alter rifaximin absorption due to the increased intestinal permeability, which is a common feature of these patients. Systemic exposure is increased by 10–13 folds in Child A and B patients, reaching 20-fold increased values in Child C cirrhosis. Since rifaximin is presumably acting locally, in case of liver impairment no dose adjustment is required by the manufacturer; however, a careful use is advisable in this category of patients. P-glycoprotein is also involved in rifaximin metabolism and *in vitro* studies reported an increase in rifaximin *C*<sub>max</sub> and area under the curve in presence of P-glycoprotein inhibitors, such as verapamil and cyclosporine; however, the clinical consequences are unknown.

No major safety issues in the elderly have been raised in published studies,[86] even if increased sensitivity should not be overlooked in these category of patients. Even if there are no adequate and well-controlled studies in humans, administration of rifaximin has demonstrated teratogenic risk in animal models, and the amount of drug excreted in maternal milk is unknown; the decision on whether to use the drug during pregnancy or lactation should be taken only if the potential benefits may justify the risk for the fetus.[83]

Data about use of rifaximin in patients aged 18 years with renal impairment and in specific races or ethnicities are lacking. However, use of rifaximin has been recently demonstrated to be safe in children (10–13 years) with SIBO and IBS.[82]
A final consideration regards generic formulations of rifaximin. A recent study demonstrated a higher systemic bioavailability of the generic drug compared to the branded one, which contains only the polymorph-α.[83] This may obviously impact the incidence of systemic effects of rifaximin, with a consequent failure of an important feature of this antibiotic.

5. Conclusion

Although the exact mechanisms of action of rifaximin have not been completely clarified, this drug has proven to be effective in reducing/resolving intestinal symptoms in patients affected by IBS, as shown by large clinical trials. Additional effects overcoming the traditional antibiotic activity may contribute to the eutrophic effects of rifaximin on the gut microbiota. Clinical benefits of rifaximin are paralleled by a high safety profile: metabolic interactions and the development of resistant bacterial strains are nearly absent, and drug-related AEs are mild and infrequent. Moreover, properties of rifaximin seem to be maintained even after repeated treatment courses. All these features make rifaximin a safe antibiotic for the management of IBS patients.

6. Expert opinion

IBS is a functional gastrointestinal disease with a multifactorial etiology. Several evidences indicate gut microbiota plays a role in IBS pathogenesis. Indeed, an unbalanced microbial composition has been observed in IBS patients. For these reasons, local-acting antibiotics have an important therapeutic role. Rifaximin is a non-absorbable antibiotic with additional anti-inflammatory and gut microbiota-modulating activity. It is able to relieve symptoms in IBS patients even after repeated treatment courses. Clinical benefits of rifaximin are associated with high safety profile: metabolic interactions and the development of resistant bacterial strains are nearly absent, drug-related AEs are mild and infrequent. Future studies will need to clarify the exact mechanisms of rifaximin action in IBS, and in the meanwhile these findings should guide the optimization of use of rifaximin in these patients. In this scenario, the development of a ‘long-acting’ molecule may allow to prolong the beneficial gut microbiota modulation produced by rifaximin, favoring the maintenance of homeostasis with the end goal of promoting gut health.

Declaration of interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as:
• of interest
 ↔ of considerable interest.


 ↔ This interesting review highlights the potential mechanisms of action of rifaximin in the management of irritable bowel syndrome, suggesting that rifaximin may lead to a decrease in bacterial fermentation and to a reduction in clinical symptoms through its direct and indirect bactericidal effects.


In this important double-blind, randomized, placebo-controlled study, participants were randomly assigned to receive 400 mg of rifaximin three times daily for 10 days or placebo. The trial demonstrated that rifaximin was associated with a statistically superior improvement in IBS symptoms than placebo, and that this was maintained through 10 weeks of follow-up.


This important paper is the backbone of the current knowledge on the clinical effects of rifaximin in IBS without constipation, showing that 2-week rifaximin treatment provides significant relief of IBS symptoms, bloating, abdominal pain, and loose or watery stools.


In this systematic review and meta-analysis, the effect of rifaximin on global symptoms relief in IBS patients is confirmed, and it also highlights a similar incidence of adverse events between patients receiving rifaximin or placebo across all studies. Furthermore, serious AEs in rifaximin group were rare (<1%) and similar to placebo group.


This study included 62 patients with IBS who underwent small-bowel manometry and culture of jejunal aspirate.
demonstrating that a mild increase in small-bowel bacteria counts was more common in IBS patients, representing the basis for following investigations.


