Rifaximin: a nonabsorbable rifamycin antibiotic for use in nonsystemic gastrointestinal infections

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Rifaximin is a poorly water-soluble and minimally absorbed (<0.4%) rifamycin with *in vitro* activity against enteric Gram-negative bacteria including enteric pathogens. Fecal levels of the drug after 3 days' oral therapy exceed 8000 µg/g. Rifaximin is effective in the treatment and prevention of travelers' diarrhea due to *Escherichia coli*-predominant bacterial pathogens. It shows lower activity against dysenteric forms of bacterial diarrhea. The drug may be useful in other enteric infectious diseases, including *Clostridium difficile* colitis, pediatric bacterial diarrhea and *Helicobacter pylori* gastritis and chronic gastrointestinal disorders including hepatic encephalopathy, small bowel bacterial overgrowth, inflammatory-bowel disease, irritable-bowel syndrome and pouchitis. Importantly, rifaximin does not appear to lead to bacterial resistance. Rifaximin has an excellent safety profile and adverse drug reactions have been comparable to those associated with the placebo control agent.

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Infectious diarrheal diseases are estimated to be the second leading cause of morbidity and mortality worldwide. In the USA, an estimated 211 to 375 million episodes of diarrheal illness occur each year, which account for approximately 900,000 hospitalizations and 6000 deaths annually [1,2]. The utility of antimicrobials for the treatment of bacterial diarrhea is limited by increasing bacterial resistance and adverse effects associated with pharmacologic therapy.

The use of nonabsorbed, gastrointestinal-specific antimicrobials represents a novel approach to the treatment of selected gastrointestinal illnesses to overcome limitations associated with existing treatment regimens. Advantages of utilizing a nonabsorbed agent include:

- Localized treatment of nonsystemic enteric pathogens
- Increased tolerability
- Potentially decreased bacterial resistance

Rifaximin is a nonabsorbed (<0.4%) oral antibiotic derived from rifampicin. The US Food and Drug Administration (FDA) recently approved rifaximin (Xifaxan™) for the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli* in patients that are 12 years of age and older. Although not yet approved for hepatic encephalopathy, rifaximin has been granted orphan drug status for this disease. Rifaximin has been approved in Italy since 1987 for the treatment of acute and chronic infections, bacterial diarrhea, hepatic encephalopathy, and pre- and postsurgical prophylaxis [3–5], and is also licensed in 16 other countries in North and South America, Asia and Africa. The following review serves as an introduction to rifaximin and a summary of the pertinent literature.

Pharmacology & susceptibility

Rifaximin is a semisynthetic analog of the rifamycin antimicrobial, rifampin [6]. The addition of a benzimidazole ring makes rifaximin essentially nonabsorbed. Similar to all other rifamycins, rifaximin acts on the β-subunit of the DNA-dependent RNA polymerase enzyme to inhibit RNA synthesis [3].

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Travelers' diarrhea enteropathogens

The *in vitro* antibacterial susceptibility of rifaximin against various enteropathogens is displayed in TABLE 1 [3,7–14]. Owing to its lack of systemic absorption and extremely high fecal concentrations, it is likely that breakpoint determinations for the systemically absorbed rifamycins such as rifampicin will not correlate with clinical effectiveness of rifaximin for non-systemic gastrointestinal infections [11]. Overall, rifaximin displays important activity against most enteropathogens, such as *E. coli*, *Shigella* and *Salmonella* spp. *Campylobacter* spp. and the less important *Yersinia* spp. display higher minimum inhibitory concentration $(MIC)_{90}$ values, from 128 to 521 µg/ml. However, stool concentrations exceed these values by more than tenfold with levels measured after 3 days' treatment exceeding 8000 µg/g.

Vibrio cholerae

The rifaximin susceptibility of 408 *Vibrio cholerae* O1 strains from three different geographic areas (Africa, Europe and America) has been assessed [10]. African strains consisted of 16 distinct clones, while the European and American strains were classified into two clones. MIC_{90} values were less than 4 µg/ml for all three geographic areas and were comparable or lower than tetracycline (MIC_{90} range: 2–64 µg/ml).

Table 1. *In vitro* susceptibility of rifaximin against enteropathogens.

Pathogen	n	MIC_{50} range (µg/ml)	MIC_{90} range (µg/ml)	Ref.
Diarrheagenic *E. coli*				
Enterotoxigenic *E. coli*	179	8	16–32	[7–9]
Enteroaggregative *E. coli*	168	8	16–32	[7–9]
Enteropathogenic *E. coli*	21	8	16	[8]
Salmonella enteritidis	10	2	8	[11]
Salmonella spp.	60	4	4–64	[7,9]
Shigella flexneri	106	4	8–16	[8,9]
Shigella sonnei	40	4	16	[8,9]
Shigella dysenteriae	4	4	8	[8]
Shigella spp.	46	4	8–64	[7,11]
Campylobacter jejuni	12	256	512	[9]
Campylobacter spp.	9	Not reported	32	[7]
Yersinia enterocolitica	20	8–64	>8–128	[9,11]
Vibrio cholerae	403	2–4	2–4	[10]
Helicobacter pylori	82	1–4	2–8	[12,13]
Clostridium difficile	56	0.78	Not reported	[3,14]

Helicobacter pylori

Two separate studies have investigated the *in vitro* susceptibility of rifaximin to *Helicobacter pylori* [12,13]. MIC_{90} values were 2 and 8 µg/ml from these two studies, respectively, and did not vary with altered pH (as low as pH 6) [13]. Five strains were also chosen for the selection of resistant strains. No strain exhibited primary resistance, although selection of resistant strains was possible, suggesting that *H. pylori* monotherapy with rifaximin should not be recommended. Subinhibitory concentrations of amoxicillin or bismuth subsalicylate did not produce antagonism or synergy.

Clostridium difficile

MIC values of *Clostridium difficile* are among the lowest of any enteric pathogen for rifaximin [3,14]. In one study, 34 out of 56 clinical isolates of *C. difficile* were inhibited by rifaximin at a concentration of 0.78 µg/ml, with the remainder inhibited at concentrations greater than 25 µg/ml.

Other Gram-positive & -negative organisms

Rifaximin displays activity against other Gram-positive and -negative pathogens. Rifaximin generally displays good *in vitro* activity against methicillin-sensitive or -resistant *Staphylococcus aureus*. MIC_{50} values were approximately 0.015 µg/ml, although strains with higher MIC values were reported [11].

Studies are underway to examine the effect of rifaximin against protozoal pathogens.

Antimicrobial resistance

In general, rifamycin develops resistance to bacteria due to a chromosomal one-step alteration in the drug target, DNA-dependent RNA polymerase [15]. Thus, for systemic rifamycins, bacteria rapidly develop resistance if used as monotherapy. Resistance to rifaximin was first tested in ten patients with hepatic encephalopathy given rifaximin 800 mg/day for 5 days [16]. A total of 2 weeks after discontinuation of the drug, MIC values were within 20% of baseline for most organisms, with the exception of *Bacteroides* spp. A total of 3 months after treatment, no resistant organisms were noted. More recently, pre- and postfecal samples were obtained from a group of students from the USA in Mexico treated with 3 days of rifaximin for travelers' diarrhea [17]. Stools of 27 subjects were plated on media containing 200 µg/ml rifaximin before therapy (day 0), after treatment was completed (day 3) and 2 days later (day 5). No statistical increase in the growth of rifaximin-resistant coliform bacteria was observed in rifaximin-treated patients compared with placebo. Pre- and postfecal sample MIC ranges for enterococci also did not differ (8–64 µg/ml) and were identical to placebo. The lack of alteration of flora may relate to drug solubility (see pharmacodynamics).

Pharmacokinetics

Oral rifaximin is characterized by less than 0.4% systemic absorption. Animal studies in rats and dogs given single or multiple doses of rifaximin at doses over 100 mg/kg displayed

minimal systemic absorption [18]. Similar results were seen in 18 male volunteers given a single oral dose of rifaximin (400 mg). Maximum serum concentrations were consistently below the detectable level, and less than 0.01% of the total dose was recovered in the urine [19]. Presence of gastrointestinal disease does not increase systemic absorption. A pharmacokinetic study of 12 patients (11 male and one female) with mild-to-moderate ulcerative colitis assessed the systemic absorption of a single dose of rifaximin (400 mg) [20]. Urinary recovery was similar to the observations from the volunteer study with negligible passage into the systemic circulation. Rifaximin also does not undergo enterohepatic recirculation [3]. Bile samples were obtained from 13 patients undergoing cholecystectomy who received 2 days of rifaximin 400 mg four-times daily. Two out of the 13 patients had detectable concentrations of rifaximin, which were 20-times lower than an equivalent dose of the absorbable cousin, rifampin.

Oral rifaximin achieves very high fecal concentrations. Rifaximin concentrations were measured in the stool of 39 patients with travelers' diarrhea after receiving 3 days of rifaximin 400 mg twice daily [21]. Stool concentrations averaged almost 8000 µg/g of stool, and averaged approximately 2500 µg/g 4 days after discontinuation of the drug.

Pharmacodynamics

A number of studies have investigated pharmacologic effects of rifaximin in addition to bacterial killing. An animal model investigated the ability of rifaximin to prevent bacterial translocation in mice with experimental ulcerative colitis [22]. Administration of rifaximin increased survival rates of mice with colitis. Rifaximin administration caused a significant reduction of colonic bacterial translocation towards mesenteric lymph nodes. In addition, gastrointestinal mononuclear cells from rifaximin-treated mice released significantly lower amounts of interferon-γ, suggesting an anti-inflammatory effect of rifaximin. Similar anti-inflammatory effects were observed in 14 patients with pouchitis given rifaximin and ciprofloxacin [23]. In this study, the neutrophil marker, elastase, decreased significantly after antibiotic administration along with the chemokines interleukin (IL)-8, monocyte chemoattractant protein (MCP)-1, MCP-3 and IL-10. Whether these results are a function of bacterial killing or an anti-inflammatory effect of rifaximin requires further study. The pathophysiology of travelers' diarrhea due to diarrheagenic *E. coli* involves the formation of gastrointestinal biofilms, most likely due to a contribution from both bacteria and intestinal mucosa [24–26]. *In vitro* studies have demonstrated an antibiofilm effect of other rifamycins, including rifampin [27–29]. It is possible that the positive effect of rifaximin on travelers' diarrhea caused by *E. coli* strains also involves an antibiofilm effect. Rifaximin is poorly soluble in water but is bile soluble. While it is likely that the drug is dispersed and highly active in the small bowel, much of the drug may be less available in the aqueous colon.

Clinical studies

Rifaximin has been shown to be superior to placebo and as efficacious as ciprofloxacin for the treatment of travelers' diarrhea [30–32]. Studies are also underway to evaluate the potential role of rifaximin in patients with hepatic encephalopathy, small-intestinal bacterial overgrowth (SIBO) and irritable-bowel syndrome, inflammatory-bowel disease (including Crohn's disease and postsurgical Crohn's relapse), pouchitis, travelers' diarrhea chemoprophylaxis, *C. difficile*-associated diarrhea (CDAD) and in combination with loperamide for the treatment of acute travelers' diarrhea. Results of some of these studies are presented below and are summarized in TABLE 2.

Hepatic encephalopathy

Hepatic encephalopathy is a metabolic and neuropsychiatric syndrome in patients with acute and chronic liver failure. Rifaximin has been compared with lactulose, lactitol or neomycin and was found to have equal efficacy to these standard treatments [4,33–36]. Published studies have used rifaximin at a higher dose than that for enteric bacterial infection. The dose commonly used in hepatic encephalopathy is 400 mg three-times daily for as long as needed (generally weeks to months). The major advantage of rifaximin over other drugs is equal or improved efficacy with a lower side-effect profile.

Small-intestinal bacterial overgrowth

SIBO is a condition characterized by nutrient malabsorption due to an excessive amount of colonic bacteria in the lumen of the small intestine. Clinical symptoms associated with SIBO include chronic diarrhea, bloating, abdominal discomfort, weight loss and malabsorption. Therapy for SIBO includes suppression of bacterial colonization using antibiotics as well as nutritional support, correction of small intestinal abnormality, and adjuvant therapy for dysmotility. See TABLE 2 for details of published studies.

Di Stefano and colleagues conducted a randomized, double-blind comparison of the safety and efficacy of rifaximin and chlortetracycline in the short-term treatment of SIBO [37]. Efficacy was measured by changes in H_2 breath-test results and improvement in malabsorption symptoms based on a four-point scale. Rifaximin was superior to chlortetracycline and adverse effects were not reported as attributable to drug therapy in either group. Corazza and colleagues conducted an open-label study to characterize the optimal dose and efficacy of rifaximin in patients with SIBO [5]. The study included 12 adults with SIBO verified by H_2 breath test. End points included pre- and post-treatment disease severity assessed by symptoms and H_2 breath test. The two rifaximin doses were equally effective in treating the condition. There were no reports of side effects attributed to drug therapy. Trespi and colleagues conducted an open-label study to characterize the incidence of SIBO in patients with chronic pancreatitis and assess the efficacy of rifaximin in this patient population [38]. A total of 12 patients with chronic pancreatitis, steatorrhea (fecal fat excretion >15 g/day) and SIBO detected via the H_2 breath test were included. Rifaximin was effective in normalizing breath hydrogen

Table 2. Summary of rifaximin efficacy in gastrointestinal infections (excluding infectious diarrhea).

Study design	n	Treatment	Study results	Ref.
Hepatic encephalopathy				
Rifaximin plus lactulose	55	Rifaximin 1200 mg/day	Combination was effective in improving clinical parameters	[35]
Rifaximin versus neomycin	30	Rifaximin 400 mg three-times daily for 21 days	Rifaximin reduced serum ammonia faster, both improved CNS symptoms	[36]
Rifaximin versus neomycin	49	Rifaximin 400 mg three-times daily for 14 days each month for 6 months	Both drugs decreased serum ammonia and improved symptoms	[4]
Rifaximin versus lactitol	103	Rifaximin 1200 mg/days for 5–10 days	Rifaximin was more active against CNS symptoms and reducing blood ammonia; both were effective overall	[34]
Rifaximin versus lactulose	58	Rifaximin 1200 mg/day for 15 days	Both drugs were effective and rifaximin was better tolerated	[33]
Small intestinal bacterial overgrowth				
Randomized, double-blind comparison of safety and efficacy of rifaximin and chlortetracycline	21	Rifaximin 400 mg three-times daily for 7 days Chlortetracycline 333 mg three-times daily for 7 days	H_2 breath test normalized in 70% of patients receiving rifaximin compared with 27% receiving chlortetracycline ($p < 0.01$)	[37]
Open-label study to characterize optimal dose and efficacy of rifaximin	12	Rifaximin 400 mg twice daily or rifaximin 400 mg three-times daily	H_2 breath tests normalized in 67%, and 83% showed symptomatic improvement in symptoms after 5 days There were no significant differences between the groups	[5]
Open-label study to characterize the incidence of SIBO in patients with chronic pancreatitis and assess efficacy of rifaximin	35	Rifaximin 400 mg three-times daily for 7 days/month for 3 months	SIBO detected in 12 out of 35 patients with chronic pancreatitis All 12 patients had normalization of H_2 breath tests and diarrhea resolved in addition to a reduction in steatorrhea to <15 g/day fecal fat	[38]
Inflammatory bowel disease				
Open-label, single-center study investigating the safety and efficacy of rifaximin	29	Rifaximin 200 mg three-times daily for 16 weeks	Clinical remission, defined as CDAI score of less than 150, was achieved in 33, 52, 52 and 62% of patients at the end of treatment weeks 4, 8, 12 and 16 weeks, respectively	[43]
Randomized, double-blind, placebo-controlled comparison of the efficacy of rifaximin as an adjunct to standard steroid therapy in patients with moderate to severe ulcerative colitis refractory to steroid therapy	28	Rifaximin 400 mg twice daily or placebo for 10 days plus standard steroid treatment	Nine out of 14 (64.3%) in the rifaximin group and five out of 12 (41.7%) in placebo group showed a positive response to therapy (p = nonsignificant), as defined by improvement of disease's clinical activity	[44]
Open-label, uncontrolled study of the safety and efficacy of rifaximin in the treatment of ulcerative colitis and Crohn's disease refractory to standard treatments in patients with positive stool cultures for pathogenic bacteria	12	Rifaximin 400 mg twice daily for 5 days plus standard initial treatment	Seven out of nine ulcerative colitis patients achieved remission and two out of nine had significant improvement Three out of three Crohn's disease patients improved	[45]

CDAI: Crohn's disease activity index; SIBO: Small intestinal bacterial overgrowth.

Table 2. Summary of rifaximin efficacy in gastrointestinal infections (excluding infectious diarrhea). (Cont.)

Study design	n	Treatment	Study results	Ref.
Pouchitis				
Open-label study to determine the safety and efficacy of rifaximin plus ciprofloxacin in the treatment of chronic, treatment-resistant pouchitis	18	Rifaximin 1000 mg twice daily plus ciprofloxacin 500 mg twice daily for 15 days	16 out of 18 patients (88.8%) either improved or went into remission after 15 days	[47]
Clostridium difficile-associated diarrhea				
Randomized, open-label study compared the efficacy of rifaximin versus oral vancomycin	20	Rifaximin 200 mg three-times daily or vancomycin 500 mg twice daily for 10 days	Disappearance of toxins and resolution of colitis was observed in ten out of ten patients treated with vancomycin and nine out of ten patients treated with rifaximin. The duration of diarrhea was similar in both treatment arms	[49]

CDAI: Crohn's disease activity index; SIBO: Small intestinal bacterial overgrowth.

test and improving steatorrhea. All studies for the use of rifaximin in the treatment of SIBO were performed outside of the USA with small sample sizes. Despite some design limitations, positive results indicate that further study of rifaximin for SIBO is warranted.

Inflammatory-bowel disease

Crohn's disease and ulcerative colitis represent the two major forms of inflammatory-bowel disease. Although the two share some clinical similarities, they are believed to be two distinct diseases [39]. Crohn's disease is an inflammatory disorder that can affect any part of the gastrointestinal tract and diseased intestinal segments may be separated by healthy intestinal segments [40]. The distribution of ulcerative colitis is nonsegmental and exclusively affects the colon [39]. The pathophysiology of Crohn's disease and ulcerative colitis is not fully understood; however, it is thought to involve a complex relationship between genetic susceptibility, enteric bacteria and the immune system [41]. The role of enteric flora or pathogenic bacteria has raised interest in the use of antibiotic therapy in the treatment of Crohn's disease [42]. Rifaximin clinical trials in patients with either ulcerative colitis or Crohn's disease are shown in Table 2.

Shafran and colleagues conducted an open-label, single-center study investigating the safety and efficacy of rifaximin in the treatment of moderate Crohn's disease [43]. Clinical remission without drug side effects occurred in 62% of patients at 16 weeks. Gioncetti and colleagues reported results of a randomized, double-blind, placebo-controlled comparison of the efficacy of rifaximin as an adjunct to standard steroid therapy in patients with moderate-to-severe ulcerative colitis refractory to steroid therapy [44]. Patients were eligible if they had no response to methylprednisolone 1 mg/kg/day for 7 to 10 days. Two patients in the placebo group were withdrawn due to side effects and were not included in analysis. Overall, nine out of 14 (64.3%) patients in the rifaximin group and five out of 12 (41.7%) patients in the placebo group showed a positive response to therapy (p = nonsignificant), as defined by improvement of disease clinical activity. Pinto and colleagues reported results of an open-label, uncontrolled study of the safety and efficacy of rifaximin in the treatment of ulcerative colitis and Crohn's disease refractory to standard treatments in patients with positive stool cultures for pathogenic bacteria [45]. Seven ulcerative colitis patients achieved remission and two showed significant improvement, while all three Crohn's disease patients improved.

Pouchitis

Pouchitis is a nonspecific inflammation of the ileal reservoir and represents a major long-term complication after ileal pouch–anal anastomosis for the management of ulcerative colitis [46]. Clinical symptoms are characterized by diarrhea, rectal bleeding, fecal urgency, abdominal cramping, malaise and fever. Clinical, endoscopic and histologic criteria are assessed using the Pouchitis Disease Activity Index (PDAI), which may be used to diagnose the condition. Pouchitis is defined as a PDAI score of seven or more.

Gionchetti and colleagues conducted an open-label study to determine the safety and efficacy of rifaximin plus ciprofloxacin in the treatment of chronic, treatment-resistant pouchitis, defined as no response after 4 weeks of antibiotic treatment (see TABLE 2) [47]. Eligible subjects were 18 years of age or older, with a confirmed diagnosis of treatment-resistant disease. Failed treatments included metronidazole, ciprofloxacin and amoxicillin–clavulanic acid. A total of 18 patients with chronic, treatment-resistant pouchitis were identified and received rifaximin 1000 mg twice daily plus ciprofloxacin 500 mg twice daily for 15 days. The primary clinical end point was reduction of PDAI score. Treatment successfully led to remission or clinical improvement with both drugs being well tolerated.

Clostridium difficile-associated diarrhea

C. difficile is a Gram-positive, spore-forming anaerobic bacillus, and is the most common cause of nosocomial diarrhea [48]. Treatment of CDAD includes either oral metronidazole or oral vancomycin; however, recurrence of symptoms can occur in 10 to 20% of patients.

A study conducted by Boero and colleagues compared the efficacy of rifaximin 200 mg three-times daily with oral vancomycin 500 mg twice daily for 10 days in patients with CDAD [49]. Results of the study are shown in TABLE 2. While duration of diarrhea was similar between the rifaximin and vancomycin groups, time to elimination of toxins was significantly longer in the rifaximin group compared with the oral vancomycin group. Rifaximin has not been compared with oral metronidazole and this warrants further study.

Infectious diarrhea in travelers

Therapy

Four randomized, double-blind, placebo- or comparator-control clinical trials have been conducted in the therapy of patients with travelers' diarrhea during travel to Guatemala, India, Kenya, Mexico, Jamaica or Peru [6,30,31]. These studies enrolled patients with diarrhea during international travel, defined as at least three unformed stools within the 24 h preceding randomization, with at least one additional sign or symptom of enteric infection (abdominal pain or cramping, nausea, vomiting, fever of at least 37.8°C, fecal urgency, excessive gas/flatulence or tenesmus). The primary end point of these studies was time from taking the first dose of therapy until passage of the last unformed stool after being declared well or time to last unformed stool (TLUS). Secondary end points included the number of patients with improvement in diarrhea (≥50% reduction in bowel movements), the number of unformed stools passed per time interval, the number of patients with clinical cure (no unformed stool or fever over 48-, or 24-h period with no watery stool, maximum of two soft stools, and no fever or clinical symptoms), the number of treatment failures (clinical deterioration or worsening of clinical symptoms after at least 24 h of therapy, illness continuing after 120 h, or patient too ill to continue in study), and the number of patients with microbiologic cure (post-treatment stool culture negative for pretreatment pathogen). A summary of these studies for the treatment and prophylaxis of travelers' diarrhea can be found in TABLE 3.

Steffen and colleagues conducted a multicenter, 1:1:1 randomized, parallel group, double-blind study to compare the efficacy and safety of rifaximin at doses of 200 mg three-times daily and 400 mg three-times daily (600 and 1200 mg daily) with placebo in patients with travelers' diarrhea [6]. The study was conducted in 380 adult volunteers, and treatment was administered for 3 days. Study subjects were traveling to Guatemala, Mexico and Kenya. Improvement in diarrhea during the 48- to 72-h time period after initiating therapy was observed in 91 and 88% of patients treated with rifaximin 600 and 1200 mg/day, respectively, compared with 78% of patients taking placebo. The mean number of unformed stools was lower on days 1 and 2 and upon completion of therapy for patients receiving rifaximin compared with placebo ($p = 0.001$). The rate of microbiologic cure was not significantly different among treatment groups. Study drug-related adverse events were reported by 69.8% in the placebo group compared with 59.7 and 69.7% in the low- and high-dose rifaximin groups, respectively. Most reported adverse events were gastrointestinal related, which may have related more to underlying illness than drug effect. The most frequent nongastrointestinal adverse event was headache, reported in 15% of patients receiving rifaximin 1200 mg/day, 8% of patients receiving rifaximin 600 mg/day, and 8% of patients receiving placebo (no statistically significant difference).

DuPont and colleagues conducted a randomized, double-blind, double-dummy clinical trial comparing rifaximin 400 mg twice daily (800 mg/day) for 3 days and ciprofloxacin 500 mg twice daily (1000 mg/day) for 3 days for travelers' diarrhea [30]. The study was conducted in 187 adults traveling to Mexico or Jamaica. The study was statistically powered to demonstrate noninferiority of rifaximin. The drugs were equivalent in terms of shortening diarrhea and improving illness (see TABLE 3). The mean number of unformed stool during the first 48 h post dose was 5.1 for patients in the rifaximin group and 4.5 for the ciprofloxacin group ($p > 0.05$). Clinical cure was obtained in 87% of the patients in the rifaximin group, while 88% experienced clinical cure in the ciprofloxacin group ($p > 0.05$). Treatment failure was observed in 10% of the rifaximin and 6% of the ciprofloxacin group ($p > 0.05$). Microbiologic cure was obtained in 74% of the rifaximin group and 88% of the ciprofloxacin group ($p > 0.05$). The results demonstrated equivalence in both primary and secondary end points. Both drugs were well tolerated and the incidence of adverse events was similar between both groups. Of the subjects randomized to receive rifaximin, 33% experienced at least one adverse event, compared with 36% of the ciprofloxacin group. The complaints were nonspecific and mild in both treatment groups and included weakness, dizziness, headache, fatigue, constipation, cough, insomnia and respiratory symptoms.

Another study conducted by DuPont and colleagues was a randomized, double-blind study that compared three dosing regimens of rifaximin (200 mg three-times daily, 400 mg three-times daily, and 600 mg three-times daily) to trimethoprim/sulfamethoxazole (160/800 mg twice daily) for 5 days for the treatment of travelers' diarrhea [31]. A total of 72 adults traveling to Mexico were included. The results demonstrated that rifaximin was at least as effective as trimethoprim/sulfamethoxazole in the treatment of travelers' diarrhea; however, statistically significant results were not observed due to the small sample size and low statistical power. The percent of patients who reported improvement in diarrhea at 48 h post dose was 83, 78 and 89% in the rifaximin 200, 400 and 600 mg three-times daily groups, respectively, compared with 76% of patients in the trimethoprim/sulfamethoxazole group. Clinical cure was experienced by 89, 100 and 90% in the rifaximin 200, 400 and 600 mg three-times daily groups, respectively, compared with 82% in the trimethoprim/sulfamethoxazole group. The combined treatment failure rate in the three rifaximin groups was 11%, compared with 29% in the trimethoprim/sulfamethoxazole group. Potential side effects were reported in all drug groups. Neither a dose-related

Table 3. Summary of rifaximin efficacy in infectious diarrhea in travelers.

Study design	n	Treatment	Study results	Ref.
Treatment of travelers' diarrhea				
Multicenter, 1:1:1 randomized, parallel group, double-blind study comparing the efficacy and safety of rifaximin	380	Rifaximin 200 mg three-times daily or rifaximin 400 mg three-times daily or placebo	Median TLUS was 33 h in both rifaximin groups, compared with 60 h with placebo Significantly more patients treated with rifaximin experienced clinical cure compared with placebo Treatment failures were observed in 35% of patients in the placebo group compared with 16–17% of patients treated with low- or high-dose rifaximin	[6]
Multicenter, 1:1:1 randomized, parallel group, double-blind study comparing the efficacy and safety of rifaximin in subpopulation of patients with EAEC diarrhea	44	Rifaximin 200 mg three-times daily or rifaximin 400 mg three-times daily or placebo	Median TLUS was significantly shorter for subjects with EAEC-positive travelers' diarrhea treated with rifaximin versus placebo Steffen and colleagues reported results of the parent study as described above	[50]
Multicenter, 1:1:1 randomized, parallel group, double-blind study comparing the efficacy and safety of rifaximin in a subpopulation of patients with EAEC diarrhea	44	Rifaximin 200 mg three-times daily or rifaximin 400 mg three-times daily or placebo	Median TLUS was significantly shorter for subjects with EAEC-positive travelers' diarrhea treated with rifaximin versus placebo Steffen and colleagues reported results of the parent study as described above	[50]
Randomized, double-blind, double-dummy clinical trial	187	Rifaximin 400 mg twice daily for 3 days or ciprofloxacin 500 mg twice daily for 3 days	Demonstrated equivalence of rifaximin and ciprofloxacin for the median TLUS in addition to secondary efficacy end points Median TLUS was 25.7 h for rifaximin treated subjects compared with 25.0 h for ciprofloxacin-treated patients. Patients with improvement in diarrhea 48 h post dose were 83% in the rifaximin group and 85% in the ciprofloxacin group	[30]
Randomized, double-blind study	72	Rifaximin (200 mg three-times daily, 400 mg three-times daily or 600 mg three-times daily) for 5 days or TMP/SMX (160/800 mg) twice daily for 5 days	Results concluded rifaximin was at least as effective as TMP/SMX in the treatment of travelers' diarrhea; however, statistically significant results were not observed due to small sample size and low statistical power Median TLUS were 26, 41 and 35 h in the rifaximin 200, 400 and 600 mg three-times daily groups, respectively, compared with 47 h for the TMP/SMX group	[31]
Randomized, double-blind, placebo- and comparator-control, parallel group study	399	Rifaximin 200 mg three-times daily or ciprofloxacin 500 mg twice daily or placebo for 3 days	Rifaximin and ciprofloxacin were both statistically superior to placebo Median TLUS was 32 h in the rifaximin group compared with 65 h in the placebo group.	[TAYLOR ET AL., UNPUBLISHED DATA]
Prophylaxis of travelers' diarrhea				
Clinical trial	220	Rifaximin 200 mg daily, twice daily, or three-times daily or placebo for 2 weeks	Significantly more patients in the rifaximin remained free of diarrhea throughout the treatment period Of the patients in the rifaximin daily, twice daily and three-times daily groups, 82, 75 and 85%, respectively, remained free of diarrhea compared with 42% of patients treated with placebo	[51]

EAEC: Enteroaggregative *E. coli*; TLUS: Time to last unformed stool; TMP/SMX: Trimethoprim/sulfamethoxazole.

increase in the rifaximin groups nor a pattern of complaints were identified. The side effects appeared to be related to the underlying enteric disease.

The most recently completed trial was a randomized, double-blind, placebo- and comparator-control, parallel group study comparing rifaximin 200 mg three-times daily, ciprofloxacin

500 mg twice daily or placebo for 3 days [TAYLOR DN, UNPUBLISHED DATA]. Study subjects consisted of 399 adults traveling to Mexico, Guatemala, India and Peru. Median TLUS was statistically similar in the ciprofloxacin group. Rifaximin and ciprofloxacin were both statistically superior to placebo. In the study, rifaximin was not effective in the treatment of travelers with fever or when an invasive bacterial pathogen was isolated [TAYLOR DN, UNPUBLISHED DATA]. This was most clear for *campylobacter*, that shows high MIC values to the drug. The tolerability profile of rifaximin in the trial was similar to that of the placebo.

Infante and colleagues described a subpopulation of patients with laboratory-confirmed enteroaggregative *E. coli* (EAEC) travelers' diarrhea [50], based on the study by Steffen and colleagues reported above [32]. This was a multicenter, 1:1:1 randomized, parallel group, double-blind study to compare the efficacy and safety of rifaximin at doses of 200 mg three-times daily and 400 mg three-times daily (600 and 1200 mg daily) with placebo in patients with travelers' diarrhea. From a group of 137 subjects identified for the parent study whose stool samples tested negative for routinely definable travelers' diarrhea pathogens, 44 were found to have EAEC-associated travelers' diarrhea. Median TLUS was significantly shorter for subjects with EAEC-positive travelers' diarrhea treated with rifaximin versus placebo (22 vs. 72 h, respectively; $p = 0.03$). For subjects with EAEC-negative diarrhea, the median duration of diarrhea was shorter in the rifaximin group (33 h) compared with the placebo group (52 h); however, the difference was not statistically significant ($p = 0.14$).

Prevention

DuPont and colleagues evaluated the use of rifaximin in prophylaxis of travelers' diarrhea when traveling to a high-risk area [51]. Rifaximin 200 mg given daily, twice daily, three-times daily or placebo were prescribed for 2 weeks to 220 adults from the USA. Subjects were followed for 3 weeks for the occurrence of diarrhea (>2 unformed stools/day plus one additional sign/symptom of enteric disease), mild diarrhea (≥2 unformed stools/day plus one additional sign/symptom), or severe diarrhea (diarrhea requiring antibiotics for treatment). These subjects were followed for a total of 5 weeks to assess adverse events possibly related to study medication. Significantly more patients in the rifaximin groups remained free of diarrhea throughout the treatment period ($p = 0.0001$). In the rifaximin groups combined, 62% of patients remained free of mild diarrhea compared with 28% of the placebo group ($p = 0.0001$). Only minimal changes in fecal flora were noted during 2 weeks of rifaximin at all doses. The incidence of adverse effects was comparable between each rifaximin group and the placebo group. Based on this study, rifaximin may be given as prophylaxis to patients traveling to high-risk areas to prevent travelers' diarrhea. A recently completed study demonstrated that rifaximin could be used successfully to prevent experimental *Shigella*-induced diarrhea in a volunteer-challenge model [52]. Preventing invasive bacterial infection is likely to be achieved by rifaximin where treatment of established infection is less successful.

Safety & tolerability

Rifaximin appears to be a very safe product with a low incidence of side effects, comparable to placebo [6,53]. Isolated cases have reported side effects that included flatulence, abdominal pain, nausea and vomiting (all reported in <1% of patients) [3]. Allergic reactions have been reported, including allergic dermatitis, rash, angioneurotic edema, urticaria and pruritis, and thus the drug is contraindicated in patients allergic to rifamycins [53]. Clinical trials have shown adverse event rates comparable to placebo. Very few clinical laboratory abnormalities have been reported with rifaximin during clinical trials [31]. A single patient experienced mildly increased transaminases (<2 × normal) and an additional patient experienced an increased eosinophilia count by up to 9%. In other studies with travelers' diarrhea, no laboratory abnormalities have been reported [6,32].

Rifaximin has not been studied in pregnant women [53]. While possessing some teratogenicity in mice given two- to 33-times the normal human oral dose adjusted for body surface area, this appears not to have relevance for a very poorly absorbed drug.

Drug interactions

In vitro, rifaximin can induce cytochrome P450 (CYP)3A4, similar to other rifamycins [53]. However, unlike rifampin, rifaximin has not been shown to undergo clinically relevant interactions with drugs metabolized by CYP3A4 such as oral contraceptives or midazolam; this is probably due to the lack of systemic absorption of the drug.

Dosage & administration

Rifaximin is a nonabsorbed oral antibiotic that was approved by the FDA in May 2004 for the treatment of travelers' diarrhea caused by noninvasive diarrheagenic strains of *E. coli* in patients 12 years of age and older. The current recommended dose of rifaximin for the treatment of travelers' diarrhea is 200 mg three-times daily for 3 days. Dosing for other conditions can be seen in TABLE 2.

Expert opinion

Many aspects of rifaximin make this agent an excellent choice for the treatment of nonsystemic gastrointestinal infections. Rifaximin possesses a broad spectrum of activity against enteric organisms, including pathogens responsible for travelers' diarrhea, and other noninvasive bacterial infections such as *C. difficile*. Since rifaximin achieves such high fecal concentrations with virtually no systemic absorption, there are very few side effects associated with the drug without clinically relevant resistance. Unlike rifampin, rifaximin does not undergo interactions with drugs metabolized by CYP3A4. Several randomized, placebo-controlled trials have

shown rifaximin to be superior to placebo in travelers' diarrhea and as efficacious as ciprofloxacin, which is considered a first-line agent for adults with the condition when fever or dysentery does not complicate the illness. While the illness is self-limiting, even with dysentery, patients with extensive mucosal infection with an invading strain of campylobacter or shigella will benefit from treatment with an absorbed preparation.

Rifaximin's potential value in gastroenterology appears to be high with new uses emerging as clinical trials are developed. Rifaximin has orphan status from the FDA for use in hepatic encephalophy. It is as effective as all standard drugs with fewer side effects. The drug can be employed empirically in small bowel bacterial overgrowth states and refractory cases of inflammatory-bowel disease and pouchitis. Research is needed to determine the value of rifaximin in irritable-bowel syndrome and diverticular disease.

Five-year view

In the future, rifaximin should be considered a first-line agent for the treatment of afebrile, nondysenteric travelers' diarrhea, especially as resistance to ciprofloxacin continues to increase. We predict that the public health implications of travelers' diarrhea will become clearer. Preventing 24 h of illness with low-dose rifaximin used prophylactically during high-risk travel should become routine for many. If studies show that rifaximin prevents the chronic complications of travelers' diarrhea including irritable-bowel syndrome, then even broader use will occur. Also, rifaximin may be of value for other settings as a prophylactic agent. The obvious one is for military populations entering into areas of reduced hygiene. The drug may also have utility in disease prevention in the case of an intentional contamination of the food or water supply with enteric bacterial pathogens. Studies are being planned to evaluate rifaximin in infants and children with bacterial diarrhea. In view of the high relapse rate of *C. difficile* diarrhea and colitis treated with metronidazole, an effective new agent is needed. Rifaximin should be evaluated for the treatment and prevention of *C. difficile* diarrhea and colitis. Additional clinical trials are needed to determine the value and indication of rifaximin for the treatment of irritable-bowel syndrome, diverticular disease, and as a bowel prep in preventing post-gastrointestinal tract-surgery infection.

Conflict of interest

DuPont has served as a consultant to the marketer of rifaximin in the USA, Salix Pharmaceuticals; has received honoraria for talks given; and has received research grants from the company through his university.

Key issues

- Rifaximin, a rifamycin derivative, is a nonabsorbed (<0.4%) oral antibiotic recently approved by the US Food and Drug Association for the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli* in patients of 12 years of age and older.
- Rifaximin possesses a broad spectrum of activity against Gram-positive and -negative bacteria, both aerobic and anaerobic.
- Rifaximin therapy is not associated with the rapid development of bacterial resistance.
- In travelers' diarrhea, rifaximin has been shown to be superior to placebo, and at least as efficacious as ciprofloxacin in randomized, controlled trials with patients without fever or dysenteric illness.
- Unlike rifampin, rifaximin has not been shown to undergo clinically relevant interactions with drugs metabolized by cytochrome P450 3A4; this is probably due to the lack of systemic absorption of the drug.
- Rifaximin has been well tolerated and reported side effects occur in less than1% of patients; these may include flatulence, abdominal pain, nausea and vomiting.
- Rifaximin is now approved in 17 countries, including the USA, with over 500 million tablets distributed over nearly 20 years.
- More studies are needed to better understand the role of rifaximin in the treatment of hepatic encephalopathy, *Clostridium difficile* diarrhea and colitis, Crohn's disease, irritable-bowel syndrome, as well as the use of rifaximin in the chemoprophylaxis of travelers' diarrhea due to invasive pathogens.

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