Rifaximin Is Safe and Well Tolerated for Long-term Maintenance of Remission From Overt Hepatic Encephalopathy

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BACKGROUND & AIMS: Rifaximin is a gut-selective, oral antimicrobial agent shown to reduce the recurrence of overt hepatic encephalopathy (HE) and HE-related hospitalizations in a 6-month, randomized, controlled trial (RCT). We performed a phase 3, open-label maintenance study to assess the safety and rate of hospitalization with long-term rifaximin use.

METHODS: We conducted a 24-month, open-label maintenance study of rifaximin (550 mg, twice daily) in patients with HE who participated in the previous RCT of rifaximin or new patients enrolled from March 2007 to December 2010. Safety was assessed (adverse events, clinical laboratory parameters) for the integrated population of all patients, who were given rifaximin 550 mg twice daily (all-rifaximin population, N = 392). Safety and hospitalization data were compared between the group given placebo in the original RCT (n = 159) and those given rifaximin (n = 140).

RESULTS: In the all-rifaximin population, the median exposure to rifaximin was 427.0 days (range, 2–1427 d), with 510.5 person-years of exposure. The profile and rate of adverse events with long-term rifaximin treatment were similar to those of the original RCT. There was no increase in the rate of infections, including with *Clostridium difficile*, or development of bacterial antibiotic resistance. Rates of hospitalizations with long-term rifaximin administration remained low: the HE-related hospitalization rate, normalized for exposure (0.21; all-rifaximin population), was similar to that of the rifaximin group in the original RCT (0.30), and lower than that for the placebo group (0.72).

CONCLUSIONS: Long-term treatment (≥24 mo) with rifaximin (550 mg, twice daily) appears to provide a continued reduction in the rate of HE-related and all-cause hospitalization, without an increased rate of adverse events. ClinicalTrials.gov number: NCT00686920.

Keywords: Xifaxan; Cirrhosis; Chronic Liver Disease; Antimicrobial Agent.

Hepatic encephalopathy (HE) is a serious and potentially progressive neurologic syndrome in patients with cirrhosis. The neuropsychiatric symptoms and neuromuscular dysfunction associated with HE significantly contribute to the clinical and socioeconomic burden of chronic liver disease for patients and their caregivers.[1,2] HE frequently results in hospitalizations[3] and is associated with decreased survival in patients with cirrhosis.[4,5] Prevention of HE episodes may improve outcomes for patients while awaiting transplantation and improve post-transplant function.[4,5] A long-term therapeutic intervention to prevent recurrent HE is needed to decrease health care burden, improve quality of life, and improve outcomes for chronically ill patients.

Historically, lactulose and lactitol (available outside of the United States), and antibiotics have been used as short-term overt HE treatments.[6,7] The presumed mechanism of action is a reduction in the burden of neurotoxins derived from both intestinal enterocyte metabolism (via glutaminase) and gut bacterial metabolism that may contribute to altered mental status; these toxins accumulate as a result of liver dysfunction and portosystemic shunting in patients with cirrhosis and portal hypertension.[8] Lactulose therapy can prevent recurrent HE[9]; however, long-term use is limited by

numerous adverse effects, often resulting in non-adherence to therapy.[10]

Rifaximin (Xifaxan; Salix Pharmaceuticals, Inc, Raleigh, NC) is an oral antimicrobial agent with broad-spectrum activity that is gut-selective and nonsystemic.[11] Rifaximin appears to have a low level of selection for resistant bacterial mutants[12] and may not confer the same risks as those associated with systemic antibiotics. In a randomized, double-blind trial, rifaximin therapy significantly reduced the risk of overt HE recurrence and HE-related hospitalizations during a 6-month period in patients with cirrhosis and a recent history of recurrent, overt HE.[13] The safety profile was favorable and indistinguishable from that of placebo. Nevertheless, theoretical concerns remain regarding the safety and durability of treatment response during long-term antibiotic use.

The objectives of this open-label study were to examine the effect of long-term (≥24 mo) rifaximin administration on safety, survival, underlying disease, and rate of hospitalizations in patients with cirrhosis and recurrent HE.

Methods

Patients

Males and females 18 years of age and older were eligible if they had a history of overt HE episodes with documented severity of Conn score of 2 or higher within 12 months before screening, and a Conn score of 2 or less at enrollment. Patients from a previous randomized controlled trial (RCT) (ClinicalTrials.gov number: NCT00298038) were permitted to enroll. Exclusion criteria included history of allergy to rifampin or rifaximin, renal insufficiency (serum creatinine level, >2.0 mg/dL), severe anemia (hemoglobin level, <8 g/dL), clinically significant hypovolemia or any electrolyte abnormality that could affect mental function (eg, serum sodium level, <125 mEq/L; serum calcium level, >10 mg/dL), severe hypokalemia (serum potassium level, <2.5 mEq/L), intestinal obstruction, active inflammatory bowel disease, diagnosis of human immunodeficiency virus, history of active tuberculosis, or current spontaneous bacterial peritonitis. The study protocol and the informed consent form were approved by the institutional review boards of each center. The trial complied with the Declaration of Helsinki. All enrolled patients or their legally authorized representatives provided informed consent. Patients were enrolled from March 2007 to December 2010.

Study Design, Intervention, and Assessments

This study was a phase 3, multicenter, open-label maintenance study (OLM) (ClinicalTrials.gov number: NCT00686920) evaluating oral rifaximin 550 mg administered twice daily for 24 months or more. Concomitant therapy with lactulose was optional. Clinic visits occurred at 1 and 3 months, and then every 3 months until the end of treatment, followed by a 2-week posttreatment clinic visit. Patients also were monitored by telephone 2 weeks after beginning rifaximin, and then every 6 weeks after the third month until the end of treatment.

The primary objective was to evaluate the long-term safety of rifaximin 550 mg twice daily. Adverse events (AEs) were assessed during each clinic visit and telephone interview, vital sign measurements, hematology, blood chemistry, urinalysis, and coagulation tests were conducted during each clinic visit, and a physical examination was conducted during the end-of-treatment visit and during clinic visits as needed to evaluate patient symptoms. Data on infections were captured from the AE database. Data on *Clostridium difficile* infections were investigated further to evaluate the clinical context, nature, and outcome of the infection. Data on hospitalizations were collected prospectively as part of the primary objective to analyze safety. Hospitalization data were investigated further and compared post hoc to assess the rate of HE-related and all-cause hospitalizations. Overall, the inclusion/exclusion criteria and safety evaluations and definitions were consistent with those in the RCT clinical trial,[13] with the exception of enrollment of patients with Conn scores of 2 in the OLM.

Statistical Analyses

The planned sample size for the OLM was approximately 300 patients. All analyses were performed for the safety population, defined as all patients who received 1 or more doses of study medication and had 1 or more postbaseline safety assessments.

Data were analyzed for all patients treated with rifaximin 550 mg twice daily during either the OLM or the previously published RCT[13] (all-rifaximin population) and for a subset of this population: patients who had received placebo during the RCT[13] and received rifaximin during the OLM, plus patients who only participated in the OLM (new-rifaximin population). Differences in demographics and baseline characteristics were determined using the Fisher exact test or the *t* test. Nonstatistical comparisons to historical data from the placebo control group and rifaximin group from the previously published RCT[13] were included, based on methodology and recommendations from regulatory guidance and published literature.[14–16] This historical RCT and current OLM included similar enrollment criteria and were supported by the same organization and investigators. In addition, demographic and baseline characteristics of the historical placebo and rifaximin groups were similar to those for the OLM population, and many of the patients in the placebo arm of the RCT continued in the OLM.

All continuous and categoric variables were summarized using descriptive statistics. Adherence was determined at each clinic visit and was calculated as follows: ([number of tablets dispensed – number of tablets

returned] ÷ [duration of drug exposure × number of tablets that should have been taken daily]) × 100. The person-years of exposure (PYE) were calculated as follows: (total exposure in days ÷ 365.25), and AE rates were calculated as follows: (number of patients ÷ PYE), in which PYE reflected exposure up until the AE occurrence and therefore may have differed from the PYE for the entire patient group; and the rate of hospitalization events was calculated as follows: (number of events ÷ PYE), where PYE reflected exposure up until the time the event occurred.

All authors had access to the study data and reviewed and approved the final manuscript.

Results

Patient Population

Of the 392 patients in the integrated all-rifaximin population, 83.7% (n = 328) were from the United States or Canada, and 16.3% (n = 64) were from Russia. Of the 392 patients (Supplementary Figure 1), 322 were enrolled in the OLM (70 were treated with rifaximin during the RCT, 82 were treated with placebo during the RCT, and 170 were new patients [new-rifaximin population, n = 252]). Reasons for discontinuation from the RCT have been described by Bass et al[13] and reasons for OLM discontinuation are described in Supplementary Figure 1. Overall demographics, liver disease history, and HE severity (baseline Conn score and asterixis grade) were similar among the all-rifaximin, new-rifaximin, and historical-rifaximin populations, with generally no significant differences among these groups vs historical placebo (Table 1).[13] With regard to the historical placebo and rifaximin populations, 69.8% and 69.3% of patients, respectively, had a history of 2 HE episodes in the previous 6 months, with the remaining patients having more than 2 HE episodes. During the OLM, 71.4% of patients in the new-rifaximin population had 2 or more HE episodes during the previous 12 months. The median exposure was 427.0 days (range, 2–1427 d; PYE, 510.5) for the all-rifaximin population and 475.5 days (range, 2–1147 d; PYE, 342.3) for the new-rifaximin population. Of the 322 patients in the OLM, 92.2% were 80% or more adherent to treatment.

Safety

Adverse events. The summary of AEs (Table 2) and cirrhosis complication AEs (Table 3) suggest that AE rates during long-term rifaximin treatment did not increase compared with historical rates observed for rifaximin or placebo groups over 6 months. The event rate for serious AEs per PYE in all-rifaximin patients (0.48) was lower than in the historical placebo group (1.37). In addition, results for the new-rifaximin population were similar to those for the all-rifaximin population.

Adverse events involving cirrhosis complications. Most AEs observed in all groups were related to underlying liver disease, consistent with a population with cirrhosis. Infection event rates per PYE for all-rifaximin patients (0.73) were lower than those observed in the historical-rifaximin (1.12) and placebo groups (1.33) (Table 3), and the use of antibiotics (Supplementary Figure 2) did not generally increase during the long term. Six rifaximin-treated patients (2 in the RCT and 4 in the OLM) had C difficile infections (event rate, 0.012); the rates of C difficile occurrence remained stable with long-term rifaximin treatment. In addition, all 6 patients had multiple risk factors for C difficile infection (Supplementary Table 1). The rates of occurrence of other complications of cirrhosis, including ascites and edema, variceal bleeding, anemia, or prolongation of coagulation tests, did not change appreciably with long-term use of rifaximin and appeared similar to rates noted in the historical placebo group (Table 3).

Among the 392 patients in the all-rifaximin population, 352 (89.8%) received concomitant lactulose (range, 15–300 mL/d) and 40 (10.2%) received rifaximin alone. PYE for rifaximin was 452.9 in the rifaximin-plus-lactulose group and 57.6 in the rifaximin-alone group. The incidence of gastrointestinal-related AEs was significantly higher in patients treated with rifaximin plus lactulose compared with rifaximin alone (69.6% vs 47.5%; P < .001) (Table 4), including the incidences of nausea and abdominal pain.

Survival. In the all-rifaximin population, 76 patients died (8 deaths occurred ≥30 days after the last dose of study drug). The majority of the 76 deaths were attributed to liver disease complications (56.6% [n = 43]; with the majority from liver failure); 19.7% (n = 15) were attributed to cardiac causes, and 10.5% (n = 8) were attributed to infection (pneumonia or sepsis). No deaths were attributed to rifaximin treatment. The mortality rate (deaths ÷ PYE) for the all-rifaximin population (0.15) was similar to the rate reported for the historical placebo group (0.24), and causes of death in the OLM were consistent with previous reports in the RCT.[13]

Changes in underlying liver disease. There was also no apparent difference in the rate of change of Model for End-Stage Liver Disease scores among the all-rifaximin population (0.004) and the historical rifaximin (0.006) and placebo groups (0.005).[17]

All-Cause and Hepatic Encephalopathy–Related Hospitalizations

The rates of HE-related hospitalizations in the all-rifaximin (109 HE-related hospitalizations/510.5 PYE = 0.21 events/PYE) and new-rifaximin (79 HE-related hospitalizations/342.3 PYE = 0.23 events/PYE) populations, normalized for exposure, were similar to the rate observed in the historical rifaximin group (15 HE-related hospitalizations/50.0 PYE = 0.30 events/PYE), and lower than the rate observed in the historical

Table 1. Demographics, Baseline Characteristics, and Duration of Exposure

Characteristic	Historical placebo (n = 159)[13]	Historical rifaximin (n = 140)[13]	P value vs historical placebo	New rifaximin (n = 252)	P value vs historical placebo	All rifaximin (N = 392)	P value vs historical placebo
Age, y, mean (SD)	56.8 (9.18)	55.5 (9.57)	.22	57.5 (8.93)	.47	56.8 (9.21)	.95
<65 y	128 (80.50)	113 (80.71)	1.0	197 (78.17)	.62	310 (79.08)	.82
Sex, n (%)							
Male	107 (67.30)	75 (53.57)	.02	158 (62.70)	.40	233 (59.44)	.10
Female	52 (32.70)	65 (46.43)		94 (37.30)		159 (40.56)	
Race, n (%)							
White	139 (87.42)	118 (84.29)		233 (92.46)		351 (89.54)	
Black	5 (3.14)	7 (5.00)	.51	10 (3.97)	.12	17 (4.34)	.46
Other/missing	15 (9.43)	15 (10.71)		9 (3.57)		24 (6.12)	
Duration of current remission, d, mean (SD)	73.1 (51.33)	68.8 (47.68)	.45	111.1 (108.63)	<.0001	95.9 (93.73)	.004
Time since diagnosis of liver disease, mo, mean (SD)	60.51 (64.89)	51.22 (49.17)	.17	74.91 (83.49)	.07	66.45 (73.92)	.38
Time since diagnosis of HE, mo, mean (SD)	21.85 (26.41)	20.84 (23.13)	.73	20.02 (25.26)	.48	20.31 (24.50)	.52
MELD score, mean (SD)	12.7 (3.94)	13.1 (3.64)	.39	12.6 (4.11)	.82	12.8 (3.95)	.84
MELD score category, n (%)[a,b]							
≤10	48 (30.19)	34 (24.29)		88 (34.92)		122 (31.12)	
11–18	96 (60.38)	94 (67.14)	.45[c]	137 (54.37)	.74[c]	231 (58.93)	.53[c]
19–24	14 (8.81)	12 (8.57)		23 (9.13)		35 (8.93)	
Conn score, n (%)							
0	107 (67.30)	93 (66.43)		157 (62.30)		250 (63.78)	
1	52 (32.70)	47 (33.57)	.90	83 (32.94)	.34[d]	130 (33.16)	.49[d]
≥2	0	0		12 (4.76)		12 (3.06)	
Asterixis grade, n (%)							
0	108 (67.92)	96 (68.57)		172 (68.25)		268 (68.37)	
1	45 (28.30)	41 (29.29)	1.00	64 (25.40)	1.00[d]	105 (26.79)	.92[d]
≥2	6 (3.77)	3 (2.14)		16 (6.35)		19 (4.85)	
Renal impairment (serum creatinine), n (%)[e]							
≥1.5 ULN	3 (1.89)	4 (2.86)		5 (1.98)		9 (2.30)	
≤1.5 ULN	156 (98.11)	136 (97.14)	.71	245 (97.22)	1.00	381 (97.19)	1.00

MELD, Model for End-Stage Liver Disease; ULN, upper limit of normal.
[a]Data missing for 1 patient in historical placebo group.
[b]Data missing for 4 patients in the new- and all-rifaximin groups.
[c]P value determined for categories ≤18 and >18.
[d]P value determined for categories 0 and ≥1.
[e]Data missing for 2 patients in the new- and all-rifaximin groups.

placebo group (33 HE-related hospitalizations/46.0 PYE = 0.72 events/PYE; Figure 1). In addition, the rates of all-cause hospitalizations, normalized for exposure, were lower during treatment with rifaximin compared with the historical placebo group (Figure 1).

Discussion

This open-label study of long-term (≥24 mo) rifaximin 550 mg administered twice daily included patients

Table 2. Summary of AEs

	Historical placebo (n = 159)[a]	Historical rifaximin (n = 140)[a]	New-rifaximin population (n = 252)	All-rifaximin population (N = 392)
PYE	46.0	50.0	342.3	510.5
AEs, number of patients (rate[b])				
Any AE	127 (2.76)	112 (2.24)	236 (0.69)	362 (0.71)
Any serious AE	63 (1.37)	51 (1.02)	158 (0.46)	244 (0.48)
Discontinuations because of AEs	45 (0.98)	30 (0.60)	77 (0.22)	130 (0.25)

[a]Primary results were published previously.[13]
[b]AE rates were calculated as follows (number of patients ÷ PYE), in which PYE reflected the exposure up until the AE occurrence and therefore may have differed from the PYE for the entire patient group.

Table 3. Complications of Cirrhosis

	Historical placebo (n = 159)[a]	Historical rifaximin (n = 140)[a]	All-rifaximin population (N = 392)
PYE	46.0	50.0	510.5
Infections (all), n (rate[b])	49 (1.33)	46 (1.12)	214 (0.73)
Infections of special interest[c]			
Cellulitis	3 (0.07)	3 (0.06)	34 (0.07)
C difficile	0	2 (0.04)	6 (0.01)
Peritonitis	6 (0.13)	3 (0.06)	22 (0.04)
Pneumonia	1 (0.02)	4 (0.08)	42 (0.08)
Sepsis/septic shock	5 (0.11)	2 (0.04)	31 (0.06)
Urinary tract/kidney	14 (0.32)	9 (0.19)	83 (0.19)
Complications of portal hypertension, n (rate)	37 (0.89)	40 (0.96)	195 (0.57)
Acute kidney injury/ hepatorenal syndrome	9 (0.20)	2 (0.04)	74 (0.15)
Ascites and edema	29 (0.69)	34 (0.81)	147 (0.39)
Varices and variceal/GI bleed	7 (0.15)	6 (0.12)	58 (0.12)
Hematologic complications, n (rate)	7 (0.16)	13 (0.27)	80 (0.18)
Anemia	6 (0.13)	11 (0.23)	65 (0.14)
Thrombocytopenia/ coagulation	1 (0.02)	3 (0.06)	33 (0.07)
Other, n (rate)			
Electrolyte imbalances	3 (0.07)	6 (0.12)	52 (0.11)
Fatigue/sleep disorders	29 (0.70)	26 (0.58)	93 (0.2)
Muscular atrophy	2 (0.04)	0	8 (0.02)

GI, gastrointestinal.
[a]Primary results were published previously.[13]
[b]AE rates were calculated as follows: (number of patients ÷ PYE), in which PYE reflected the exposure up until the AE occurrence and therefore may have differed from the PYE for the entire patient group.
[c]Infections of special interest include infections that commonly occur among patients with cirrhosis. Patients who had a C difficile infection had recent clinical histories that included several risk factors for the infection: hepatic cirrhosis, advanced age, hepatitis C infection, numerous hospitalizations, multiple courses of antibiotics, and concurrent use of proton pump inhibitors.

Table 4. Gastrointestinal Event Rates for Patients Treated With Rifaximin With or Without Lactulose

	Rifaximin alone (n = 40)	Rifaximin + lactulose (n = 352)
PYE	57.6	452.9
Gastrointestinal disorders, % of patients (rate[a])		
Overall	47.5 (0.51)	69.6 (1.19)
Abdominal pain	12.5 (0.09)	21.3 (0.20)
Ascites	12.5 (0.09)	17.6 (0.15)
Gastrointestinal bleeding event[b]	10.0 (0.08)	15.9 (0.14)
Nausea	7.5 (0.05)	24.1 (0.23)
Constipation	7.5 (0.06)	12.2 (0.11)
Vomiting	5.0 (0.04)	15.1 (0.13)
Diarrhea	5.0 (0.04)	13.6 (0.12)
Esophageal varices	5.0 (0.04)	5.7 (0.05)
Diverticulum	5.0 (0.04)	1.1 (0.01)
Abdominal distension	2.5 (0.02)	6.3 (0.05)

NOTE. Event rates were reported in ≥5% of patients in either group.
[a]AE rates were calculated as follows: (number of patients ÷ PYE), in which PYE reflected the exposure up until the AE occurrence and therefore may have differed from the PYE for the entire patient group.
[b]Gastrointestinal bleeding AEs collectively included the following individual events: gastric hemorrhage, gastritis hemorrhagic, gastroduodenal hemorrhage, gastrointestinal hemorrhage, hematochezia, hemorrhoidal hemorrhage, lower gastrointestinal hemorrhage, melena, esophageal variceal hemorrhage, rectal hemorrhage, and upper gastrointestinal hemorrhage.

awaiting liver transplantation, to prevent recurrent overt HE episodes and potentially permanent neurologic sequelae.[21] In addition, the rates of HE-related and all-cause hospitalizations, which were considered serious AEs, appeared to be lower for patients treated with rifaximin 550 mg twice daily than for the historical placebo group over 6 months[13]; this apparent protective effect was maintained with long-term use.

Patients with cirrhosis have increased susceptibility to bacterial infections[22] that may increase the risk of
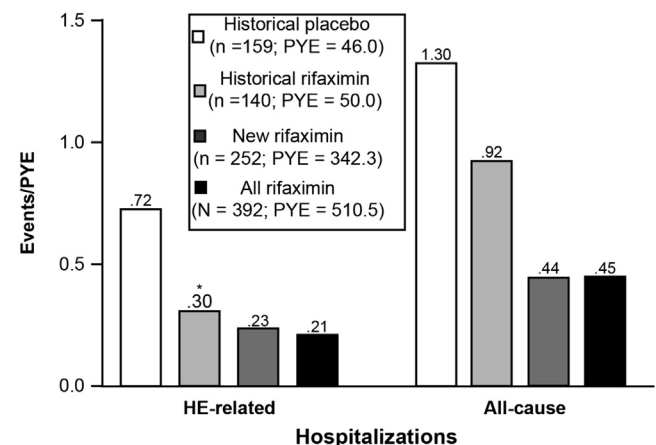

Figure 1. Rates of HE-related and all-cause hospitalizations for the all-rifaximin and new-rifaximin populations in the OLM compared with patients receiving historical placebo or rifaximin in the 6-month RCT. *P < .0001 vs placebo. Inferential statistics were not conducted for the all-rifaximin and new-rifaximin populations.

from a 6-month RCT[13] and new patients with cirrhosis and recurrent HE. Rifaximin appeared to provide a continued decrease in HE-related and all-cause hospitalizations, without an increased rate of AEs or change in survival rates.

The profile and rates of AEs with long-term rifaximin treatment appeared similar to data previously reported in the 6-month RCT.[13] The lower incidence of gastrointestinal-related AEs in patients treated with rifaximin alone is interesting but not unexpected given the known AE profile of oral disaccharides. However, this observation may have major treatment implications for HE because lactulose effectiveness for HE prevention often is limited by gastrointestinal adverse effects that can lead to nonadherence to therapy.[18–20] Studies comparing rifaximin plus lactulose vs rifaximin alone are ongoing.

The event rate for serious AEs was low, and there were no new serious AEs that emerged with long-term rifaximin treatment. Rifaximin, therefore, appears to be suitable for maintenance therapy in patients with cirrhosis. This may be especially important for patients

mortality 4-fold.[23] The event rate for any infection in patients receiving long-term therapy with rifaximin appeared lower than historical placebo and rifaximin 6-month rates. In addition, event rates for the most common bacterial infections in patients with cirrhosis (eg, urinary tract infections, upper respiratory tract infections, sepsis, and spontaneous bacterial peritonitis)[22] appeared similar or lower than historical placebo and rifaximin rates. In addition, there was no apparent increase in the rate of infection associated with use of antibiotics, including *C difficile* infection, with long-term rifaximin treatment. Six patients developed *C difficile* infection; this rate of *C difficile* infection (∼1%) is similar to that reported in patients with advanced liver disease.[24] In addition, all 6 patients had multiple risk factors for *C difficile* infection, including advanced age, numerous hospitalizations, multiple courses of antibiotics, and concurrent proton pump inhibitor use. All of the *C difficile* infections resolved with standard antibiotic therapy, and 3 patients continued rifaximin treatment postresolution without recurrence.

Although the current study did not assess microbial antibiotic resistance, rifaximin appears to have a low level of selection for resistant bacterial mutants.[12] In the current study, rates of infection and the percentage of patients treated with antibiotics remained stable or decreased and was comparable with the historical 6-month RCT rates, indicating no increased risk of developing infection with long-term exposure to rifaximin. In addition, there was no observed rifaximin tachyphylaxis, which would have been expected in the face of substantial bacterial antibiotic resistance. Rifaximin is associated with lower rates of selection of antimicrobial-resistant bacterial mutants compared with other antibiotics[12]; additional studies are needed to confirm this finding. Furthermore, nonabsorbed antibiotics (rifaximin) have not been associated with an increased risk of antibiotic-resistant bacterial infections within 30 days of exposure in hospitalized patients with cirrhosis (odds ratio, 0.4; 95% confidence interval, 0.04–2.8).[25]

No death during the study was attributable to rifaximin. In addition, the number of deaths during the study was lower than expected for this population.[26] A 2013 case-controlled study showed an independent association between rifaximin therapy and greater survival, and a lower risk of developing variceal bleeding, HE, spontaneous bacterial peritonitis, and hepatorenal syndrome.[27] Importantly, decreasing hospitalization rates in this high-risk population may decrease rates of nosocomial infections. The observed mortality during the current study was consistent with the natural history of advanced liver disease, and liver disease severity at baseline is likely the most important factor in determining survival in these chronically ill patients. As expected for this patient population, most deaths resulted from the progression of underlying disease and included liver failure and hepatic neoplasms. This study also examined the effect of chronic rifaximin use on underlying liver disease, which

remained stable; no adverse effects on cirrhosis progression or mortality were noted.

The hospitalization and tolerability data reported in this study have several beneficial implications for treating patients with cirrhosis. Although this study was not designed to explore the relative benefits of rifaximin use for disease maintenance in patients with cirrhosis, these data, together with results from other studies, present a favorable profile for long-term treatment with rifaximin with respect to morbidity and mortality in this chronically ill population. A study in patients with alcohol-related decompensated cirrhosis reported that rifaximin treatment reduced endotoxin levels and resulted in significantly decreased hepatic venous pressure gradient values, which decreased the occurrence of complications in advanced liver disease.[28] Intestinal decontamination with rifaximin has been shown to increase platelet count significantly in thrombocytopenic patients with cirrhosis. This benefit is thought to be achieved through a concomitant reduction of endotoxemia.[29] Hypothetically, improvements in platelet counts in patients with thrombocytopenia could decrease bleeding risks and complications of medical procedures, and help stabilize underlying liver disease. Intestinal decontamination is also known to increase peripheral blood counts by suppressing endotoxemia and inhibiting the effects of cytokines and nitric oxide on blood counts.[30]

A potential limitation of this study was that because it was not a randomized trial with a prospective control group, there is a potential risk of heterogeneity among patients when comparing the data from the current study with historical data. However, regulatory guidance and published recommendations have provided guidance on situations in which comparisons to a historical control may be appropriate (eg, historical controls being part of recent clinical trials with identical eligibility requirements; the same organization and clinical investigators that performed the clinical trial performing the newer trial; and inclusion of patients with similar baseline characteristics).[14–16] As mentioned in the Methods section, nonstatistical comparisons with the historical RCT,[13] including the placebo arm, were considered methodologically appropriate in the current study based on multiple factors, such as similar enrollment criteria and patient population homogeneity. Nevertheless, corroborating the current findings with a long-term, prospectively designed, controlled study to control for potential population heterogeneity and provide statistical analyses is warranted. Another potential limitation is that 89% of patients took concomitant lactulose during the study. Although this study was not powered to assess the effects of rifaximin alone, it is notable that in the aforementioned RCT, approximately 91% of patients in both the rifaximin and placebo groups took concomitant lactulose.[13]

In conclusion, long-term rifaximin 550 mg twice daily was well tolerated and appeared to confer a protective effect against the risk of hospitalizations in patients in remission from recurrent HE. This open-label study

was an analysis of rifaximin treatment administered for 24 months or longer, and established the reproducibility and durability of hospitalization and safety results reported previously for a 6-month treatment period.[13] The safety profile of long-term rifaximin treatment remained favorable, and no negative effects on survival or underlying cirrhotic disease were noted. With these encouraging data, more attention should be paid to the population of patients with cirrhosis and history of overt HE in an effort to reduce HE recurrence and potentially preserve long-term and post-transplantation cognition in these patients.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2013.12.021.

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Supplementary Figure 1. CONSORT flow diagram. [a]The integrated safety population (all-rifaximin population, N = 392) included the new-rifaximin population plus all patients who received rifaximin during the RCT regardless of enrollment into the OLM (*gray shaded boxes*). CONSORT, Consolidated Standards of Reporting Trials.
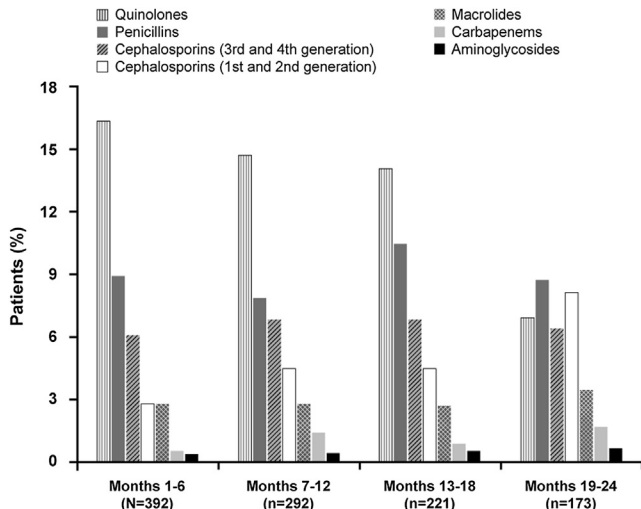
Supplementary Figure 2. Antibiotic use time in the all-rifaximin population.

Supplementary Table 1. Cases of *C difficile* Reported During a 6-month Randomized Trial and ≥24-month, Open-Label Trial of Rifaximin 550 mg Twice Daily

Age, y/sex	Diagnosis	Time to onset of *C difficile* diagnosis	Outcome	Prior or concurrent antibiotic use	PPI	Treatment	Action with study drug
60/F	*C difficile* colitis, worsening encephalopathy	17 d	Resolved	Numerous hospitalizations during previous 6 mo involving treatment with multiple courses of antibiotics, started empirically on piperacillin + tazobactam (3375 mg IV every 6 hours) on day 15	Pantoprazole	Metronidazole, vancomycin	Permanently discontinued at day 15 because of SAE of breakthrough HE
51/M	*C difficile* colitis	52 d	Resolved	Ciprofloxacin	Pantoprazole	Metronidazole	Continued on rifaximin and ciprofloxacin 107 d after *C difficile* diagnosis, died study day 159 of disseminated intravascular coagulation following hepatectomy for liver transplant
53/F	End-stage liver disease, sepsis MRSA, vancomycin-resistant enterococcal infection, *C difficile* colitis	24 d after discontinuation of rifaximin (total exposure to rifaximin, 47 d)	Resolved	Ciprofloxacin, vancomycin, daptomycin	Esomeprazole, lansoprazole	Metronidazole	Rifaximin discontinued on day 47 owing to hepatic failure, *C difficile* culture negative on day 81; nonresuscitation order day 82, died of multiorgan failure and end-stage liver disease on day 86
71/F	Severe hyponatremia, hypoglycemia, CHF, hospital-acquired pneumonia, *C difficile* colitis	20 d after discontinuation of rifaximin (total exposure to rifaximin, 106 d)	Resolved	Ceftriaxone, levofloxacin, vancomycin, piperacillin + tazobactam	Esomeprazole	Metronidazole	Withdrew from study because of AE of genital bumps, continued on non-study rifaximin
40/M	*C difficile* toxin (+), *C difficile* colitis	297 d	Resolved	Nafcillin, levofloxacin, and cephalexin administered for cellulitis and pseudomonal bacteremia	Omeprazole	2 courses of metronidazole	Continued on rifaximin
67/F	End-stage liver disease, *C difficile* colitis	19 d after discontinuation and 18 d after orthotopic liver transplant (total rifaximin exposure, 343 d)	Resolved	Multiple courses of antibiotics before *C difficile* diagnosis, including ceftriaxone, ampicillin, ciprofloxacin, and sulfamethoxazole + trimethoprim	Pantoprazole	Metronidazole	Discontinued study because of liver transplant

CHF, congestive heart failure; IV, intravenously; MRSA, methicillin-resistant *Streptococcus aureus*; PPI, proton pump inhibitor; SAE, serious adverse event.