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Rifaximin: A reasonable alternative for norfloxacin in the prevention of spontaneous bacterial peritonitis in patients with HCV-related liver cirrhosis

Mohammed M. Shamseya [1], **Marwa A. Madkour** *

Department of Clinical and Experimental Internal Medicine, Medical Research Institute, University of Alexandria, Egypt

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KEYWORDS

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Abstract *Background:* Norfloxacin is the most commonly used agent for the prophylaxis against spontaneous bacterial peritonitis (SBP) in patients with liver cirrhosis. Rifaximin, another broad spectrum antibiotic, is used for the treatment of traveler's diarrhea and hepatic encephalopathy.
Objective: We aimed to test the efficacy of rifaximin versus norfloxacin for prevention of SBP in patients with hepatitis C virus (HCV)-related liver cirrhosis.
Patients and methods: 86 patients with HCV-related liver cirrhosis and ascites were enrolled and divided into two groups of matching age, sex and Child–Pugh class. Group I was given norfloxacin 400 mg/day as single dose, and group II rifaximin 1200 mg/day in three divided doses. They were followed for up to one year. Study endpoints were SBP, hepatocellular carcinoma, compliance failure, death, or liver transplantation.
Results: More than 70% of patients received the antimicrobial as primary prophylaxis and the rest were given secondary prophylaxis against SBP. The mean follow-up period was 10.16 ± 2.64 months for norfloxacin and 10.26 ± 2.32 months for rifaximin ($p = 0.863$). Although statistically insignificant ($p = 0.265$), patients on rifaximin developed fewer episodes of SBP than those on norfloxacin (4.7% vs. 14%). Also, the infection-free duration before SBP was longer ($p = 0.129$) with rifaximin than norfloxacin (9.5 vs. 5.0 months). Rifaximin significantly reduced the rate of new compared to past episodes of SBP by 20.9% ($p = 0.007$) vs. 13.9% for norfloxacin ($p = 0.112$). Overall survival was equal in both groups. Patients adhered to therapy regimen of norfloxacin for significantly longer time than rifaximin ($p = 0.010$).
Conclusion: Rifaximin is – at least – as good as norfloxacin. It seems to be an appropriate alternative for long-term primary and secondary prophylaxis of SBP in cirrhotic patients with ascites. Modification of dose regimen should be considered to improve patient's compliance to rifaximin.

* Corresponding author at: Department of Clinical and Experimental Internal Medicine, Medical Research Institute, Alexandria University, 165 Horreya Avenue, Hadara, Alexandria, Egypt. Tel.: +20 3 4282331, +20 3 4282373, mobile: +20 01281761402.
E-mail addresses: mohamed.shamseya@yahoo.com (M.M. Shamseya), madkourmarwa@yahoo.com (M.A. Madkour).
[1] Tel.: +20 3 4282331, +20 3 4282373, mobile: +20 01222990618.

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1. Introduction

Spontaneous bacterial peritonitis (SBP) is a common bacterial infection in patients with cirrhosis and ascites, occurring in up to 30% of patients with cirrhosis, and having an estimated in-hospital mortality rate of 20%. Half the episodes of SBP are present at the time of hospital admission, while the rest are acquired during hospitalization.[1–3] Patients with SBP may present with a wide spectrum of manifestations, ranging from local symptoms and/or signs of peritonitis (abdominal pain, abdominal tenderness, vomiting, diarrhea, ileus) with or without signs of systemic inflammation (hyper- or hypothermia, altered white blood cell count, tachycardia, and/or tachypnea, shock); to unexplained renal failure or unexplained worsening of liver function and hepatic encephalopathy. At the very end of this spectrum, however, lies a good percentage of patients with SBP who are asymptomatic.[4,5] Hence, the diagnosis of SBP is based mainly on diagnostic paracentesis.[6]

Ascitic fluid cell analysis usually shows an increased number of neutrophils, which must reach a count of at least 250/mm^3 in order to confirm the diagnosis of SBP. If ascitic fluid culture is positive (which is the case only in 40% of patients with proved SBP), the most common pathogens include Gram-negative bacteria (usually *Escherichia coli*) and Gram-positive cocci (mainly streptococcus species and enterococci).[1–3] Ascites culture, however, might be negative in up to 60% of patients who have increased ascites neutrophil count, a category also known as "culture-negative SBP". A third category of patients might have "bacterascites", in which cultures are positive but ascitic neutrophil count is less than 250/mm^3. In both categories the clinical presentation is similar to classic SBP, and patients should be treated in a similar manner.[6] Small intestinal dysmotility and bacterial overgrowth, which are commonly encountered in patients with liver cirrhosis, are the major contributing factors for inviting enteric bacterial "translocation" from the intestinal lumen to mesenteric lymph nodes and other extra intestinal sites, resulting in SBP.[7–9] In addition, several humoral and cell-mediated abnormalities of the immune system increase the susceptibility for bacterial infections in cirrhotic patients, particularly for SBP.[10,11]

When first described, the mortality from SBP exceeded 90%, but it has been reduced to approximately 20% with early diagnosis and treatment.[12,13] Typical treatment of SBP includes empirical antibiotic therapy, which must be initiated immediately after its diagnosis, without awaiting the results of ascitic fluid culture.[3,6] Cefotaxime, a third-generation cephalosporin, is the drug of choice with a recommended dose of 6 g/day for a minimum of 5 days, because it covers most causative organisms and has high ascitic fluid concentrations.[14,15] Ciprofloxacin, given either for 7 days intravenously or for 2 days intravenously followed by 5 days orally, results in a similar SBP resolution rate and achieves hospital survival comparable with cefotaxime.[16]

Cirrhotic patients with low ascitic fluid protein concentration (<1.5 g/dl) and/or high serum bilirubin levels are at high risk of developing a first episode of SBP.[17–19] Also, patients who have survived an episode of SBP were proved to have a 1-year recurrence rate of about 70%.[13] Studies have evaluated long-term prophylaxis in patients with or without prior history of SBP. The ideal prophylactic agent should be safe, affordable, and effective at decreasing the amounts of pathogenic microorganisms from the gut while preserving the protective flora (selective intestinal decontamination).

Norfloxacin is a quinolone with limited absorption from the gastrointestinal tract which has antibacterial activity against Gram-negative but not against Gram-positive cocci or anaerobic bacteria. It is the most commonly used approach for the prophylaxis of SBP in patients with ascites, at a dose of 400 mg/day orally.[20–22] Several guidelines (including those of the American Association for the Study of Liver Diseases; AASLD) suggested the long-term prophylactic use of norfloxacin or trimethoprim/sulfamethoxazole against SBP.[23] However, given the cost and unavoidable hazard of developing resistant organisms, the use of prophylactic antibiotics is firmly restricted to patients at high risk for developing SBP. Nevertheless, recent years have witnessed a significant change in the epidemiology of bacterial infections in cirrhosis, with an increasing incidence of quinolone-resistant bacteria.[2,24,25] One study has shown that a considerable number of infections following acute gastrointestinal hemorrhage were caused by Gram-positive bacteria, which was likely related to invasive procedures used in these patients. In addition, 30% of the isolated Gram-negative bacteria were resistant to quinolones and 30% were resistant to trimethoprim–sulfamethoxazole.[2] Another trial tested norfloxacin for primary prophylaxis against SBP in 109 patients with cirrhosis and ascitic fluid total protein level <15 g/L or serum bilirubin level >2.5 mg/dl. SBP was reduced at the expense of more resistance of gut flora to norfloxacin in that group.[26]

Rifaximin is another broad spectrum antibiotic with only trivial absorption from the gut. It acts by inhibiting bacterial RNA synthesis. Since the mid-80s, rifaximin has been extensively investigated for its anti-diarrheal properties, and since 2004 it has received approval from the American Food and Drug Administration (FDA) for the treatment of traveler's diarrhea, followed by approval for treatment of hepatic encephalopathy in 2010.[27] Till now, rifaximin has demonstrated broad spectrum antibacterial activity against Gram-positive and Gram-negative organisms, both aerobes and anaerobes, with low risk of introducing bacterial resistance.[28–30] The aim of this study was to test the efficacy of rifaximin in comparison with norfloxacin for the prevention of spontaneous bacterial peritonitis in patients with HCV-related liver cirrhosis and ascites.

2. Patients and methods

A total of 86 consecutive patients with decompensated HCV-related liver cirrhosis (Child–Pugh classes B and C) who were admitted to the Hepatology and Gastroenterology Unit, Medical Research Institute, Alexandria University, during the period from January 2012 till December 2013 were enrolled in the study. Patients were selected for long-term antibiotic prophylaxis according to the recommendations (Evidence class I, level A) of the AASLD for participating in this study.[23] Patients who proved to have survived a previous episode of SBP were given secondary prophylaxis. Also, high risk patients with baseline ascitic fluid protein <1.5 g/dl along with impaired renal function (creatinine $\geqslant 1.2$, blood urea nitrogen $\geqslant 25$ mg/dl or serum sodium level $\leqslant 130$ mEq/L) or patients with liver failure (Child score $\geqslant 9$ and serum bilirubin

$\geqslant$3 mg/dl) with no proof of previous attack of SBP were included for primary prophylaxis. Exclusion criteria were etiologies of liver cirrhosis other than HCV, recent abdominal surgery (within past 6 months), abdominal malignancy (including hepatocellular carcinoma), portal vein thrombosis, splenectomy and hypersensitivity to norfloxacin or rifaximin.

Patients were divided into two groups of matching age, sex and Child–Pugh class. Group I (43 patients) were given norfloxacin 400 mg/day as a single dose, and group II (43 patients) were given rifaximin 1200 mg/day in three divided doses.

Diagnosis of cirrhosis was based on clinical findings (ascites, splenomegaly, lower limb edema and/or esophageal varices by upper gastrointestinal endoscopy), imaging (abdominal ultrasound) and laboratory findings. HCV infection was proved by Real Time-Polymerase Chain Reaction (RT-PCR). The severity of cirrhosis was graded according to the Child–Pugh's classification. Presence of ascites was confirmed by abdominal ultrasound, and baseline diagnostic ascitic fluid protein analysis was performed to identify high risk patients.

Patients were followed for up to one year. Other study endpoints were developing SBP (or any other infection requiring systemic antibiotic treatment), emergence of hepatocellular carcinoma, compliance failure, death, or liver transplantation. The term "overall survival" referred to continuing the one-year study duration without facing any of the study endpoints. Monthly planned follow-up visits were scheduled to record treatment compliance, as well as diagnose and manage complications. Patients lost to follow-up or who discontinued prophylaxis without permission for more than seven days were designated as "compliance failure" on the day of last visit or last dose taken. Patients requiring alternative intervention for complications (hepatic encephalopathy, variceal bleeding or hepatorenal syndrome) were managed according to the guidelines of the AASLD.[23] During an active variceal bleeding attack, oral prophylaxis was discontinued and the only antibiotic given to patients of both groups to prevent bacterial infections was Ceftriaxone (1 g/day for seven days). During an episode of overt hepatic encephalopathy, the planned oral antibiotic prophylaxis was continued without change (via nasogastric tube if necessary), and only the concomitant use of lactulose was permitted. Hepatorenal syndrome was managed by albumin infusion (10–20 grams/day) plus octreotide with a target dose of 200 μgrams subcutaneously 3 times per day, and midodrine titrated up to a maximum of 12.5 mg orally 3 times/day. If SBP was suspected, diagnostic paracentesis of ascitic fluid sample and microbiological culture were done to confirm the diagnosis. SBP was defined as the presence of a polymorphonuclear count in ascitic fluid $\geqslant$250/ml irrespective of the result of the microbiological culture. Patients with proved SBP were censored from the study on the day of confirmed diagnosis.

3. Statistical analysis

Data were analyzed using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. Quantitative data were described using mean and standard deviation for normally distributed data while abnormally distributed data were expressed using median, minimum and maximum. Comparison between different groups regarding categorical variables was tested using Chi-square test. When more than 20% of the cells have expected count less than 5, correction for chi-square was conducted using Fisher's Exact test. For normally distributed data, comparison between the two studied groups was done using independent *t*-test while for abnormally distributed data, comparison was done using Mann Whitney test. Significance of the obtained results was judged at the 5% level. Kaplan–Meier analysis was used to examine the cumulative probability of overall survival and patient's compliance to therapy.[31]

4. Results

The baseline characteristics of the study population are summarized in Table 1. A total of 86 patients with HCV-related liver cirrhosis were included in the study. They were divided into two groups (Norfloxacin versus Rifaximin group; 43 patients each) of matching age, sex and Child–Pugh class. 23.3% of patients in both groups were Child class B, while 76.7% were Child class C. All patients had ascites. More than 70% of patients received the antimicrobial agent as primary prophylaxis against SBP, while the rest had previous history of SBP and were given secondary prophylaxis, with no significant difference between the two groups. Also, baseline values for liver profile parameters, renal function and ascitic fluid albumin concentration were similar in both groups ($p > 0.05$).

4.1. Follow-up

The mean follow-up period of patients till occurrence of any of the study endpoints was 10.16 ± 2.64 (range 3–12) months for norfloxacin and 10.26 ± 2.32 (range 5–12) months for rifaximin, with no significant difference between both groups. During this period, patients on rifaximin developed fewer episodes of hepatic encephalopathy (HE) than patients on norfloxacin (4.7% and 9.3%, respectively). Also, when comparing the number of patients with past history of HE to those who developed new episodes of HE during the study duration, rifaximin was found to reduce the number of episodes by 11.6% versus 4.7% for norfloxacin. The difference, however, was not statistically significant in both occasions. The two groups had comparable number of variceal bleeding episodes during the follow-up period, and only one patient in each group developed hepatorenal syndrome. Four patient (9.3%) in the norfloxacin group developed hepatocellular carcinoma versus 5 patients (11.6%) in the rifaximin group, with no significant difference between them, as demonstrated in Table 2. None of the patients underwent liver transplantation during the study period.

4.2. Spontaneous bacterial peritonitis (SBP)

Patients who received rifaximin prophylaxis developed fewer episodes of SBP than those on norfloxacin (4.7% vs. 14%, respectively), with statistically nonsignificant difference. Also, the duration before developing a new attack of SBP was longer with rifaximin compared to norfloxacin patients (9.5 vs. 5.0 months, respectively). Additionally, rifaximin significantly reduced the rate of new compared to past episodes of SBP by 20.9% ($p = 0.007$), while the rate reduction with norfloxacin was only by 13.9% and not statistically significant ($p = 0.112$), as demonstrated in Table 2 and Fig. 1. Cultures of ascitic fluid from patients who developed new SBP were

Table 1 Comparison between the two groups according to baseline characteristics.

	Norfloxacin (n = 43)	Rifaximin (n = 43)	p
Age (years)	50.3 ± 9.0	52.7 ± 8.5	0.425
Sex			
Male	34 (79.1%)	34 (79.1%)	1.000
Female	9 (20.9%)	9 (20.9%)	
Prophylaxis type			
Primary (high risk)	31 (72.1%)	32 (74.4%)	0.808
Secondary (previous SBP)	12 (27.9%)	11 (25.6%)	
Child–Pugh class			
B	10 (23.3%)	10 (23.3%)	1.000
C	33 (76.7%)	33 (76.7%)	
Child score	11.51 ± 2.06	11.47 ± 2.04	0.917
Ascites			
Mild	8 (18.6%)	7 (16.3%)	0.823
Moderate/severe	35 (81.4%)	36 (83.7%)	
Serum bilirubin (mg/dl)	2.9 ± 1.7	2.3 ± 1.0	0.192
Serum albumin (g/dl)	2.9 ± 0.4	2.8 ± 0.5	0.121
Prothrombin time (s)	17.1 ± 1.8	16.9 ± 2.0	0.324
Blood urea nitrogen (mg/dl)	23 (16–54)	24 (14–61)	0.533
Serum creatinine (mg/dl)	1.10 (0.70 − 3.10)	1.0 (0.70 − 3.10)	0.562
Serum sodium (mEq/L)	129.5 ± 7.3	130.0 ± 5.5	0.487
Ascitic fluid protein (g/dl)	0.9 ± 0.6	1.0 ± 0.5	0.253

SBP: spontaneous bacterial peritonitis. Qualitative data were expressed using number and percent and compared using Chi square test. Normally distributed quantitative data were expressed in (Mean ± SD) and compared using t-student test. Abnormally distributed quantitative data were expressed in Median (Min. – Max.) and compared using Mann Whitney test.
* Statistically significant at $p \leqslant 0.05$.

Table 2 Comparison between the two groups according to follow-up events.

	Norfloxacin (n = 43)	Rifaximin (n = 43)	p_1
Hepatic encephalopathy			
Past	6 (14.0%)	7 (16.3%)	0.763
New	4 (9.3%)	2 (4.7%)	0.676
p_2	0.501	0.156	
Variceal bleeding			
Past	7 (16.3%)	6 (14.0%)	0.763
New	6 (14.0%)	7 (16.3%)	0.763
p_2	0.763	0.501	
SBP			
Past	12 (27.9%)	11 (25.6%)	0.808
New	6 (14.0%)	2 (4.7%)	0.265
p_2	0.112	0.007*	
Months till SBP	5.0 (3.0 − 10.0)	9.50 (9.0 − 10.0)	0.129
Ascites culture			
Positive	1/6 (16.7%)	0/2 (0%)	1.000
Negative	5/6 (83.3%)	2/2 (100%)	
Hepatorenal syndrome	1 (2.3%)	1 (2.3%)	1.000
Hepatocellular carcinoma	4 (9.3%)	5 (11.6%)	1.000
Death	4 (9.3%)	3 (7.0%)	1.000

SBP: spontaneous bacterial peritonitis. p_1: p value for Chi square test for comparing between the two studied groups. p_2: p value for Chi square test for comparing between past and new. Abnormally distributed quantitative data were expressed in Median (Min. – Max.) and were compared using Mann Whitney test.
* Statistically significant at $p \leqslant 0.05$.

mostly negative. The only positive culture was detected in one patient from the norfloxacin group, and it was positive for *E. coli*.

Patients who developed SBP were significantly more likely to have a past history of previous SBP (p = 0.029), and had significantly worse overall survival (p < 0.001) compared to patients who did not develop SBP during the study duration. Significantly higher baseline values for serum bilirubin (3.2; vs. 2.9 mg/dl; p = 0.007), prothrombin time (17.8 vs. 15.9 s, p = 0.040) and Child–Pugh score (11.67 vs. 9.75, p = 0.011) were also found among patients who developed SBP compared with those who did not, whereas ascitic fluid total protein and renal function tests were comparable in both. Although 75% of SBP patients were on norfloxacin vs. 25% on rifaximin,

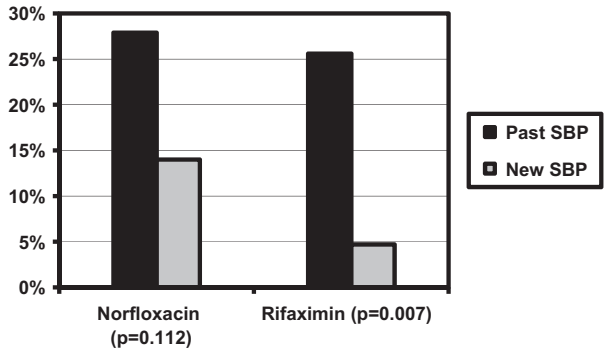

Figure 1 Frequency of past and new episodes of spontaneous bacterial peritonitis.

Table 3 Factors associated with SBP.

	SBP (n = 8)	No SBP (n = 78)	p
Age (years)	53.3 ± 7.3	51.7 ± 10.5	0.566
Sex (male)	6 (75.0%)	62 (79.5%)	0.976
Past SBP	5 (62.5%)	18 (23.1%)	0.029*
Child–Pugh class			
B	1 (12.5%)	39 (50.0%)	0.081
C	7 (87.5%)	39 (50.0%)	
Child score	11.67 ± 1.92	9.75 ± 2.49	0.011*
Serum bilirubin (mg/dl)	3.2 ± 1.7	2.9 ± 1.2	0.007*
Serum albumin (g/dl)	2.6 ± 0.5	2.9 ± 0.4	0.231
Prothrombin time (sec)	17.8 ± 1.6	15.9 ± 1.9	0.040*
Blood urea nitrogen (mg/dl)	25 (17–56)	23 (15–51)	0.503
Serum creatinine (mg/dl)	1.0 (0.80 – 1.20)	1.05 (0.70 – 3.10)	0.525
Serum sodium (mEq/L)	126.9 ± 7.6	131. ± 5.3	0.407
Ascitic fluid protein (g/dl)	0.8 ± 0.4	1.1 ± 0.5	0.063
Antimicrobial			
Norfloxacin	6 (75.0%)	37 (47.4%)	0.265
Rifaximin	2 (25.0%)	41 (52.6%)	
Overall survival (months)	6.50 ± 2.78	10.59 ± 2.11	< 0.001*

SBP: spontaneous bacterial peritonitis. Qualitative data were expressed using number and percent and compared using Chi square test. Normally distributed quantitative data were expressed in (Mean ± SD) and compared using t-student test. Abnormally distributed quantitative data were expressed in Median (Min. – Max.) and compared using Mann Whitney test.
* Statistically significant at $p \leqslant 0.05$.

the difference, however, did not prove to be statistically significant (p = 0.265), as shown in Table 3.

4.3. Patient's compliance and drug safety

The rate of adherence to therapy (compliance) was higher with norfloxacin (90.7%) compared to rifaximin (81.4%), with statistically nonsignificant difference. Moreover, among the patients who failed to adhere to the drug regimen, the time lapse till compliance failure was significantly longer for

Table 4 Comparison according to compliance and overall survival.

	Norfloxacin (n = 43)	Rifaximin (n = 43)	p
Compliance	39 (90.7%)	35 (81.4%)	0.213
Months till compliance failure	9.0 ± 0.82	6.75 ± 1.28	0.010*
Overall survival	25 (58.1%)	25 (58.1%)	1.000
Months till study endpoint	10.16 ± 2.64	10.26 ± 2.32	0.863

Qualitative data were expressed using number and percent and compared using Chi square test. Quantitative data were expressed in (Mean ± SD) and compared using t-student test.
* Statistically significant at $p \leqslant 0.05$.

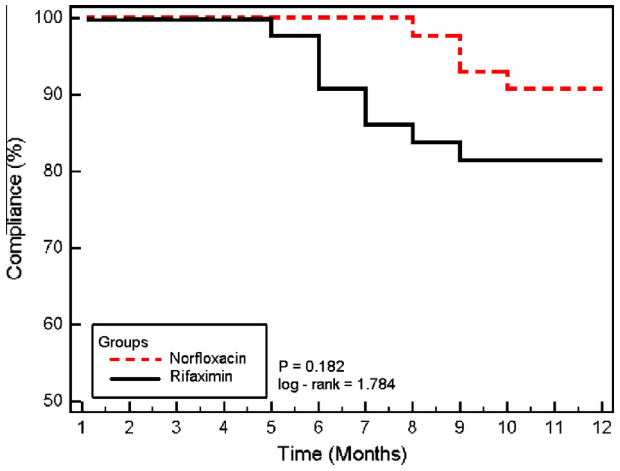

Figure 2 Kaplan Meier curve for patient's compliance to therapy.

norfloxacin versus rifaximin (Table 4, Fig. 2). Most patients reported a difficulty to adhere to the three times per day-regimen of rifaximin, while the rest (in both groups) reported that the problem was financial. The monthly cost for norfloxacin regimen was estimated at about 38.50 LE, while that of rifaximin was about 306 LE.

The most commonly reported adverse effects in the norfloxacin group were gastrointestinal (nausea, abdominal cramps and flatulence; 27.9%), in addition to headache, dizziness and asthenia (9.3%), while in the rifaximin group the main adverse effects were gastrointestinal (nausea, vomiting and abdominal cramps; 25.6%) and generalized weakness or fatigue (4.7%) with no significant difference of overall frequency between both groups (p = 0.741).

4.4. Overall survival

Patient's survival was equal for norfloxacin and rifaximin patients (58.1%, both), as demonstrated in Table 4 and Kaplan Meier curve in Fig. 3. They also had similar duration of time lapse till occurrence of one of the study endpoints (p = 0.863). The death rate was comparable in both groups (9.3% for norfloxacin vs. 7.0% for rifaximin; Table 1), and

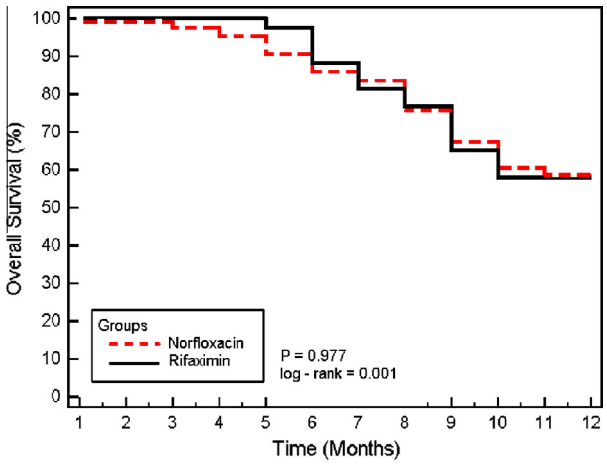

Figure 3 Kaplan Meier curve for overall survival.

the leading causes of death were hepatorenal syndrome, massive variceal bleeding and hepatic encephalopathy.

5. Discussion

Numerous clinical trials and post-marketing surveillance programs have clearly proved the antibiotic rifaximin to have an excellent safety profile, probably due to its negligible absorption from the gut, and consequently its lack of systemic activity.[32,33] The only few adverse reactions reported were gastrointestinal (GIT) in nature, such as flatulence and nausea. Norfloxacin, on the other hand, is readily absorbed from the gut, which makes it more likely to induce systemic side effects. GIT effects (such as nausea, vomiting, and diarrhea), as well as neurological manifestations (such as headache, insomnia, dizziness and asthenia) are common. Other rare but serious side effects include tendonopathy, exacerbation of myasthenia gravis and life threatening arrhythmias.[34] In the present work, both agents showed only mild to moderate, generally tolerated side effects, with no significant difference between both. Nevertheless, it was challenging to differentiate between the true side effects of the tested antimicrobials (particularly rifaximin) and the usual common dyspeptic symptoms of the portal hypertensive state (caused by gastropathy, enteropathy, colopathy and cholecystopathy). This issue was similarly encountered in other studies testing the efficacy of rifaximin for treatment of hepatic encephalopathy.[35–37] The authors explained that the GIT adverse events – which were frequently reported in their trials – were not surprising because patients with advanced liver disease were involved, and that most of the symptoms were rather due to progression of disease or complications of cirrhosis. All three studies even stated that there were no differences in adverse-event profiles between patients on rifaximin and those on placebo.

The European Association for the Study of the Liver (EASL) has identified three patient populations at high-risk for developing SBP: patients with acute gastrointestinal hemorrhage; those with low total protein content in ascitic fluid and no prior history of SBP; and those with a previous history of SBP.[38] In comparison, our patients who developed SBP during the study duration were significantly more likely to have had a history of previous SBP, higher baseline values for serum bilirubin, prothrombin time and Child–Pugh score. As expected, they also had significantly worse overall survival compared to patients who did not develop SBP.

Despite the fact that 75% of patients who developed SBP in our study were on norfloxacin versus 25% on rifaximin, the difference, however, did not prove to be statistically significant. Rifaximin patients also developed fewer episodes of SBP and had longer infection-free periods than those on norfloxacin, although, again, with no statistically significant difference between both drugs. Nevertheless, rifaximin significantly reduced the rate of new compared to past episodes of SBP by 20.9% ($p = 0.007$) versus 13.9% ($p = 0.112$) with norfloxacin.

To the best of our knowledge so far, no published studies are available comparing norfloxacin to rifaximin for SBP prophylaxis. Only one recent study by Lutz et al. prospectively evaluated 152 ascitic patients for the risk of developing SBP under the use of antimicrobial prophylaxis with rifaximin versus the systemically absorbed antibiotic ciprofloxacin.[39] It was a four-week follow-up study, after which they reported a significantly lower rate of SBP in patients treated with systemic antibiotic prophylaxis ($n = 17$), while SBP rates in patients with no prophylactic treatment ($n = 108$) and in patients taking rifaximin ($n = 27$) were comparable. They hypothesized that the higher rate of SBP episodes under rifaximin in comparison with ciprofloxacin might be attributed to rifaximin resistance, or to the fact direct bacterial translocation from the intestine might not be the only route of infection in SBP patients. Bacteremia related to poor oral hygiene, for example, might represent another possible source of SBP which could be prevented only by the use of a systemic antibiotic. However, this study is limited by its short duration, small number of patients, and neglecting to mention the possible long-term systemic side effects of ciprofloxacin, which is known to be more readily absorbed via oral route (80–100% bioavailable), in comparison with the limited 30–40% bioavailability of our tested antimicrobial, norfloxacin.[40]

On the other hand, few studies have investigated rifaximin versus placebo for SBP prophylaxis in cirrhotics. A cohort study by Hanouneh et al. found a transplant-free survival benefit with the use of rifaximin in cirrhotic patients with ascites and no prior history of SBP than those who didn't receive antibiotic prophylaxis.[41] Another prospective case-control study by Danulescu et al. suggested that rifaximin can significantly decrease the polymorphonuclear leukocytic count in ascitic fluid of cirrhotic patients with refractory ascites compared to placebo, with a net improvement of the general condition.[42]

Vlachogiannakos et al. also showed that patients who received rifaximin had a significantly lower risk of developing variceal bleeding, hepatic encephalopathy (HE), SBP and hepatorenal syndrome than matched control subjects who did not receive antibiotic prophylaxis, in addition to significantly higher five-year cumulative probability of survival.[43] In comparison, our results demonstrated that patients on rifaximin developed fewer episodes of HE than patients on norfloxacin (4.7% and 9.3%, respectively). Additionally, rifaximin was found to reduce the number of new compared to past episodes of HE by 11.6% versus 4.7% for norfloxacin. The difference, however, was not statistically significant in both occasions. Patient's survival was also found equal in both the norfloxacin and rifaximin groups, with comparable death rates.

Interestingly, patient succeeded to adhere to therapy slightly better with norfloxacin than rifaximin, and for a significantly longer time. Most patients reported a difficulty to adhere to the three times per day-regimen of rifaximin, while the rest (in both groups) reported that the problem was financial. The monthly cost for norfloxacin regimen was estimated at about 38.50 LE, while that of rifaximin was about 306.00 LE, which – of course – points out a great difference in financial burden between the two drugs (almost eightfold monthly cost for rifaximin regimen). One of the weaknesses of our study was – may be – allowing the patients to buy the medications themselves, which might have reduced their compliance. On the other hand, it gave us a better hint about the extent of their "real" ability to comply with such an expensive drug regimen intended for long-term use, and whether or not they would be able to afford it later on.

The most important limitation of our study is that it was not a randomized, placebo controlled trial, but rather a prospective longitudinal observational study with a relatively limited sample size. In this type of study, a selection and observer bias cannot be ruled out completely. However, given the high mortality of SBP, ethical concerns must be raised against a randomized controlled trial withholding any form of antimicrobial prophylaxis to the placebo group in spite of being candidates for prophylaxis according to guidelines.

In conclusion, rifaximin has proved itself to be – at least – as good as norfloxacin, and seems to be an appropriate antibiotic alternative for long-term primary and secondary prophylaxis of SBP in cirrhotic patients with ascites with outcomes comparable to norfloxacin. Financial burden on the patient, however, remains an issue. Larger randomized controlled trials are needed to confirm our results, and it should take into consideration possible modifications of rifaximin dose regimen to improve patient's compliance to therapy. Also, follow-up should continue for a longer period of time to capture any unidentified long-term adverse effects of the drug, and because it is up till now uncertain whether prophylaxis in patients with prior SBP should be continued without interruption until liver transplantation or death, or whether treatment could be discontinued in patients showing an improvement of liver disease.

Conflict of interest

The authors declare that there are no conflicts of interest.

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