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ORIGINAL ARTICLE

Rifaximin Decreases the Incidence and Severity of Acute Kidney Injury and Hepatorenal Syndrome in Cirrhosis

Tien Dong[1] · Andrew Aronsohn[2] · K. Gautham Reddy[2] · Helen S. Te[2]

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Abstract
Background While the effects of rifaximin have been shown to be protective against acute kidney injury (AKI) and hepatorenal syndrome (HRS) in alcohol-induced cirrhosis, its long-term effects on the renal function of other cirrhotic patients are unknown.
Aim To examine the long-term effects of rifaximin on the renal function of patients with cirrhosis from various etiologies.
Methods In a retrospective study, we examined cirrhotic patients at the University of Chicago Liver Clinic from January 1, 2011, to December 31, 2014. The study enrolled patients on rifaximin for ≥90 days, who were then matched by age, gender, and MELD score to a control group. Patients with malignancy and renal replacement therapy (RRT) at baseline were excluded. Data were censored at the last follow-up, termination of rifaximin therapy, initiation of RRT, death, or liver transplant.
Results Eighty-eight rifaximin cases were identified and matched to 88 control cases. Baseline characteristics were similar, with the exceptions of more prevalent long-term midodrine use (≥90 days) (17.0 vs 4.5 %, $p = 0.01$) and baseline ascites (37.5 vs 23.8 %, $p = 0.05$) in the rifaximin group. There was no difference in the frequency of infections, deaths, liver transplants, or hospitalizations. After controlling for cofounders, the incidence rate ratio of AKI (IRR 0.71, $p = 0.02$) and HRS (IRR 0.21, $p = 0.02$), as well as the risk of requiring RRT (OR 0.23, $p = 0.01$), was lower in the rifaximin group.
Conclusions Long-term use of rifaximin is associated with a decrease incidence of AKI and HRS and a decrease risk of requiring RRT in a general population of cirrhotic patients.

Keywords Cirrhosis · Portal hypertension · Liver · Microbiome

Abbreviations

AKI	Acute kidney injury
HRS	Hepatorenal syndrome
IRR	Incidence rate ratio
IQR	Interquartile range
IL-6	Interleukin-6
ICD-9	International Classification of Diseases, Ninth
CM	Revision, Clinical Modification
LOS	Length of stay
OR	Odds ratio
RRT	Renal replacement therapy
SCr	Serum Cr
SD	Standard deviation
SBP	Spontaneous bacterial peritonitis
TNF-α	Tumor necrosis factor-α
95 % CI	95 % confidence interval

Background

The intestinal bacterial flora plays an important and complex role in patients with cirrhosis. It has been implicated in the pathogenesis of spontaneous bacterial peritonitis, hepatic encephalopathy, and even in the development of increased portal pressure [1]. In the setting of cirrhosis,

✉ Tien Dong
tsdong@mednet.ucla.edu

[1] Department of Medicine, UCLA Hospitals, 10945 Le Conte Ave, PVUB 2114 MC694907, Los Angeles, CA 90095, USA

[2] Department of Medicine, Center for Liver Diseases, University of Chicago Medicine, Chicago, IL, USA

patients are prone to intestinal bacterial overgrowth, increased intestinal permeability, and increased bacterial translocation and endotoxemia [2, 3]. Patients with cirrhosis and evidence of bacterial translocation and endotoxemia show hemodynamic abnormalities such as lower systemic vascular resistance, higher cardiac output, and lower mean arterial pressure [4]. Studies have shown that the increase in endotoxin that is seen in the systemic and portal circulation of cirrhotic patients may be correlated with disease severity [4]. Therefore, the use of antibiotics and its effects on the intestinal flora may be important in many complications related to cirrhosis.

Rifaximin is a minimally absorbed oral antibiotic that is concentrated in the gastrointestinal tract. It has broad-spectrum in vitro activity against gram-positive and gram-negative aerobic and anaerobic enteric bacteria and has a low risk of inducing bacterial resistance [5]. It is an effective agent in the treatment and prophylaxis of hepatic encephalopathy (HE) [6], which has been the focus of the majority of its research. However, in small studies on alcohol-related cirrhotic patients, rifaximin has also been shown to affect the hepatic venous system and reduce the frequency of acute kidney injury (AKI) and hepatorenal syndrome (HRS) [7, 8]. Whether this effect can be generalized to other cirrhotic patients is not known. Therefore, we investigated the effect of long-term rifaximin use on the renal function of patients with other causes of cirrhosis.

Patient Selection and Methods

This study examined patients seen at the University of Chicago Liver Clinic from January 1, 2011, to December 31, 2014, with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) diagnosis code of cirrhosis (571.2, 571.5, 571.6, 572.2, 572.3, 572.4, 572.8). Patients with a diagnosis of biliary or hepatic malignancy (ICD 9 CM codes: 155.0, 155.1, 155.2, 156.0, 156.1, 156.2, 156.8, 156.9) at baseline were excluded to remove any confounding effect of malignancy on death or liver transplantation. Patients with renal replacement therapy (RRT) at baseline were also excluded. Chart review was performed on each patient identified to confirm the diagnoses of cirrhosis. Long-term rifaximin therapy was defined as continual use of 550 mg of rifaximin twice a day for $\geq$90 days as determined by each patient's medication list during the study period. Eighty-eight cirrhotic patients who were on long-term rifaximin therapy were identified. Patients who were never on rifaximin at any time during the study period but otherwise met the above criteria became the cohort of control patients. The 88 rifaximin patients were then randomly matched via a random number generator by age ($\pm$5 years), gender, and baseline MELD score to the cohort of control patients. Demographic data, laboratory data, concurrent midodrine use, incidence of AKI, incidence of HRS type 1, incidence of RRT, frequency of hospitalizations, frequency of infections, and patient outcomes (alive, dead, or transplanted) were collected. Because we were unable to extrapolate the incidence of HRS type 2 due to inconsistent outpatient documentation, the incidence of HRS type 2 was excluded. Concomitant long-term midodrine use was defined as continual use of any dosage for $\geq$90 days within the same follow-up period. AKI was defined as an increase in serum creatinine (SCr) by >0.3 mg/dl within 48 h or an increase in SCr >1.5-fold above baseline (International Society of Nephrology criteria) [9]. HRS type 1 was defined as at least a twofold increase in SCr to a level greater than 2.5 mg/dl during a period of <2 weeks refractory to fluid administration consistent with current guidelines [10]. HRS type 1 episodes were confirmed with chart review of inpatient hepatology consult documentation. The presence or absence of ascites was determined by clinical documentation of physical examination findings in hepatology outpatient or inpatient notes. Time zero in the exposed group was the date that rifaximin was first initiated, while time zero in the control group was the first encounter within the study period. Data were censored at the last follow-up, termination of rifaximin therapy, initiation of RRT, death, or liver transplant. The above protocol was approved by the University of Chicago institutional review board.

Data Analysis

Demographic data are expressed as either categorical means (standard deviation, SD) or medians (interquartile range, IQR) as appropriate. Means were compared using the Student's paired t-test, and medians were compared using the Wilcoxon matched pair test. Differences in categorical data are expressed as odds ratio (OR) with 95 % confidence interval (95 % CI). Frequency is expressed as incidence rate ratio (IRR) and was calculated using a Poisson regression model. Cumulative risk is expressed using the Nelson–Aalen cumulative hazard function and Cox competing risk regression model. All statistical analysis was performed using Stata 14 for Windows (StataCorp, Texas, USA). A p value <0.05 was considered statistically significant.

Results

Eighty-eight patients on chronic rifaximin therapy were identified and matched to 88 control cases. Age, gender, race, duration of follow-up, baseline MELD score, kidney

function (SCr and GFR), serum sodium, and etiology of cirrhosis were not significantly different between the two groups. At baseline, more patients in the rifaximin group had ascites and were on long-term midodrine than the control group (37.5 vs 23.8 %, $p = 0.05$ and 17 vs 4.5 %, $p = 0.01$, respectively) (Table 1).

When analyzing the effect of rifaximin on the renal function of cirrhotic patients, there were several significant differences between the two groups. Forty patients in the control group had a total of 86 AKI episodes during the follow-up period, while 37 patients in the rifaximin group had a total of 76 AKI episodes. Fourteen patients in the control group had a total of 15 HRS episodes, while 4 patients in the rifaximin group had a total of 4 HRS episodes. The incidence rate ratio of AKI (IRR 0.71 [95 % CI 0.54–0.94]) and HRS (IRR 0.21 [95 % CI 0.06–0.70]), when controlled for long-term midodrine use and ascites, was statistically lower in the rifaximin group than the control group (Table 2). If patients developed AKI, they were less likely to have HRS as a cause if they were in the rifaximin group as compared to the control group (OR 0.23 [95 % CI 0.07–0.84]). In addition, 5 patients in the rifaximin group required RRT at the end of follow-up compared to 14 patients in the control group (OR 0.23 [95 % CI 0.07–0.74]) (Table 3). The cumulative risk of RRT is represented in Fig. 1 using the Nelson–Aalen cumulative hazard function (Cox test p value = 0.04). The absolute risk of requiring RRT at the end of follow-up in the rifaximin groups is 5.7 versus 15.9 % in the control group. The number needed to treat to prevent one episode of RRT is 10.

At the end of follow-up, 10 patients in the rifaximin group and 9 patients in the control group died, while 13 patients in the rifaximin group and 8 patients in the control group received liver transplants. When analyzing for patient outcome, there was no significant difference in the frequency of deaths (OR 0.99 [95 % CI 0.43–2.92]) or liver transplants (OR 1.47 [95 % CI 0.68–4.41]) between the two groups.

There was no difference in the incidence rate of hospitalization, hepatic encephalopathy, or variceal bleeds (Table 2). Seven patients in the rifaximin group developed spontaneous bacterial peritonitis (SBP) compared to only 1 patient in the control group. However, this difference was

Table 1 Baseline characteristics of the study population

	Control group	Rifaximin group	p value
No. of cases	88	88	
Median age in years (IQR)	57.5 (12)	59.5 (12.5)	0.36
Male sex (%)	41 (46.6 %)	46 (52.3 %)	0.41
Race	White (44.3 %)	White (65.9 %)	0.08
	African American (44.3 %)	African American (29.5 %)	
Median duration of follow-up in days (IQR)	364 (523)	309 (410)	0.43
Median MELD score at baseline (IQR)	14 (7)	14.5 (6.7)	0.46
No. of patients transplanted at end of follow-up	8 (9.1 %)	13 (14.7 %)	0.45
No. of patients on long-term midodrine	4 (4.5 %)	15 (17.0 %)	**0.01**
Median MELD score at follow-up (IQR)	13 (10)	15 (10)	0.12
Median baseline serum creatinine in mg/dl (IQR)	1.0 (0.5)	0.95 (0.4)	0.23
Median baseline GFR in ml/min (IQR)	68 (44)	73 (47)	0.18
Median baseline sodium in mEq/L (IQR)	138 (3)	137 (2)	0.60
Baseline ascites	23.8 %	37.5 %	**0.05**
Etiology of cirrhosis	Alcoholic (21.6 %)	Alcoholic (22.7 %)	0.38
	HCV (36.4 %)	HCV (27.3 %)	
	Alcoholic + HCV (12.5 %)	Alcoholic + HCV (10.2 %)	
	NASH (5.7 %)	NASH (12.5 %)	
	AIH (3.4 %)	AIH (4.5 %)	
	Cryptogenic (3.4 %)	Cryptogenic (10.2 %)	
	PBC (3.4 %)	PBC (2.3 %)	
	PSC (2.3 %)	PSC (0 %)	
	Other (11.4 %)	Other (10.1 %)	

Bold values are statistically significant ($p < 0.05$)

HCV hepatitis C, *NASH* nonalcoholic steatohepatitis, *AIH* autoimmune hepatitis, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis

Table 2 Effect of rifaximin on incidence rate of multiple variables

	Rifaximin group Incidence rate Per 1000 days	Control group Incidence rate Per 1000 days	Rifaximin group as compared to control (incidence rate ratio)	95 % CI of IRR	*p* value
Acute kidney injury	1.46	3.71	0.71	0.54–0.94	**0.02**
Hepatorenal syndrome	0.076	0.65	0.21	0.06–0.70	**0.01**
Hospitalization	6.35	5.78	1.14	0.97–1.34	0.12
Hepatic encephalopathy	0.86	0.78	1.14	0.94–1.37	0.21
Paracentesis	1.21	0.87	1.45	0.78–2.71	0.25
Variceal bleeds	0.09	0.19	0.49	0.11–2.19	0.35
Spontaneous bacterial peritonitis	0.14	0.039	3.67	0.32–42.02	0.30
Clostridium difficile	0.13	0.19	0.67	0.19–2.24	0.52
Bacteremia	0.40	0.39	1.01	0.43–2.39	0.98
pulmonary infections	0.18	0.49	0.36	0.10–1.34	0.13

Controlling for long-term midodrine use and ascites

Bold values are statistically significant ($p < 0.05$)

Table 3 Effects of rifaximin on renal reperfusion therapy and hepatorenal syndrome

Odds ratio	Rifaximin group as compared to control	95 % CI	*p* value
Renal reperfusion therapy	0.23	0.07–0.74	**0.01**
Having HRS at least once	0.15	0.04–0.59	**0.01**

Controlling for long-term midodrine use and ascites

Bold values are statistically significant ($p < 0.05$)

HRS hepatorenal syndrome

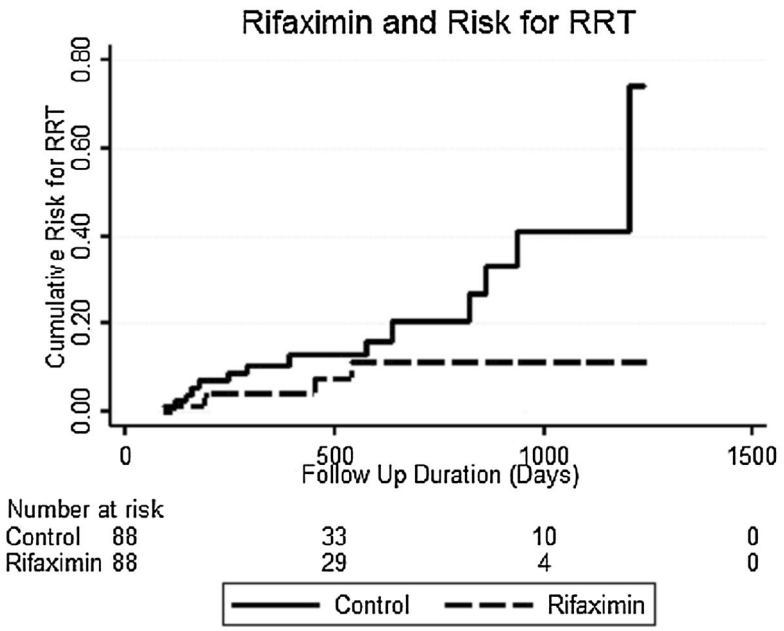

Fig. 1 Cumulative risk for renal reperfusion therapy

Cox competing risk regression p-value = 0.04 (competing variables: death, liver transplant)

not significant when baseline presence of ascites and long-term midodrine use were controlled for. There were no differences in other infections (i.e., clostridium difficile, pulmonary infections, or bacteremia) between the two groups (Table 2).

Discussion

Bacterial infections in cirrhotic patients are common. These patients are predisposed to bacterial overgrowth, intestinal dysmotility, and increased bacterial translocation

[11]. The passage of viable and nonviable microbes and their products has been associated with disease severity in cirrhosis [4, 12].

Selective intestinal decontamination with norfloxacin in 14 patients with alcoholic cirrhosis improved vascular tone by partially reversing the chronic portal and systemic vasodilation seen in alcoholic cirrhotics [13]. Similarly, Fernández et al. [14] demonstrated that norfloxacin decreased the incidence of SBP and delayed the onset of HRS in 35 patients with advanced cirrhosis. Chronic rifaximin use was also shown to decrease the risk of variceal bleeding, hepatic encephalopathy, SBP, and HRS in 23 patients with alcoholic cirrhosis [8].

In this study, we compared the clinical outcomes of cirrhotic patients from various etiologies who were on chronic rifaximin therapy to those of matched control patients. Despite having more ascites and therefore more risk of renal dysfunction at baseline, patients on long-term rifaximin had fewer episodes of renal dysfunction than control patients. In addition to a lower incidence of renal injury in cirrhotic patients, our study also showed that the severity of renal injury was less in the rifaximin group as represented by a decreased risk of RRT. In previous literature, requiring RRT for AKI or HRS has been proven to be a significant predictor of mortality [15–18]. While RRT is certainly a significant morbidity, our study did not show any differences in the rate of death or liver transplantation. We speculate that the effect of rifaximin on patient outcome may have been less evident due to the shorter duration of follow-up and smaller sample size as compared to prior literature evaluating renal injury and mortality [15, 16].

The mechanism by which rifaximin affects renal perfusion in cirrhotic patients is still speculative. Cirrhotic patients with bacterial translocation and endotoxemia manifest hemodynamic derangements with lower systemic vascular resistance, higher cardiac output, and lower mean arterial pressure. In cirrhosis, bacterial overgrowth and translocation have been shown to be associated with increased levels of endotoxins and cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [19]. High concentrations of IL-6 and TNF-α have been shown to be associated with lower systemic vascular resistance and higher cardiac output [19]. In cirrhotic patients with SBP, higher levels of these cytokines have been associated with an increased risk of developing renal injury and in-hospital mortality [20]. Selective intestinal decontamination in animal models and in patients has been shown to decrease circulating levels of TNF-α and improve circulatory hemodynamics [13, 21]. In a small prospective study of alcoholic cirrhotic patients, rifaximin administration for 4 weeks showed a decrease in circulating IL-6, TNF-α, endotoxemia and an increase in systemic vascular resistance and glomerular filtration rate [7]. Moreover, endotoxins may increase portal pressure by increasing portal vascular resistance, which may be promoted through the cytokine-stimulated intrahepatic release of endothelin and cyclooxygenase products [22–24]. Therefore, these studies suggest that selective bacterial decontamination and its benefits to liver hemodynamics are in part related to a decrease or alteration of endotoxins and/or cytokines in cirrhotic patients.

The limitations of this study are its relatively small sample size and retrospective nature; hence, it is a study that can only show associations and not causal relationships. The lack of benefit of rifaximin in preventing hepatic encephalopathy in this study may have been due to the fact that patients who are on long-term rifaximin who were enrolled in this study already had hepatic encephalopathy as the indication for the medication, and therefore, are more prone to recurrent exacerbations of this symptom than the control group.

In conclusion, our results provide novel data that suggest a potential beneficial role of rifaximin in patients with various etiologies of cirrhosis in preventing the occurrence of AKI, HRS, and need for RRT. These findings should be further investigated in a large prospective, double-blinded randomized placebo-controlled clinical trial.

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Compliance with ethical standards

Conflict of interest None.

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