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ORIGINAL ARTICLE

Effect of rifaximin on infections, acute-on-chronic liver failure and mortality in alcoholic hepatitis: A pilot study (RIFA-AH)

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Abbreviations: ACLF, acute-on-chronic liver failure; AH, alcoholic hepatitis; AKI, acute kidney injury; ALD, alcohol-related liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRBSI, catheter-related bloodstream infection; EH, hepatic encephalopathy; GIB, gastrointestinal bleeding; HBV, hepatitis B virus; HCV, hepatitis C virus; INTEAM, Integrated Approaches for Identifying Molecular Targets in Alcoholic Hepatitis; MELD, model for end-stage liver disease; PAMPs, pathogen-associated molecular patterns; SAEs, serious adverse events; SB, spontaneous bacteraemia; SBP, spontaneous bacterial peritonitis; SID, selective intestinal decontamination; SIRS, systemic inflammatory response; UTI, urinary tract infection.

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Abstract

Background & Aims: Alcoholic hepatitis (AH) is associated with a high incidence of infection and mortality. Rifaximin reduces bacterial overgrowth and translocation. We aimed to study whether the administration of rifaximin as an adjuvant treatment to corticosteroids decreases the number of bacterial infections at 90 days in patients with severe AH compared to a control cohort.

Methods: This was a multicentre, open, comparative pilot study of the addition of rifaximin (1200 mg/day/90 days) to the standard treatment for severe AH. The results were compared with a carefully matched historical cohort of patients treated with standard therapy and matching by age and model of end-stage liver disease (MELD). We evaluated bacterial infections, liver-related complications, mortality and liver function tests after 90 days.

Results: Twenty-one and 42 patients were included in the rifaximin and control groups respectively. No significant baseline differences were found between groups. The mean number of infections per patient was 0.29 and 0.62 in the rifaximin and control groups, respectively ($p = .049$), with a lower incidence of acute-on-chronic liver failure (ACLF) linked to infections within the treatment group. Liver-related complications were lower within the rifaximin group (0.43 vs. 1.26 complications/patient respectively) ($p = .01$). Mortality was lower in the treated versus the control groups (14.2% vs. 30.9, $p = .15$) without significant differences. No serious adverse events were associated with rifaximin treatment.

Conclusions: Rifaximin is safe in severe AH with a significant reduction in clinical complications. A lower number of infections and a trend towards a lower ACLF and mortality favours its use in these patients.

KEYWORDS
acute-on-chronic liver failure, alcohol-related liver disease, bacterial infection, cirrhosis, rifaximin, severe alcoholic hepatitis

1 | INTRODUCTION

Alcoholic hepatitis (AH) is characterized by an abrupt increase in serum bilirubin levels, jaundice and liver-related decompensations.[1] Furthermore, it is the most severe form of alcohol-related liver disease (ALD), with mortality rates reaching 30% at 3 months.[2] Infection is one of the most frequent complications among patients with AH. According to a recent meta-analysis, the incidence of infection at 28 days was 20%, regardless of whether the patients received corticosteroid treatment.[3] AH patients who presented with infections and/or systemic inflammatory response (SIRS) at baseline were more likely to present with multiorgan failure, and their 28-day mortality rate increased up to 40%.[4] This detrimental inflammatory response is the result of a complex interaction between inflammatory microbial and non-microbial inducers. Microbial inducers of inflammation include pathogen-associated molecular factors (PAMPs) and virulence factors,[5] which are part of exogenous inflammatory components and are the most well-known and well-studied factors. In AH, excessive alcohol consumption induces gut dysbiosis and increases the permeability of the intestinal barrier, resulting in different PAMPs and inducing bacterial translocation.[6] Endogenous inducers of inflammation are produced as a result of tissue injury

Lay Summary

Rifaximin, a non-absorbable antibiotic, may be useful in patients with severe alcoholic hepatitis, reducing the number of infections and complications. This study is relevant because there are currently few treatment options for severe alcoholic hepatitis.

or damage and play a major role during AH episodes. Furthermore, there is a non-microbial component of inflammation linked to the adaptive response of the tissue to stress or malfunction.[7] All these components are key to the development of SIRS and infections.

Selective intestinal decontamination (SID) has proven useful in reducing the incidence of infections in patients with cirrhosis when used either for primary or secondary prophylaxis.[8–10] Rifaximin is a non-absorbable antibiotic that has been broadly used in cirrhotic patients and has emerged as an alternative to standard therapy with quinolones, avoiding the adverse effects of conventional therapy and the development of bacterial resistance to quinolones.[11,12]

The main aim of the current study was to explore the safety and overall effects of rifaximin as an add-on therapy to conventional treatment in reducing the incidence of infection in patients with severe AH as compared with a historical control cohort.

2 | PATIENTS AND METHODS

2.1 | General characteristics

The study was designed as a pilot study. We choose the case–control design over a randomized clinical trial since there was no evidence to support the efficacy and safety of rifaximin treatment in alcoholic hepatitis before the recruitment period started.

This is a multicentre, pilot, study and an open-label evaluation of rifaximin effects as an add-on therapy to conventional treatment in reducing the incidence of infection in patients with severe AH compared with a matched control cohort. Severity was defined by a model for end-stage liver disease (MELD) score of ≥21 or a Maddrey discriminant function ≥32. The study included 21 consecutive patients recruited from June 2013 to June 2015 who were admitted to four tertiary academic medical centres in Barcelona (Figure 1).

An additional prospective cohort of patients with severe AH who received the current standard treatment, including corticosteroids, was recruited between May 2014 and April 2019. These patients belonged to the INTEAM consortium (Integrated Approaches for Identifying Molecular Targets in Alcoholic Hepatitis). From this cohort, we selected 42 patients who fulfilled the same inclusion and exclusion criteria of the study cohort, including a liver biopsy consistent with AH, who did not receive rifaximin or prophylactic antibiotics and were matched by age and MELD to the study cohort. A total of 268 patients were recruited for the INTEAM consortium observation at the time of selection. A total of 94 patients with severe alcoholic hepatitis, with no history of antibiotics for prophylaxis or treatment, were assessed for eligibility. Of these patients, only 49 had a definite diagnosis of AH as assessed by liver biopsy. Patients were then matched by MELD allowing a maximum deviance of 2.5 points and ± 3 years of age for each study patient. Forty-two patients fulfilled all requirements and were included allowing a 2:1 matching. No differences in any analytical parameters or risk scores were observed between both groups (Table 1).

The Institutional Review Board at the study sites and 'Agencia Española de Medicamento' approved the study. Written informed consent was obtained from all participants before enrolment. The study was conducted in accordance with the Declaration of Helsinki and the current laws and regulations ('Real Decreto' 223/2004). Both studies were registered on the ClinicalTrials.gov website (NCT02116556 and NCT02075918).

2.2 | Patient selection and the study protocol

Subjects from the study group were eligible for inclusion if they met the following criteria: age between 18 and 70 years, a history of active alcohol intake (>60 g OH/day for men and >40 g OH/day for women) during the previous 3 months to admission, level of aspartate aminotransferase (AST) > alanine aminotransferase (ALT), bilirubin level ≥ 3 mg/dl and a Maddrey discriminant function ≥32 or MELD ≥21. Subjects were excluded from enrolment if they met one of the following criteria: hypersensitivity or allergic reaction to the drug components, terminal illness (defined as any concomitant disease with a vital prognosis shorter than 3 months), autoimmune hepatitis, concomitant hepatitis B virus (HBV), hepatitis C virus (HCV) or infection by human immunodeficiency virus, chronic jaundice (more than 3 months), presence of total vein thrombosis, previous use of rifaximin (during the last 2 months), hepatocellular carcinoma beyond the Milan criteria and concomitant treatment with pentoxifylline. In premenopausal women, a negative pregnancy test result was required, and breastfeeding was ruled out. The diagnosis of AH was made based on clinical, analytical and radiological data,[13] and a biopsy-proven diagnosis was required during the first 7 days after study inclusion. If the histology was incompatible with AH, the subject was withdrawn. Another withdrawal criterion was the diagnosis of bile duct obstruction revealed by ultrasound. Notably, all patients with baseline active bacterial infections or using systemic or prophylactic antibiotics were excluded. The inclusion and exclusion criteria for the control group were the same as those for the study group (Figure 1). The study protocol patients received rifaximin 1200 mg/day (400 mg/8 h) for 90 days as an add-on to conventional therapy (support nutrition, preventive therapy for withdrawal syndrome and corticosteroids if they did not exhibit any contraindications at the time of admission). The follow-up visits were scheduled at 7 days, on discharge, and at 30, 60 and 90 days.

At all time points, the following data were collected: clinical history (demographic data, previous disease and previous episodes of acute decompensation), physical examination, laboratory measurements, presence of bacterial infections and any liver-related complications at admission and during follow-up visits, including presence or worsening of ascites, gastrointestinal bleeding (GIB) and acute-on-chronic liver failure (ACLF). Hepatic encephalopathy (HE) and acute kidney injury (AKI) were included under ACLF or assessed as unique decompensations when they did not reach the ACLF definition.[14] Finally, Maddrey, MELD, Child–Pugh and ABIC prognostic scores were used to evaluate disease severity, and the Lille score was used to evaluate the response to standard therapy.

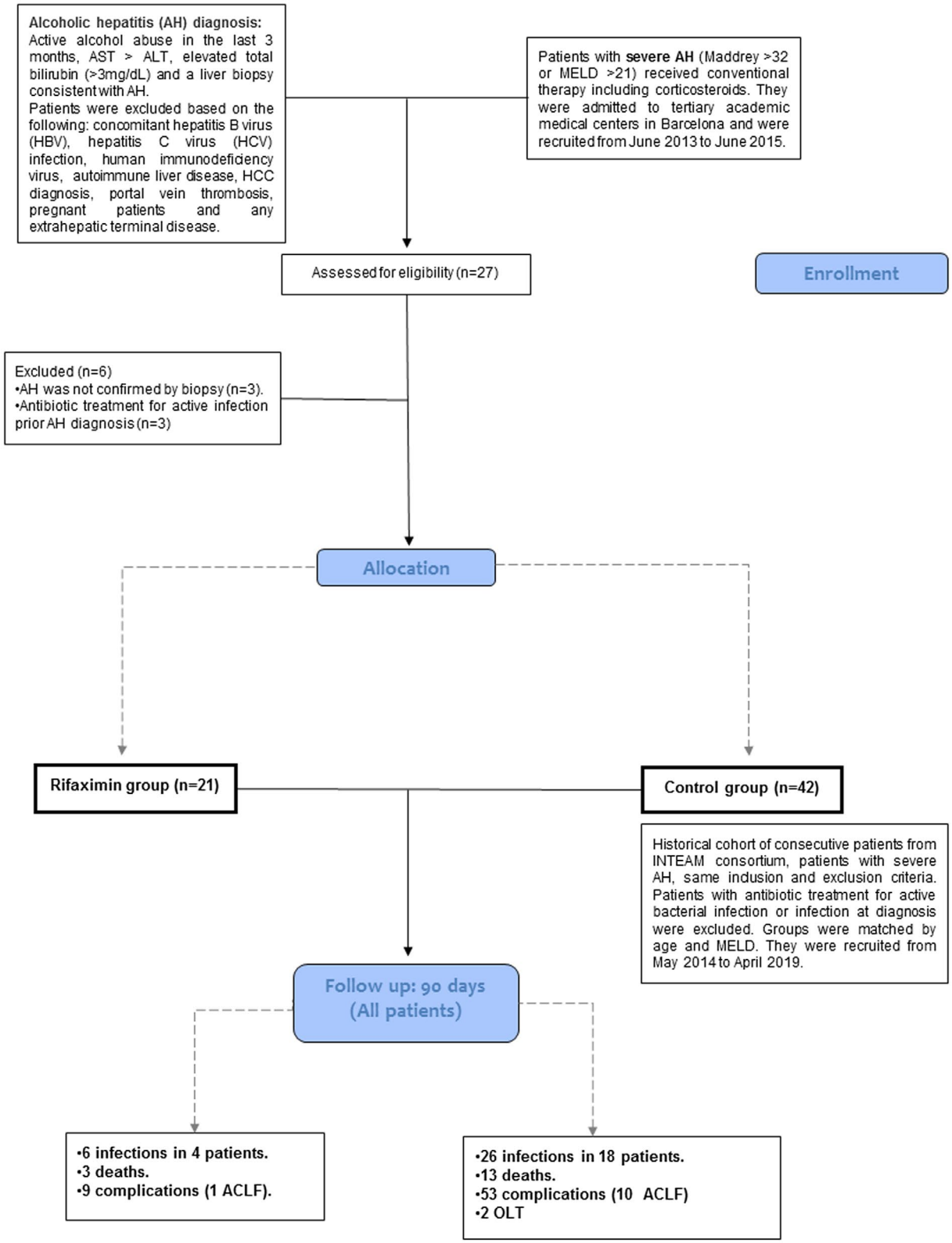

FIGURE 1 Flowchart for the inclusion and exclusion of subjects and their allocation to the rifaximin and control groups. ACLF, acute-on-chronic liver failure; OLT, orthotopic liver transplantation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; INTEAM consortium (Integrated Approaches for Identifying Molecular Targets in Alcoholic Hepatitis); MELD, model for end-stage liver disease

TABLE 1 Baseline characteristics by the group

	Rifaximin group ($n = 21$)	Control group ($n = 42$)	p
Sex (male), n(%)	16 (76.2%)	28 (66.7%)	.43
Age, median (IQR) P25–P75	55 (46.5–60.0)	53.5 (43–62)	.99
Maddrey score, median (IQR) P25–P75	49 (38–62)	49 (41.0–64.7)	.92
MELD score, median (IQR) P25–P75	22 (19–24)	23 (20.7–25.0)	.24
ABIC score, median (IQR) P25–P75	8 (7.4–8.7)	8.6 (7.3–9.1)	.09
Child–Pugh score, median (IQR) P25–P75	9 (9–11)	9 (8–10)	.78
Haemoglobin (g/dl), median (IQR) P25–P75	10.7 (9.6–13)	11.1 (9.7–12.5)	.65
Leucocytes (10e9/L), median (IQR) P25–P75	8.1 (5.5–10.3)	10.2 (7–11.8)	.32
Platelets (10e9/L), median (IQR) P25–P75	109 (76–129)	114 (94–161)	.78
INR, median (IQR) P25–P75	1.69 (1.48–1.98)	1.69 (1.50–1.98)	.92
Creatinine (mg/dl), median (IQR) P25–P75	0.68 (0.59–0.84)	0.78 (0.6–1.0)	.92
Bilirubin (mg/dl), median (IQR) P25–P75	10.22 (8.48–22.5)	15.1 (9.4–22.1)	.32
Albumin (g/dl), median (IQR) P25–P75	2.6 (2.3–3.0)	2.9 (2.4–3.1)	.13

Abbreviations: IQR, interquartile range, P25–P75, percentile 25–75.

Proven infection was defined in the following cases: spontaneous bacteraemia (SB) with positive cultures in the absence of another septic focus, catheter-related bloodstream infection (CRBSI) with positive culture, spontaneous bacterial peritonitis (SBP) with a polymorphonuclear count in ascitic fluid >250/mm^3 regardless of the result of ascitic fluid culture, urinary tract infection (UTI), signs/symptoms of infections, >20 leucocytes per field or positive urine culture, respiratory infection or pneumonia as defined by clinical criteria or compatible chest radiography, cellulitis or other infections based on clinical criteria.

2.3 | Objectives of the study

The primary aim was to investigate whether the administration of rifaximin as an adjuvant treatment to corticosteroids decreases the number of bacterial infections from baseline to 90 days in patients with severe AH compared to a control cohort. The secondary objective was to investigate whether the add-on of rifaximin to the standard therapy could result in the following: (a) decrease in the incidence of liver-related complications (non-infectious complications), (b) decrease in the 28- and 90-day mortality, c) improvement of bilirubin levels and MELD scores at 7, 30, 60 and 90 days and d) improvement of the response to corticosteroids assessed by the Lille score.

2.4 | Sample size and statistical analyses

We hypothesized that the add-on of rifaximin would decrease the proportion of infections at 90 days by 50% based on the expected incidence of infections observed in previous studies with cirrhotic patients.[15,16] The final sample size ($n = 66$) was calculated according to the potential loss of 15% of the patients. After 2 years of recruitment, we included 27 patients (40% of the expected recruitment). Recalculation of the total sample size according to the observed losses (9% of the included patients) resulted in 62 patients.

Descriptive statistics were used to summarize the data. Quantitative variables were described as mean and standard deviation for normally distributed variables or median and interquartile range if normality criteria were not met. Percentages were calculated using categorical data. Qualitative variables are described as frequencies and percentages. For categorical variables, between-group differences were calculated using the chi-square test or Fisher's exact test when necessary. For quantitative variables, between-group differences were analysed using student's t-test or the Mann–Whitney U test, as appropriate. Infection-free survival and survival times were compared using the Kaplan–Meier estimator and log-rank test. All statistical analyses were performed using the IBM SPSS Statistics version 22 software package.

3 | RESULTS

3.1 | Characteristics of patients

Twenty-seven patients were assessed for eligibility, and six of them were excluded for different reasons, mainly owing to the presence of infection at admission and the lack of histological confirmation (Figure 1). Finally, 21 patients were included in the study and matched by age and MELD to the study cohort. Patients in the two groups showed similar baseline characteristics; the proportion of males in the treatment cohort was slightly higher than the control cohort (76.2% vs. 66.7%, $p = .43$). At admission, 2 out of 21 (9.5%) patients in the rifaximin group and 4 of 42 (9.5%) in the control group presented hepatic encephalopathy. Patients in the control cohort exhibited higher bilirubin and creatinine levels without clinical or statistically significant differences (Table 1).

3.2 | Clinical outcomes

3.2.1 | Effects of treatment on infections

Six infections were reported in the rifaximin group and 26 in the control group. Therefore, the mean number of infections per patient was 0.29 in the rifaximin group, while it was 0.62 in the control group ($p = .049$). The number of *de novo* infections was lower in the rifaximin group than in the control group. In the rifaximin group, 4 out of 21 patients (19%) developed at least one infection

throughout the 90-day follow-up period, whereas in the control group, up to 18 out of 42 developed an infection (42.9%) ($p = .061$).

Six infections were reported in four patients within the rifaximin cohort. The infections included two SBPs, one CRBSI, one urinary tract infection, one pneumonia and one case of cellulitis. Regarding severity, in the rifaximin group, only one infection (16.6%) progressed to sepsis (CRBSI caused by *Candida albicans*) and caused worsening of ACLF grade (from grade II to III). All cases were successfully treated, and none of these patients died owing to infection. Twenty-six infections were reported in 18 patients in the control cohort. The most frequent infection type was UTI ($n = 7$), followed by spontaneous bacteraemia ($n = 6$) and five cases of SBP and pneumonia. Remarkably, 8 out of 26 infections (30%) progressed to sepsis, 2 sepsis resolved without further complications, while 6 developed ACLF (Table 2).

TABLE 2 Infections in the rifaximin and control groups

Patient number	Number of infections	Description (microorganisms)	Sepsis	ACLF	Death by infection
Rifaximin group					
1	1	pneumonia (*S. marcescens* + *K. oxytoca*)	No	No	N
11	1	cellulitis (unknown)	No	No	N
12	3	SBP[a] (*C. albicans*)	Yes	Yes	No
		UTI[b] (*C. albicans*)			
		CRBSI[c] (*K. oxytoca* + *E. faecium*)			
15	1	SBP[a] (*S. viridans*)	No	No	No
Control group					
3	1	SBP[a] (*E. faecium*)	Yes	Yes	No
5	1	pyelonephritis (*K. pneumoniae*)	No	Yes	No
9	2	pneumonia (*P. jirovecii*)	Yes	Yes	Yes
		SBP[a] (*E. faecium*)			
14	1	SB[d] (gram [−] bacillus)	No	No	No
16	2	SB[d] (*S. epidermidis* + *C. perfringens*)	Yes	Yes	Yes
		pneumonia (*C. albicans*)			
17	1	pneumonia (unknown)	Yes	Yes	Yes
19	1	colitis (*C. difficile* + vancomycin-resistant *Staphylococcus aureus*)	No	No	No
20	1	SB[d] (*E. coli*)	No	No	No
21	2	colitis (*Enterococcus* sp.)	No	Yes	No
		UTI[b] (*C. albicans*)			
26	1	prostatitis (*E. coli*)	Yes	No	No
30	2	UTI[b] (*E. coli*)	Yes	No	No
		SB[d] (*S. aureus*)			
31	1	UTI[b] (*E. cloacae*)	No	No	No
35	1	UTI[b] (*K. oxytoca* + *E. coli*)	No	No	No
37	1	SBP[a] (unknown)	No	Yes	No
38	2	pneumonia (*P. jirovecii*)	Yes	Yes	Yes
		SBP[a] (*E. faecium*)			
39	2	SB[d] (gram [−] bacillus)	No	No	No
		UTI[b] (*E. coli*)			
40	3	SB[d] (*E. faecium*)	Yes	Yes	Yes
		pneumonia (*P. jirovecii*)			
		SBP[a] (unknown)			
41	1	cellulitis (unknown)	No	No	No

[a]Spontaneous bacterial peritonitis.

[b]Urinary tract infections.

[c]Catheter-related bloodstream infections.

[d]Spontaneous bacteraemia.

In the control group cohort, seven patients developed '*de novo*' ACLF in addition to infection, and two patients showed worsening in the grade of the previous ACLF owing to infection, while in the rifaximin group, no patient developed "*de novo*" ACLF in addition to infection (0 vs. 7 $p = .047$) and only one patient presented with a worsening grade of ACLF during infection. Therefore, the total number of ACLF events related to infections was one versus nine ($p = .81$) (Table 2).

At 90 days, the mean infection-free survival time was higher in the treatment group; it was 70.6 days (71%) in the rifaximin group versus 57.1 days (50%) in the control group, but the difference was not statistically significant ($p = .12$) (Figure 2).

3.2.2 | Effects of treatment in liver-related complications

During follow-up, nine non-infectious complications were reported in five patients (23.8%) within the rifaximin group. In the control group, 53 non-infectious complications were reported in 23 patients (54.7%). The total number of complications per patient in the treatment group was 0.43, while the number of complications per patient in the control group was 1.26. ($p = .010$).

The most frequent non-infectious complication within the rifaximin group was ascites ($n = 3$), representing one-third of the complications. Only one patient in the rifaximin group developed a '*de novo*' ACLF not linked to an infectious episode, and only one patient developed mild hepatic encephalopathy. In the control group, hepatic encephalopathy was the most frequent complication ($n = 14$), representing 26.4% of the complications, followed by the development of ACLF ($n = 10$), representing 18.8%. Only one patient from the rifaximin group presented with gastrointestinal bleeding, while six patients from the control cohort presented with gastrointestinal bleeding. (Table 3). Finally, no effects on alcohol abstinence during follow-up were observed between the groups.

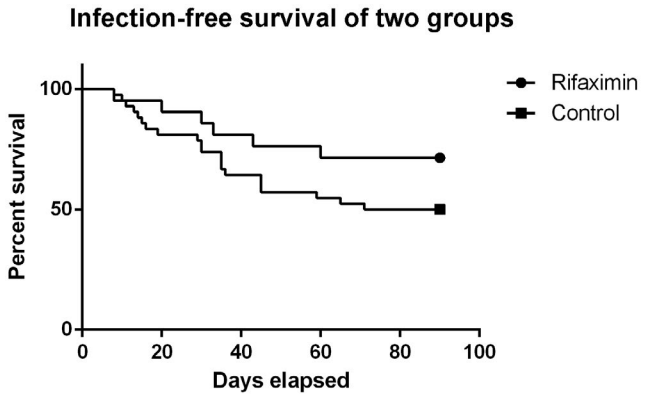

FIGURE 2 Infection-free survival in the rifaximin and control groups ($p = .12$)

3.2.3 | Impact of treatment on liver function tests

The mean bilirubin levels and MELD scores at baseline and 7, 30, 60 and 90 days were compared between groups, and statistically significant differences were only observed in bilirubin levels at day 60 between the rifaximin and control groups ($p = .023$). The changes in bilirubin levels and MELD scores during the follow-up at 7, 30, 60 and 90 days are shown in Figure 3. Finally, we assessed the corticosteroid response using the Lille score in the rifaximin group and found that 76% were responders (16/21), while in the control group, we found 61% of responders (26/42); the differences between groups were not significant.

3.3 | Mortality

Three out of 21 patients (14.2%) died during follow-up in the rifaximin group as follows: one patient died owing to a brain haematoma related to lymphoma, another patient died owing to ACLF related to severe AH and the last patient committed suicide.

In the control group, 13 out of 42 patients (30.9%) died during follow-up, as follows: 11 patients from ACLF (nine developed de novo ACLF), another patient died of massive digestive bleeding and the last one died of liver failure without ACLF criteria (Table 3). Remarkably, eight patients from the control group who died had a previous infection (in five, infection-triggered ACLF resulted in death), while no one died in the rifaximin group owing to a secondary infection. Liver-related mortality (excluding suicide) was higher in the control group (13 vs. 2) ($p = .060$).

The mean actuarial survival at 90 days was 80.7 days in the treatment group and 71.7 days in the control group, without significant differences; survival rates were 85.7% in the treatment group versus 60% in the control group ($p = .15$) (Figure 4). There were also no significant differences in mean liver transplantation-free survival.

3.4 | Adverse effects of rifaximin

A total of 25 adverse events were reported in 14 patients. Eleven were serious adverse events (SAEs). However, none of the SAEs were considered to be related to the use of rifaximin. Of the remaining 14 non-serious adverse events, only five adverse events in four patients were related to rifaximin. Four adverse events were recorded as possibly related (mild mesogastric pain, mild pruritus, moderate diarrhoea and moderate hyponatraemia), and the other was unlikely to be related to rifaximin (moderate abdominal wall haematoma). There was '*restitutio ad integrum*' in the five cases, and rifaximin was not discontinued in any case (Table 4).

TABLE 3 Non-infectious liver complications developed during follow-up and deaths in the rifaximin and control groups

Patient number	ACLF at admission	ACLF resolution	Non-infectious liver complications developed during follow-up	Number of complications	Death
Rifaximin group					
1	No		No	0	Yes
6	No		Gastrointestinal bleeding. ACLF 2 (Liver and cerebral).	3	Yes
12	ACLF 2 (Liver and coagulation)	no	Progressed to ACLF 3a for renal failure. Mild HE	2	No
13	No		Ascites	1	No
14	No		No	0	Yes
15	ACLF 1 (Liver failure)	Yes	Ascites	1	No
18	No		Ascites. Acute kidney injury	2	No
Control group					
1	ACLF 2 (Liver and renal)	No	Ascites. Mild HE	2	No (OLT)
2	No		ACLF 2 (Liver and coagulation). Gastrointestinal bleeding	3	Yes
3	No		Mild HE. ACLF 2 (Liver and kidney)	3	Yes
4	No		Gastrointestinal bleeding (massive). Acute kidney injury	2	Yes
5	ACLF 2 (Liver and coagulation)	No	Progressed to ACLF 3b for cerebral and renal failure)	2	Yes
6	No		Gastrointestinal bleeding. Mild HE. ACLF 1 (Liver failure)	3	Yes
8	ACLF 2 (Liver and renal)	Yes	No	0	Yes
9	No		Ascites. ACLF 3 (Renal, respiratory and cerebral)	4	Yes
10	No		Severe HE	1	No
16	No		ACLF 2 (Liver and respiratory)	2	Yes
17	No		ACLF 3a (Liver, respiratory and cerebral)	3	Yes
18	No		Mild HE. Ascites	2	No
20	No		ACLF 1 (renal)	1	No
21	ACLF 1 (liver)	No	Progressed to ACLF 2 for renal failure	1	No (OLT)
27	No		Ascites	1	No
30	ACLF 1 (liver)	Yes	Severe HE	1	No
32	No		Severe HE	1	No
33	No		Mild HE. Gastrointestinal bleeding. Ascites	3	No
36	ACLF 2 (Liver and renal)	No	Ascites. Mild HE. Gastrointestinal bleeding	3	Yes
37	No		ACLF 2 (Liver and renal failure)	2	Yes
38	No		Ascites. ACLF 3a (Liver, Renal and cerebral)	4	Yes
39	No		Ascites	1	No
40	No		Ascites. Gastrointestinal bleeding. ACLF 3b (Liver, renal, respiratory and circulatory)	6	Yes
41	No		Mild HE. Ascites	2	No

Abbreviations: ACLF, acute-on-chronic liver failure; HE, hepatic encephalopathy; OLT, orthotopic liver transplantation.

4 | DISCUSSION

Intestinal bacterial overgrowth and dysbiosis are key factors in the pathogenesis of AH. These events are directly related to an increase in bacterial translocation, leading to infections, systemic inflammation and vasodilation.[17] The development of infections in patients with severe AH is common. In a meta-analysis, the incidence of infection at 28 days was found to be 20%,[2] and whether the administration of corticosteroids played a role in the development of infection was unclear. No differences were documented in this meta-analysis between patients who received corticosteroid therapy and those who did not. In contrast, the STOPAH trial associated the administration of corticosteroids with a higher incidence of infections.[16]

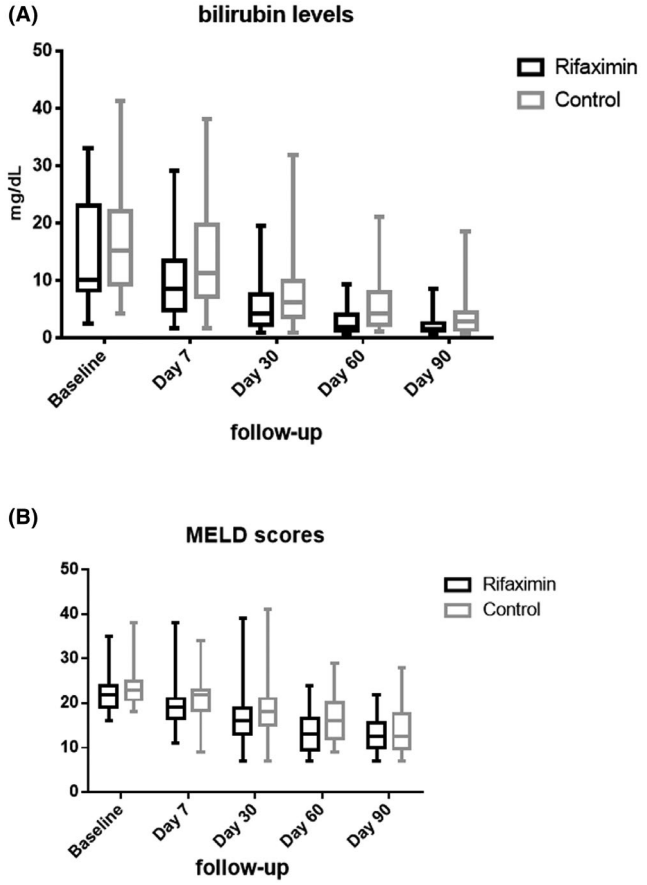

FIGURE 3 Bilirubin levels and MELD scores during the follow-up (baseline, 7, 30, 60 and 90 days). (A) Differences in the levels of bilirubin in the rifaximin and control groups at 60 days were observed. (B) No differences in MELD score during the follow-up; MELD, model for end-stage liver disease

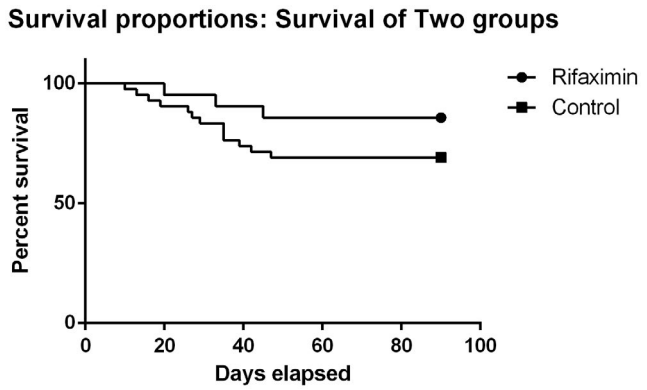

FIGURE 4 Actuarial survival in the rifaximin and control groups ($p = .15$)

Based on current evidence, targeting the microbiota seems to be a good strategy for the prevention of infections during AH episodes. Thus, to test our hypothesis, we selected rifaximin, a non-absorbable antibiotic,[18,19] whose impact on the microbiota has proven useful in patients with chronic liver disease.[8,10,20] Other studies using systemic antibiotics (amoxicillin-clavulanic acid) showed negative results.[21]

In the present pilot study, the administration of rifaximin was associated with a lower number of infections, liver-related complications and mortality rates compared to a prospectively collected cohort.

Even though the study was underpowered by the sample size, the expected decrease of infections within the rifaximin group was achieved. Remarkably, only one infection was linked with bacterial translocation (SBP caused by *Enterococcus faecium*) in the rifaximin group (21 patients). In contrast, 10 infections related to bacterial translocation were recorded in the control group (five SBP, four cases of SB and one case of colitis caused by *Clostridium difficile*). These results support the hypothesis that rifaximin prevents the translocation of bacteria from the gastrointestinal tract in patients with AH.[11,20]

Another relevant finding was the lower significant number of non-infectious complications (including ACLF) per patient in the rifaximin group. This evidence supports the hypothesis that rifaximin could exert other beneficial effects in addition to its antimicrobial effects, as previously described.[20,22–24] In fact, alcohol exerts direct toxicity on the liver and promotes intestinal dysbiosis, which favours liver dysfunction.[25] Alcohol changes the composition and biodiversity of normal flora, which increases the levels of lipopolysaccharide and other toxic substances, leading to an increase in intestinal permeability.[26,27] These changes promote bacterial infections in the liver, thereby causing a PAMP-mediated response that facilitates SIRS associated with AH.[28] Rifaximin might act on the SIRS associated with severe AH and cirrhosis via the modulation of metabiome,[29] prevention of bacterial translocation and endotoxaemia.[30,31] The high risk of infection during the time course of severe AH has been confirmed in several studies; moreover, the infection in severe AH predicts and acts as a trigger to develop ACLF.[32]

A limitation of the study was the low number of included patients, i.e., the anticipated sample size was not reached because the rigorous inclusion and exclusion criteria complicated the recruitment process. Another limitation was the comparison with a historical cohort of patients from other countries. The susceptibility to infections among groups may differ according to the geographical epidemiology and local policies on antibiotics. It is important to note that the control cohort was exclusively composed of patients from academic centres, and the source of admission was the emergency room, as for the study group.[33,34] All these factors might have impacted the clinical relevance of the findings reported in this paper.

In summary, in this pilot study, the use of rifaximin as an add-on therapy to standard therapy for severe AH was associated with a lower number of infections, liver-related complications and a trend towards lower ACLF and mortality rates. The rifaximin add-on therapy also led to an improvement in biochemical markers (bilirubin and MELD).

The promising results obtained suggest that further larger studies are warranted to validate intestinal decontamination in severe AH.

TABLE 4 Adverse events in the rifaximin group

Adverse events	Serious	Grade (1–4)	Causality	Recovered
Right upper extremity paresis	Yes	2	No	No
Epileptic crisis	Yes	3	No	No
Epileptic status	Yes	3	No	No
Cerebral vasculitis versus brain lymphoma	Yes	4	No	No
Suspected pancreatic cancer	Yes	4	No	No
Bronchoaspiration	Yes	3	No	No
Rectal ulcer	Yes	4	No	No
Laryngeal neoplasia	Yes	4	No	No
Breast cancer	Yes	4	No	No
Suicide	Yes	4	No	No
Acute pancreatitis grade A	Yes	1	No	Yes
Pleural effusion	No	2	No	Yes
Hypoglycaemia	No	1	No	Yes
Epidermoid cyst	No	1	No	Yes
Hand burn	No	2	No	Yes
Constipation (two patients	No	1	No	Yes
Hyperglycaemia (two patients)	No	2	No	Yes
Vomiting	No	1	No	Yes
Pruritus	No	1	Possible	Yes
Hyponatraemia	No	2	Possible	Yes
Abdominal wall haematoma	No	2	Unlikely	Yes
Diarrhoea	No	2	Possible	Yes
Mesogastrium pain	No	1	Possible	Yes

5 | CONCLUSIONS

In this pilot study, the use of rifaximin in patients with severe AH was proven to be safe. There was an improvement in liver function tests and a significant decrease in liver-related complications compared with the controls. There was also a lower number of infections and ACLF in patients treated with rifaximin. The observed effects may support the use of rifaximin in these patients and justify further studies in this field.

STUDIES' REGISTRY/CLINICALTRIALS.GOV IDENTIFIER

Effects of Rifaximin in Severe Alcoholic Hepatitis: A Pilot Study (RIFA-AH), NCT02116556. Integrated approaches for identifying molecular targets in alcoholic hepatitis, NCT02075918. EudraCT: 2010–000515-80.

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CONFLICT OF INTEREST

BS has been consulting for the Ferring Research Institute, Gelesis, HOST Therabiomics, Intercept Pharmaceuticals, Mabwell Therapeutics, Patara Pharmaceuticals and Takeda. BS's institution UC San Diego has received research support from Axial Biotherapeutics, BiomX, CymaBay Therapeutics, NGM Biopharmaceuticals, Prodigy Biotech and Synlogic Operating Company. BS is a founder of Nterica Bio. UC San Diego has registered several patents with BS as an inventor related to this work. DS has performed consultancy, delivered paid lectures and is taking part in two investigator-initiated studies (REEFSYS and EMITTIC) funded by Alfasigma/Norgine, who manufacture rifaximin.

ETHICS APPROVAL STATEMENT

This study was approved by the local Ethics Committee for Clinical Research (CEIC) of the Vall d'Hebron University Hospital as a reference centre.

The consent form was obtained from each patient, freely and voluntarily to participate in a particular clinical trial, after having been informed of all aspects of the clinical trial which are relevant to

the subject's decision to participate. The clinical trial was conducted according to Royal Decree 223/2004 Regulating Clinical Trials with medicinal products, ethics committees for investigation with medicinal products and the Spanish Clinical Studies Registry.

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