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Efficacy and Tolerability of Rifaximin in Hepatitis C Patients With Recurrent Hepatic Encephalopathy

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INTRODUCTION

- Infection with hepatitis C virus (HCV) is the most frequent cause of chronic liver disease[1]
  - According to the World Health Organization, ~150 million people are infected with HCV[2]
- Patients with chronic HCV infection often develop cirrhosis, which may lead to decompensation events such as hepatic encephalopathy (HE)[3,4]
- HE, a complication of advanced liver disease, is a serious neurologic syndrome with neuropsychiatric symptoms and psychomotor dysfunction of varying severity[5]
- Rifaximin, a minimally absorbed, gut-targeted antibiotic, has demonstrated efficacy and safety in a heterogenous group of patients with cirrhosis and recurrent HE[6]; efficacy and tolerability in specific subgroups of patients, such as patients with HCV, has not been examined

OBJECTIVE

- To evaluate the efficacy and tolerability of rifaximin 550 mg twice daily in maintaining overt HE remission in patients with HCV-associated liver disease and cirrhosis

METHODS

Study Design

- This subgroup analysis evaluated data from a phase 3, randomized, double-blind, placebo-controlled, multicenter trial in adults with cirrhosis and HE who were currently in remission (Conn score 0 or 1), had a history of ≥2 episodes of overt HE (Conn score ≥2) within 6 months of screening, and had a Model for End-Stage Liver Disease (MELD) score of ≤25 at study entry
- Patients were treated with rifaximin (Xifaxan®, Salix Pharmaceuticals, Inc., Raleigh, NC, USA) 550 mg twice daily or placebo for 6 months
- Concomitant lactulose administration was permitted during the study
- Exclusion criteria included renal insufficiency, severe anemia, and hypovolemia or any electrolyte abnormality that could affect mental function

Assessments

- Clinic visits occurred on days 7 and 14 and every 2 weeks thereafter through day 168 (end of treatment), with optional visits on days 42, 70, 98, 126, and 154
- The rates of overt HE breakthrough episodes were assessed based on liver disease etiology (HCV versus non-HCV)
  - Breakthrough overt HE was defined as an increase in Conn score to ≥2, or an increase in both Conn score and asterixis score of 1 grade each for patients entering with a Conn score of 0
- Safety assessments included monitoring of adverse events (AEs), clinical laboratory tests, vital signs, and concomitant medications

RESULTS

Patient Population

- Of the total 299 patients in this study, 128 patients (42.8%) had HCV etiology for advanced liver disease
  - The non-HCV group included patients with alcohol-related liver disease, nonalcoholic fatty liver disease, or nonalcoholic steatohepatitis etiologies
- Demographic and baseline characteristics were generally similar among the HCV and non-HCV groups (Table 1)

Table 1. Demographic and Baseline Characteristics

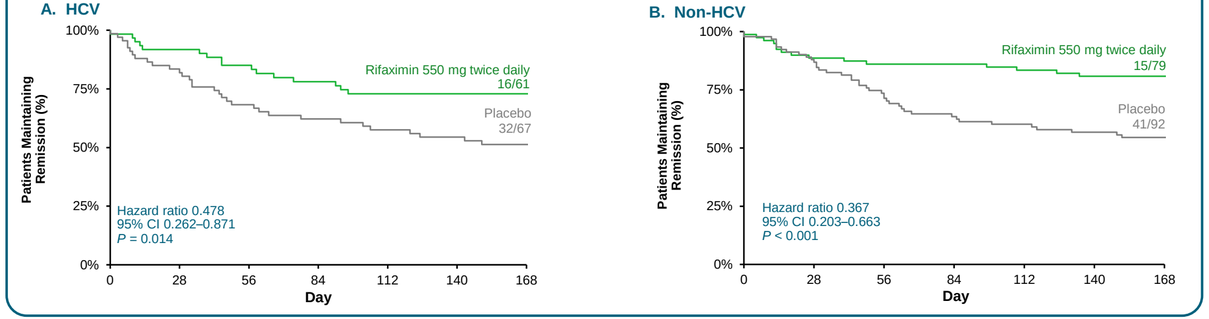
	HCV		Non-HCV	
Parameter	Rifaximin (n = 61)	Placebo (n = 67)	Rifaximin (n = 79)	Placebo (n = 92)
Age, y, mean (SD)	53.5 (8.5)	55.4 (7.9)	57.0 (10.1)	57.9 (9.9)
Sex, male, n (%)	37 (60.7)	48 (71.6)	38 (48.1)	59 (64.1)
Race, white, n (%)	47 (77.0)	59 (88.1)	71 (89.9)	80 (87.0)
Duration of current HE remission, days, mean (SD)	50.0 (36.7)	56.9 (38.8)	57.5 (39.6)	58.8 (41.4)
Time since advanced liver disease diagnosis, months, mean (SD)	61.3 (57.0)	67.2 (60.0)	43.3 (40.8)	55.6 (68.2)
MELD score, mean (SD)	13.1 (3.6)	13.0 (3.7)	13.1 (3.7)	12.4 (4.1)
≤10, n (%)	14 (23.0)	15 (22.4)	20 (25.3)	33 (35.9)
11–18, n (%)	41 (67.2)	45 (67.2)	53 (67.1)	51 (55.4)
19–24, n (%)	6 (9.8)	7 (10.4)	6 (7.6)	6 (7.6)
Conn score, n (%)				
0	39 (63.9)	48 (71.6)	54 (68.4)	59 (64.1)
1	22 (36.1)	19 (28.4)	25 (31.6)	33 (35.9)
Asterixis grade, n (%)				
0	40 (65.6)	49 (73.1)	56 (70.9)	59 (64.1)
1	20 (32.8)	15 (22.4)	21 (26.6)	30 (32.6)
≥2	1 (1.6)	3 (4.5)	2 (2.6)	3 (3.3)

Efficacy

- In the HCV group, an overt HE breakthrough episode occurred in 26.2% of rifaximin-treated patients versus 47.8% of placebo-treated patients, corresponding to relative reduction in risk of breakthrough overt HE of 52.2% (Figure 1; $P = 0.014$)
- In the non-HCV group, there was also a significant difference, with 19.0% of rifaximin-treated patients experiencing an overt HE breakthrough episode versus 44.6% of placebo-treated patients ($P < 0.001$)

RESULTS

Figure 1. Kaplan-Meier Estimates Showing the Percentage of Patients Maintaining HE Remission Over Time



Safety

- The incidence of AEs and serious AEs were similar during rifaximin and placebo treatment for both the HCV and non-HCV subgroups (Table 2)
- In the HCV subgroup, the most commonly reported AEs included nausea, fatigue, and peripheral edema

Table 2. Summary of Adverse Events

	HCV		Non-HCV	
Adverse Event, n (%)	Rifaximin (n = 61)	Placebo (n = 67)	Rifaximin (n = 79)	Placebo (n = 92)
Any AE	53 (86.9)	59 (88.1)	60 (75.9)	73 (79.3)
Serious AE	25 (41.0)	26 (38.8)	26 (32.9)	37 (40.2)
AEs reported in ≥10% of patients in rifaximin groups				
Nausea	11 (18.0)	13 (19.4)	9 (11.4)	8 (8.7)
Peripheral edema	9 (14.8)	5 (7.5)	12 (15.2)	8 (8.7)
Diarrhea	4 (6.6)	10 (14.9)	11 (13.9)	11 (12.0)
Fatigue	9 (14.8)	9 (13.4)	8 (10.1)	9 (9.8)
Dizziness	7 (11.5)	8 (11.9)	11 (13.9)	5 (5.4)
Headache	5 (8.2)	9 (13.4)	9 (11.4)	8 (8.7)
Ascites	6 (9.8)	8 (11.9)	10 (12.7)	7 (7.6)
Depression	7 (11.5)	3 (4.5)	3 (3.8)	5 (5.4)
Insomnia	7 (11.5)	6 (9.0)	3 (3.8)	5 (5.4)
Muscle spasms	7 (11.5)	1 (1.5)	6 (7.6)	10 (10.9)
Anemia	3 (4.9)	4 (6.0)	8 (10.1)	2 (2.2)
Constipation	1 (1.6)	5 (7.5)	8 (10.1)	5 (5.4)

CONCLUSION

- **In patients with HCV and a history of recurrent HE, rifaximin was efficacious and well tolerated, with a clinical profile similar to that observed for patients with other advanced liver disease etiologies**

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