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Rifaximin Plus Lactulose Versus Lactulose Alone for Reducing the Risk of Overt Hepatic Encephalopathy Recurrence: a Pooled Subgroup Analysis

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INTRODUCTION

- Prognosis of patients with cirrhosis worsens with transition from a compensated to a decompensated state (ie, occurrence of complications, such as hepatic encephalopathy [HE], ascites, or variceal bleeding), with median survival decreasing from >12 years to ~2 years, respectively[1]
- A key aspect of cirrhosis management is prevention or risk reduction of overt HE (OHE), and rifaximin (Xifaxan®) is indicated for the prevention of OHE recurrence in adults[2]
- The practice guideline from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver recommends treatment be initiated to prevent recurrence in patients who have had an OHE episode[3]
- Specifically, the guideline recommends the nonabsorbable disaccharide lactulose for prevention of HE recurrence with rifaximin as add-on therapy after the second HE episode occurs[3]

AIM

- To evaluate rifaximin plus lactulose versus lactulose alone for prevention of OHE recurrence in patients with cirrhosis and history of OHE, subgrouped by baseline characteristics

METHODS

- Data were pooled and analyzed post hoc from one phase 3, randomized, double-blind trial (ClinicalTrials.gov identifier: NCT00298038)[4] and one phase 4, open-label clinical trial (NCT01842581)
- Patient population included adults with cirrhosis with a history of OHE during the previous 6 months who were currently in OHE remission (Conn score ≤1)
- Patients were randomly assigned to treatment
  - Phase 3 trial: rifaximin 550 mg twice daily (BID) or placebo, with optional concomitant lactulose (titrated to 2-3 soft stools/day), for 6 months
  - Phase 4 trial: rifaximin 550 mg BID ± lactulose (titrated to 2-3 soft stools/day) for 6 months†
- In the phase 3 trial, clinic visits occurred on Day 0 (±1), Days (±2) 7, 14, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, 168, and the follow-up visit (14±2 days after end of treatment)
  - Clinical visits on Days 42, 70, 98, 126, and 154 were optional, unless an investigator deemed an in-person clinic visit necessary, and instead a telephone call (±2 days) was conducted
- In the phase 4 trial, clinic visits occurred on Day 1, Days (±2) 28, 56, 84, 112, 140, 168, and the follow-up visit (14±2 days after end of treatment)
- Primary efficacy endpoint for both trials was time to first breakthrough OHE episode (Conn score ≥2)
- In the current analysis, efficacy was assessed in patients subgrouped by baseline demographics or disease characteristics (for those groups with adequate sample size)
  - Age, sex, comorbid diabetes, cirrhosis etiology, Model for End-Stage Liver Disease (MELD) score, Child-Pugh class, time since diagnosis of advanced liver disease, time since first diagnosis of HE, and duration of current HE remission
- *P* values were based on the score statistic, and hazard ratio estimates were obtained using a Cox proportional hazards model with effect for treatment

†Rifaximin alone group not included in current pooled analysis.

RESULTS

- Overall pooled population included 381 patients: 236 treated with rifaximin plus lactulose and 145 treated with placebo plus lactulose (ie, lactulose alone; **Table 1**)
  - In both groups, the mean age was ~57 years and the majority of patients were male (58.9%-68.3%)
  - The mean MELD score (±SD) was comparable between the rifaximin plus lactulose and lactulose alone groups (12.5±3.5 vs 12.9±3.8, respectively)

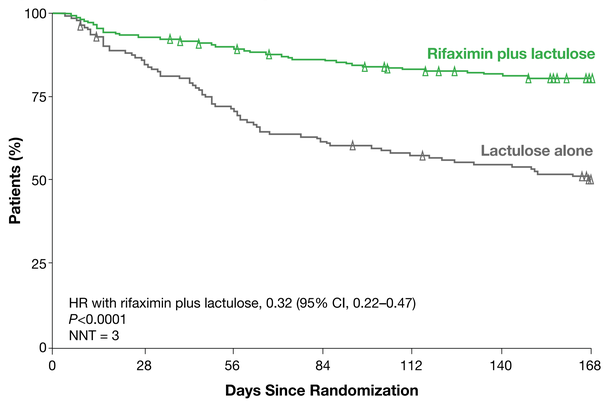
Table 1. Demographic and Baseline Characteristics

Characteristic	Rifaximin Plus Lactulose (n=236)	Lactulose Alone (n=145)
Age, y, mean (SD)	56.9 (9.7)	56.6 (9.3)
Male sex, n (%)	139 (58.9)	99 (68.3)
Race*, n (%)		
White	206 (87.3)	126 (86.9)
Black	12 (5.1)	5 (3.4)
Asian	5 (2.1)	7 (4.8)
Other	12 (5.1)	7 (4.8)
Baseline MELD score, mean (SD)	12.5 (3.5)	12.9 (3.8)
Child-Pugh class, n (%)		
A	80 (33.9)	49 (33.8)
B	124 (52.5)	67 (46.2)
C	20 (8.5)	13 (9.0)
Missing data	12 (5.1)	16 (11.0)
Baseline Conn score, n (%)		
0	159 (67.4)	98 (67.6)
1	77 (32.6)	47 (32.4)
Duration of current overt HE remission, d, mean (SD)	71.5 (52.4)	73.6 (52.0)

*Data missing for 1 patient receiving rifaximin plus lactulose.
HE = hepatic encephalopathy; MELD = Model for End-Stage Liver Disease.

- Lactulose use during treatment was stable, with a mean (±SD) change from baseline of 0.01±0.05 cups/day in the rifaximin plus lactulose group and 0.01±0.11 cups/day in the lactulose alone group
- In the overall population, patients receiving rifaximin plus lactulose had a 68% decrease in the risk of a breakthrough OHE event during 6 months of treatment versus with lactulose alone (number needed to treat = 3; **Figure**)

Figure. Time to First Breakthrough Overt HE Episode



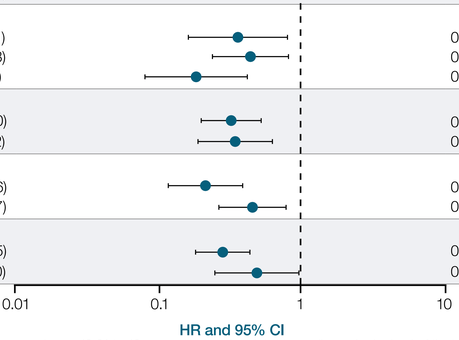
Δ = censored observation(s); HE = hepatic encephalopathy; HR = hazard ratio; NNT = number needed to treat.

RESULTS

- In addition, rifaximin plus lactulose significantly reduced the risk of OHE recurrence versus lactulose alone for all subgroups analyzed (**Table 2**)

Table 2. Subgroup Analyses of Breakthrough OHE During 6 Months of Treatment

Parameter	Patients With OHE, n/n (%) Rifaximin Plus Lactulose	Lactulose Alone	HR (95% CI)	*P* value
Overall population	45/235* (19.1)	71/145 (49.0)	0.32 (0.22-0.47)	<0.001
Age				
<65 y	31/181 (17.1)	53/116 (45.7)	0.32 (0.20-0.49)	<0.001
≥65 y	14/55 (25.4)	18/29 (62.1)	0.31 (0.15-0.62)	<0.001
Sex				
Male	24/139 (17.3)	46/99 (46.5)	0.33 (0.20-0.54)	<0.001
Female	21/97 (21.6)	25/46 (54.3)	0.29 (0.16-0.52)	<0.001
Diabetes at screening				
No	26/152 (17.1)	45/94 (47.9)	0.30 (0.19-0.49)	<0.001
Yes	19/84 (22.6)	26/51 (51.0)	0.36 (0.20-0.65)	<0.001
Cirrhosis etiology†				
Alcohol only	6/44 (13.6)	15/37 (40.5)	0.31 (0.12-0.79)	0.01
Viral hepatitis only	15/81 (18.5)	31/58 (53.4)	0.28 (0.15-0.52)	<0.001
Other	14/75 (18.7)	20/34 (58.8)	0.23 (0.12-0.46)	<0.001
Baseline MELD score category†				
≤10	5/65 (7.7)	13/39 (33.3)	0.21 (0.07-0.59)	0.001
11-18	35/158 (22.2)	50/92 (54.3)	0.32 (0.21-0.50)	<0.001
Baseline Child-Pugh class				
A	8/38 (21.1)	26/49 (53.1)	0.36 (0.16-0.78)	0.008
B	15/62 (24.2)	31/67 (46.3)	0.44 (0.24-0.82)	0.008
C	19/124 (15.3)	8/13 (61.5)	0.18 (0.08-0.41)	<0.001
Time since first diagnosis of advanced liver disease				
<50 mo	27/139 (19.4)	46/92 (50.0)	0.31 (0.20-0.51)	<0.001
≥50 mo	18/97 (18.6)	25/53 (47.2)	0.34 (0.19-0.63)	<0.001
Time since first diagnosis of HE				
<15 mo	17/122 (13.9)	43/85 (50.6)	0.21 (0.12-0.38)	<0.001
≥15 mo	27/113 (23.9)	28/60 (46.7)	0.46 (0.27-0.78)	0.003
Duration of current HE remission				
≤90 d	30/164 (18.3)	52/99 (52.5)	0.28 (0.18-0.43)	<0.001
>90 d	15/71 (21.1)	18/45 (40.0)	0.49 (0.25-0.97)	0.04



*Data missing for 1 patient.
†Alcohol and viral hepatitis etiology subgroup (n=29 [rifaximin plus lactulose] and n=13 [lactulose alone]) and MELD score category 19-24 (n=13 per arm) not analyzed due to small sample size in ≥1 of the treatment groups.
CI = confidence interval; HE = hepatic encephalopathy; HR = hazard ratio; MELD = Model for End-Stage Liver Disease; OHE = overt hepatic encephalopathy.

CONCLUSIONS

- **Rifaximin plus lactulose was superior to lactulose alone for reducing the risk of OHE recurrence in patients with cirrhosis, including when patients were grouped by the baseline characteristics analyzed**
- **The new HE-specific International Classification of Diseases, Tenth Revision, Clinical Modification code became available on October 1, 2022, and may further facilitate this type of research by improving the identification of patients with HE**

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*This author is deceased.

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