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Rifaximin Plus Lactulose Is More Efficacious Than Lactulose Alone for Risk Reduction of Overt Hepatic Encephalopathy Recurrence: a Subgroup Analysis by Viral or Alcohol Cirrhosis Etiology

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BACKGROUND

- Patients with cirrhosis are more likely to have a history of excessive alcohol consumption or viral hepatitis than individuals without cirrhosis[1]
- Reducing the risk of overt hepatic encephalopathy (OHE), a common complication of cirrhosis, is a key component of cirrhosis management[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 that all episodes of OHE be treated; furthermore, for patients who have had an OHE episode, ongoing treatment (prophylaxis) should be initiated to reduce the risk for OHE recurrence[2]
  - Lactulose is recommended as initial therapy to treat an episode of OHE and as prophylaxis after the initial episode[2]
  - Rifaximin (Xifaxan, Salix Pharmaceuticals, Bridgewater, NJ), a nonsystemic antibiotic approved for reducing the risk of OHE recurrence in adults,[3] is recommended as add-on therapy to lactulose for the prevention of OHE recurrence[2]

AIM

- To examine the efficacy of rifaximin plus lactulose compared with lactulose alone for the prevention of OHE recurrence in patients with a history of OHE, subgrouped by common cirrhosis etiology

METHODS

- Pooled subgroup analysis of a phase 3 randomized, double-blind study (ClinicalTrials.gov identifier: NCT00298038)[4] and a phase 4 open-label clinical study (NCT01842581)
- Patient population: adults with cirrhosis and a history of OHE during the previous 6 months but currently in OHE remission (Conn score ≤1), with a viral hepatitis (only) or alcohol-induced (only) cirrhosis etiology
- 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 (± 2 days) occurred on days 7, 14, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, 168, and end of study visit (14 ± 2 days after end of treatment)
  - A telephone call (± 2 days) occurred on days 42, 70, 98, 126, and 154, unless an investigator deemed an in-person clinic visit necessary
- In the phase 4 trial, clinic visits (± 2 days) occurred on days 28, 56, 84, 112, 140, 168, and end of study visit (14 ± 2 days after end of treatment)
- Efficacy assessments analyzed were time to onset of an OHE episode (Conn score ≥2) and time to first hepatic encephalopathy (HE)-related hospitalization
- Adverse events were monitored throughout the trials
- Population analyzed included all patients who received ≥1 dose of study medication
- *P* values were based on the score statistic, and hazard ratio (HR) estimates were obtained using a Cox proportional hazards model with effect for treatment

*Rifaximin alone group not included in current pooled analysis.

RESULTS

- The pooled analysis of the 2 trials included 220 patients (Table 1)
  - Viral hepatitis etiology subgroup (n=139): rifaximin plus lactulose, n=81; lactulose alone, n=58
  - Alcohol-induced etiology subgroup (n=81): rifaximin plus lactulose, n=44; lactulose alone, n=37

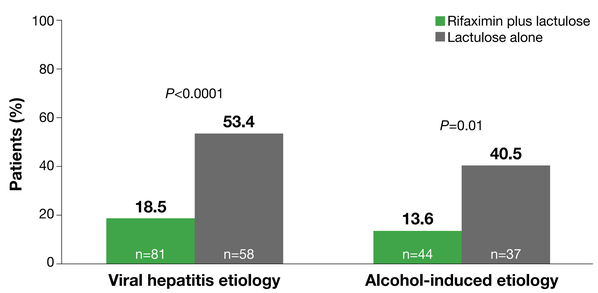
Table 1. Baseline Characteristics by Cirrhosis Etiology

	Viral Hepatitis Etiology (n=139)		Alcohol-Induced Etiology (n=81)	
Parameter	Rifaximin Plus Lactulose (n=81)	Lactulose Alone (n=58)	Rifaximin Plus Lactulose (n=44)	Lactulose Alone (n=37)
MELD, mean (SD)	12.5 (3.4)	13.3 (3.8)*	13.0 (4.0)	12.2 (4.1)
Child-Pugh class, n (%)				
A	28 (34.6)	20 (34.5)	19 (43.2)	18 (48.6)
B	44 (54.3)	28 (48.3)	19 (43.2)	13 (35.1)
C	8 (9.9)	3 (5.2)	5 (11.4)	4 (10.8)
Missing	1 (1.2)	7 (12.1)	1 (2.3)	2 (5.4)
Duration of current OHE remission, d, mean (SD)	56.0 (48.6)	70.9 (52.0)*	74.4 (46.3)	83.5 (56.1)
OHE episodes during previous 6 mo, n (%)				
1	27 (33.3)	0	18 (40.9)	0
2	38 (46.9)	44 (75.9)	16 (36.4)	24 (64.9)
3	11 (13.6)	10 (17.2)	6 (13.6)	10 (27.0)
≥4	4 (4.9)	3 (5.2)	3 (6.8)	3 (8.1)
Missing	1 (1.2)	1 (1.7)	1 (2.3)	0

*Data missing for 1 patient (n=57).
MELD = Model for End-Stage Liver Disease; OHE = overt hepatic encephalopathy.

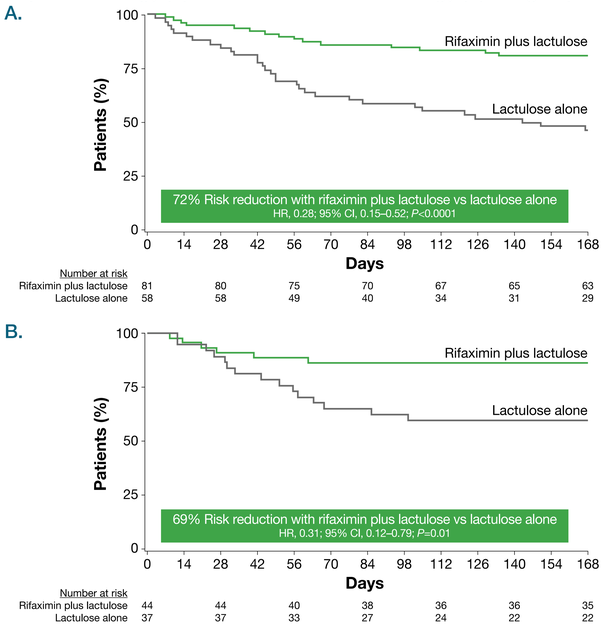
- In both subgroups, a significantly lower percentage of patients treated with rifaximin plus lactulose had an OHE episode versus lactulose alone during a 6-month period (Figure 1)
- In the viral hepatitis etiology subgroup, rifaximin plus lactulose reduced the risk of OHE, compared with lactulose alone, by 72% (Figure 2A)
- In the alcohol-induced etiology subgroup, rifaximin plus lactulose reduced the risk of OHE, compared with lactulose alone, by 69% (Figure 2B)

Figure 1. Patients Experiencing an OHE Episode



OHE = overt hepatic encephalopathy.

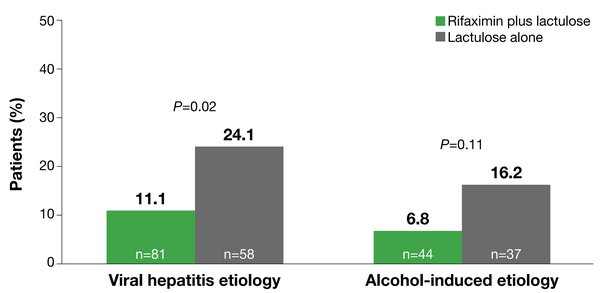
Figure 2. Time to First Breakthrough OHE Episode in the Viral Hepatitis Etiology (A) and Alcohol-Induced Etiology (B) Subgroups



CI = confidence interval; HR = hazard ratio; OHE = overt hepatic encephalopathy.

- In the viral hepatitis etiology subgroup, a significantly lower percentage of patients receiving rifaximin plus lactulose experienced a first HE-related hospitalization compared with lactulose alone (*P*=0.02; Figure 3)
  - Rifaximin plus lactulose reduced the risk of first HE-related hospitalization by 62% versus lactulose alone (HR, 0.38; 95% confidence interval [CI], 0.17–0.89)

Figure 3. Patients Experiencing a First HE-Related Hospitalization



HE = hepatic encephalopathy.

- In the alcohol-induced etiology subgroup, there was a numeric decrease in the percentage of patients experiencing an HE-related hospitalization with rifaximin plus lactulose compared with lactulose alone (6.8% vs 16.2%, respectively), but this difference was not significant (*P*=0.11; Figure 3)
  - The reduction in risk of a first HE-related hospitalization in the rifaximin plus lactulose group versus lactulose alone group was 66% (HR, 0.34; 95% CI, 0.09–1.38)
- Rifaximin plus lactulose was generally well tolerated in both subgroups (Table 2)

Table 2. Summary of AEs by Cirrhosis Etiology

	Viral Hepatitis Etiology (n=139)		Alcohol-Induced Etiology (n=81)	
AE*	Rifaximin Plus Lactulose (n=81)	Lactulose Alone (n=58)	Rifaximin Plus Lactulose (n=44)	Lactulose Alone (n=37)
Peripheral edema	14 (17.3)	4 (6.9)	1 (2.3)	2 (5.4)
HE	12 (14.8)	19 (32.8)	4 (9.1)	9 (24.3)
Ascites	11 (13.6)	5 (8.6)	6 (13.6)	3 (8.1)
Nausea	11 (13.6)	12 (20.7)	4 (9.1)	2 (5.4)
Fatigue	9 (11.1)	8 (13.8)	5 (11.4)	2 (5.4)
Diarrhea	9 (11.1)	11 (19.0)	1 (2.3)	5 (13.5)
Insomnia	7 (8.6)	6 (10.3)	6 (13.6)	1 (2.7)
Dizziness	7 (8.6)	7 (12.1)	3 (6.8)	1 (2.7)
UTI	6 (7.4)	7 (12.1)	3 (6.8)	0
Headache	4 (4.9)	9 (15.5)	6 (13.6)	2 (5.4)
Vomiting	4 (4.9)	8 (13.8)	3 (6.8)	3 (8.1)
Constipation	3 (3.7)	6 (10.3)	5 (11.4)	1 (2.7)
Cough	3 (3.7)	6 (10.3)	2 (4.5)	2 (5.4)

*AEs reported in >10% of patients in any group; ordered by frequency in viral hepatitis subgroup treated with rifaximin plus lactulose.
AE = adverse event; HE = hepatic encephalopathy; UTI = urinary tract infection.

CONCLUSION

- **The combination of rifaximin plus lactulose was more efficacious than lactulose alone for reducing the risk of OHE recurrence in adults with a viral or alcohol-induced cirrhosis etiology and a history of OHE**

REFERENCES: **1.** Scaglione S, et al. *J Clin Gastroenterol.* 2015;49(8):690-696. **2.** Vilstrup H, et al. *Hepatology.* 2014;60(2):715-735. **3.** Xifaxan tablets, for oral use. Salix Pharmaceuticals; 2020. **4.** Bass NM, et al. *N Engl J Med.* 2010;362(12):1071-1081.

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