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Rifaximin Plus Lactulose Is More Efficacious Than Lactulose Alone for the Prevention of Overt Hepatic Encephalopathy in Patients With or Without Ascites

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BACKGROUND

- Rifaximin 550 mg twice daily (BID) is indicated for the reduction in risk of overt hepatic encephalopathy (OHE) recurrence in adults[1]
- Ascites is a risk factor for OHE development[2,3]
- Data are lacking on the efficacy and safety of rifaximin in patients with baseline ascites and a history of OHE

AIM

- To evaluate the efficacy and safety of rifaximin plus lactulose versus lactulose alone in patients subgrouped by presence or absence of ascites at baseline

METHODS

- Pooled post hoc analysis of a phase 3 randomized, double-blind trial (ClinicalTrials.gov identifier: NCT00298038)[4] and a phase 4 open-label clinical trial (NCT01842581)
- Patient population: adults with cirrhosis and a history of OHE during the previous 6 months who were in OHE remission
  - Patients were subgrouped post hoc by the baseline presence or absence of ascites

Treatment

- In the phase 3 trial, rifaximin 550 mg BID (Xifaxan®, Salix Pharmaceuticals) or placebo was administered with optional lactulose (titrated to 2-3 soft stools/day) for 6 months
- In the phase 4 trial arm (included in current analysis), rifaximin 550 mg BID plus lactulose (titrated to 2-3 soft stools/day) was administered for 6 months*
- Lactulose alone was defined as placebo plus lactulose

Assessments

- 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 during the follow-up visit (14±2 days after the end of treatment)
  - Clinic visits on Days 42, 70, 98, 126, and 154 were optional (ie, only conducted if an investigator deemed an in-person clinic visit necessary); 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 during the follow-up visit (14±2 days after the end of treatment)
- Efficacy endpoints were time to first breakthrough OHE episode (Conn score ≥2) and time to first hepatic encephalopathy (HE)-related hospitalization (original trial endpoints)
- Hazard ratio estimates were obtained using a Cox proportional hazards model with effect for treatment, and *P* values were based on the score statistic
- Adverse events (AEs) were monitored throughout the trials

*The rifaximin alone group is not included in the current pooled analysis.

RESULTS

- 135 patients had ascites at baseline, and 246 patients had no ascites (**Table 1**)
- Significantly fewer patients with baseline ascites treated with rifaximin plus lactulose had an OHE episode versus lactulose alone (27.4% [23/84] vs 58.8% [30/51]; *P*<0.001)
  - Demonstrated a 63% reduction in risk of breakthrough OHE during 6 months of treatment with rifaximin plus lactulose versus lactulose alone (HR, 0.37 [**Figure 1A**]; number needed to treat [NNT] = 3)
- In addition, significantly fewer patients without baseline ascites treated with rifaximin plus lactulose versus lactulose alone had an OHE episode (14.5% [22/152] vs 43.6% [41/94]; *P*<0.0001)
  - Demonstrated a 72% reduction in risk of breakthrough OHE during 6 months of treatment with rifaximin plus lactulose versus lactulose alone (HR, 0.28 [**Figure 1B**]; NNT = 3)

Table 1. Baseline Characteristics by Presence or Absence of Ascites

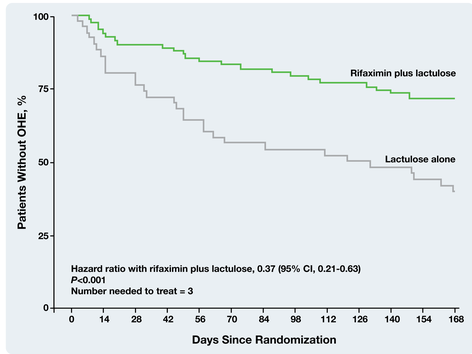
	Baseline Ascites (n=135)		No Baseline Ascites (n=246)	
Parameter	Rifaximin Plus Lactulose (n=84)	Lactulose Alone (n=51)	Rifaximin Plus Lactulose (n=152)	Lactulose Alone (n=94)
MELD				
Mean (SD)	13.5 (3.5)	14.1 (4.2)	11.9 (3.3)	12.2 (3.5)
Median	13.0	14.1	12.2	11.8
Child-Pugh class, n (%)				
A	12 (14.3)	11 (21.6)	68 (44.7)	38 (40.4)
B	55 (65.5)	30 (58.8)	69 (45.4)	37 (39.4)
C	12 (14.3)	8 (15.7)	8 (5.3)	5 (5.3)
Missing	5 (6.0)	2 (3.9)	7 (4.6)	14 (14.9)
Duration of current OHE remission, d, median	57.0	52.0	57.0	63.0
OHE episodes during previous 6 mo, n (%)				
1	29 (34.5)	0*	57 (37.5)	0*
2-3	48 (57.1)	47 (92.2)	80 (52.6)	85 (90.4)
≥4	4 (4.8)	4 (7.8)	11 (7.2)	8 (8.5)
Missing	3 (3.6)	0	4 (2.6)	1 (1.1)

*An inclusion criterion of the phase 3 trial was that patients had a history of ≥2 episodes of OHE during the previous 6 months.[4]

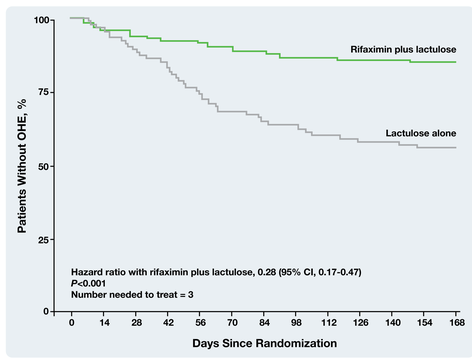
MELD = Model for End-Stage Liver Disease; OHE = overt hepatic encephalopathy.

Figure 1. Time to First Breakthrough OHE Episode in Patients With (A) or Without (B) Baseline Ascites

A. With Ascites



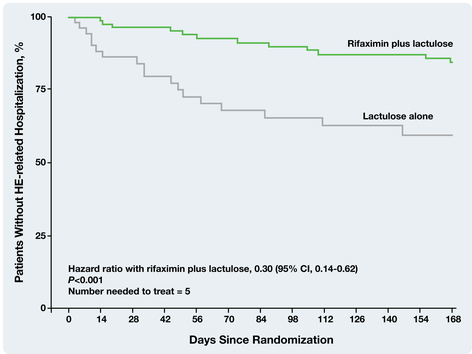
B. Without Ascites



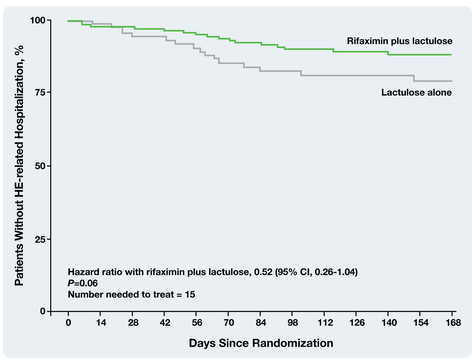
OHE = overt hepatic encephalopathy.

Figure 2. Time to First HE-Related Hospitalization in Patients With (A) or Without (B) Baseline Ascites

A. With Ascites



B. Without Ascites



HE = hepatic encephalopathy.

- In addition, patients with baseline ascites treated with rifaximin plus lactulose had a significantly lower incidence of a first HE-related hospitalization versus lactulose alone (14.3% [12/84] vs 35.3% [18/51]; *P*<0.001)
  - Demonstrated a 70% reduction in risk during 6 months of treatment with rifaximin plus lactulose versus lactulose alone (HR, 0.30 [**Figure 2A**]; *P*<0.001; NNT = 5)
- In patients without ascites at baseline, a numeric difference favoring rifaximin plus lactulose versus lactulose alone in the percentage of patients with an HE-related hospitalization was observed (10.5% [16/152] vs 17.0% [16/94]; *P*=0.06; **Figure 2B**)
  - However, this difference was not statistically significant (*P*=0.06), possibly related to the smaller sample size in the lactulose-alone arm
- Rifaximin plus lactulose was generally well tolerated, regardless of baseline ascites status (**Table 2**)

Table 2. Summary of AEs

	Baseline Ascites (n=135)		No Baseline Ascites (n=246)	
Patients With an AE, n (%)	Rifaximin Plus Lactulose (n=84)	Lactulose Alone (n=51)	Rifaximin Plus Lactulose (n=152)	Lactulose Alone (n=94)
Any AE	72 (85.7)	49 (96.1)	116 (76.3)	77 (81.9)
Serious AE	43 (51.2)	27 (52.9)	42 (27.6)	33 (35.1)
Discontinuations due to AE	23 (27.4)	24 (47.1)	23 (15.1)	33 (35.1)
Most common AEs*				
Abdominal distension	7 (8.3)	4 (7.8)	10 (6.6)	8 (8.5)
Abdominal pain	11 (13.1)	7 (13.7)	9 (5.9)	4 (4.3)
Anemia	6 (7.1)	5 (9.8)	7 (4.6)	1 (1.1)
Asthenia	3 (3.6)	5 (9.8)	3 (2.0)	7 (7.4)
Back pain	2 (2.4)	5 (9.8)	7 (4.6)	5 (5.3)
Constipation	7 (8.3)	5 (9.8)	11 (7.2)	5 (5.3)
Cough	6 (7.1)	1 (2.0)	9 (5.9)	10 (10.6)
Diarrhea	10 (11.9)	7 (13.7)	18 (11.8)	14 (14.9)
Dizziness	8 (9.5)	9 (17.6)	15 (9.9)	4 (4.3)
Dyspnea	7 (8.3)	4 (7.8)	12 (7.9)	3 (3.2)
Fatigue	11 (13.1)	7 (13.7)	15 (9.9)	11 (11.7)
Headache	5 (6.0)	6 (11.8)	13 (8.6)	11 (11.7)
HE	15 (17.9)	20 (39.2)	17 (11.2)	25 (26.6)
Insomnia	10 (11.9)	4 (7.8)	14 (9.2)	7 (7.4)
Muscle spasms	7 (8.3)	3 (5.9)	16 (10.5)	7 (7.4)
Nausea	17 (20.2)	9 (17.6)	14 (9.2)	12 (12.8)
Peripheral edema	14 (16.7)	5 (9.8)	21 (13.8)	8 (8.5)
Pruritus	14 (16.7)	4 (7.8)	3 (2.0)	5 (5.3)
Urinary tract infection	10 (11.9)	5 (9.8)	6 (3.9)	9 (9.6)
Vomiting	6 (7.1)	6 (11.8)	10 (6.6)	8 (8.5)

*AEs (excluding ascites) reported in >8.0% of patients in any group; ordered alphabetically.
AE = adverse event; HE = hepatic encephalopathy.

CONCLUSIONS

- Rifaximin plus lactulose was more efficacious than lactulose alone for reducing the risk of OHE recurrence and reducing the risk of HE-related hospitalizations in adults with or without ascites at start of therapy
  - Ascites is a risk factor for OHE development,[2,3] and rifaximin was effective in this high-risk patient population
- Therefore, patients with ascites and a history of OHE may benefit from the addition of rifaximin to lactulose therapy to reduce the risk of future OHE episodes

REFERENCES: **1.** Xifaxan tablets, for oral use. Salix Pharmaceuticals; 2022. **2.** Tapper EB, et al. *Hepatology*. 2018;68(6):1498-1507. **3.** Vilstrup H, et al. *Hepatology*. 2014;60(2):715-735. **4.** Bass NM, et al. *N Engl J Med*. 2010;362(12):1071-1081.

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