Rifaximin Monotherapy Reduced Hepatic Encephalopathy and Mortality Risk Versus Lactulose

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PURPOSE

- Hepatic encephalopathy (HE) is a debilitating neuropsychiatric complication of cirrhosis and is associated with a poor prognosis[1]
- Patients who have an initial episode of HE and do not receive secondary prophylaxis have a >40% cumulative risk of additional HE episode(s) at 12 months[1,2]
- Lactulose monotherapy is recommended as secondary prophylaxis after an initial episode of overt HE (OHE)[1,3]
- Rifaximin (Xifaxan®; Salix Pharmaceuticals) is indicated for the reduction in risk of OHE recurrence in adults and recommended as add-on therapy when additional episodes occur[1,3]
- Nonadherence to lactulose therapy can precipitate recurrence of HE[4-5]

Potential barriers to lactulose adherence include[6,7]:

- Gastrointestinal (GI) adverse effects (eg, diarrhea, nausea, and vomiting)
  - Can lead to dehydration or electrolyte imbalances, which are also precipitating factors of OHE[7,8]
- Dosing and volume requirements
- Unpleasant taste

- These lactulose-related issues indicate that alternative management strategies to reduce the risk of OHE recurrence may be required

AIM

- To compare rifaximin monotherapy versus lactulose monotherapy for reducing the risk of OHE recurrence and all-cause mortality in patients with cirrhosis and a history of OHE

METHODS

- **Study design:** post hoc analysis of 2 randomized trials (phase 3 double-blind; phase 4 open-label)
- **Population:** adults with cirrhosis and a history of OHE occurrence in the previous 6 months (in remission)
- **Treatment**
  - Rifaximin 550 mg twice daily (ie, rifaximin monotherapy) for up to 6 months
  - Lactulose (titrated; 2-3 soft stools/d) plus placebo (ie, lactulose monotherapy) for up to 6 months
- **Primary efficacy endpoint (in both trials):** time to first breakthrough OHE episode (Conn score ≥2)

RESULTS

- 270 patients were included in the analysis (**Table 1**)

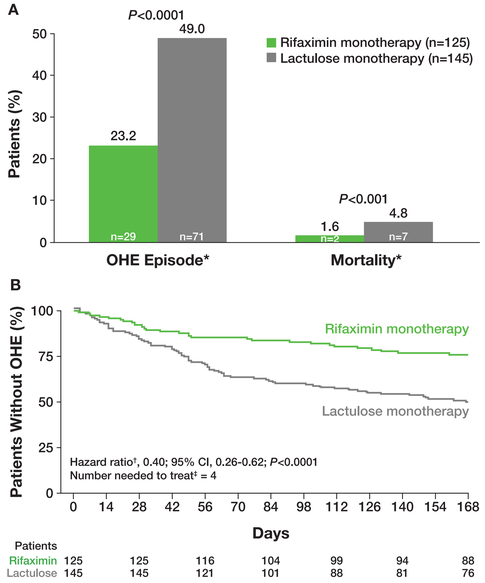
Table 1. Demographic and Baseline Clinical Characteristics

Characteristic	Rifaximin Monotherapy (n=125)	Lactulose Monotherapy (n=145)
Age, y, median (range)	58 (32-83)	57 (21-78)
Male, n (%)	75 (60.0)	99 (68.3)
Race, n (%)		
White	113 (90.4)	126 (86.9)
Black	8 (6.4)	5 (3.4)
Other	4 (3.2)	14 (9.7)
Baseline median MELD score (range)	12 (6-24)	12 (6-23)
MELD category, n (%)*		
≤10	46 (36.8)	39 (26.9)
11-18	74 (59.2)	92 (63.4)
19-24	5 (4.0)	13 (9.0)
Missing data	0	1 (0.7)
Child-Pugh class, n (%)†		
A	54 (43.2)	49 (33.8)
B	64 (51.2)	67 (46.2)
C	7 (5.6)	13 (9.0)
Missing data	0	16 (11.0)
HE episodes during previous 6 months, n (%)		
1-2	106 (84.8)	99 (68.3)
≥3	8 (6.4)	45 (31.0)
Missing data	11 (8.8)	1 (0.7)
Duration of current OHE remission, d, mean (SD)	89.7 (56.0)	73.6 (52.0)‡

*P=0.09 for comparison of rifaximin and lactulose monotherapy data for this category (Chi-square test). †P=0.36 for comparison of rifaximin and lactulose monotherapy data for this category (Chi-square test). ‡Data missing for 1 patient.
MELD = Model for End-Stage Liver Disease; OHE = overt hepatic encephalopathy.

- Significantly fewer patients treated with rifaximin monotherapy experienced an OHE episode versus lactulose monotherapy (23.2% vs 49.0%, respectively; P<0.0001 **Figure 1A**), indicating a 60% reduction in the risk of an OHE event during 6 months of treatment with rifaximin versus lactulose (**Figure 1B**; number needed to treat = 4)

Figure 1. Percentage of Patients (A) Experiencing an OHE Episode or Mortality and (B) Time to First Breakthrough OHE Episode



*Through Day 168. †Hazard ratio for the risk of a breakthrough OHE episode in the rifaximin group compared with the lactulose group. ‡Rifaximin group vs lactose group.
OHE = overt hepatic encephalopathy.

- There was a significantly lower rate of mortality in the rifaximin monotherapy group compared with the lactulose monotherapy group during 6 months of treatment (1.6% vs 4.8%; P<0.001; **Figure 1A**), with a number needed to treat of 19 (HR, 0.048; 95% CI, 0.01-0.29)

- Study discontinuation was higher in the lactulose monotherapy group (62.1%) compared with the rifaximin monotherapy group (36.0%), most commonly due to OHE recurrence
- The most commonly reported adverse events overall (excluding HE) were nausea, fatigue, and peripheral edema (**Table 2**)
  - A higher percentage of patients treated with lactulose monotherapy compared with rifaximin monotherapy reported diarrhea (14.5% vs 4.8%) and vomiting (9.7% vs 4.8%)

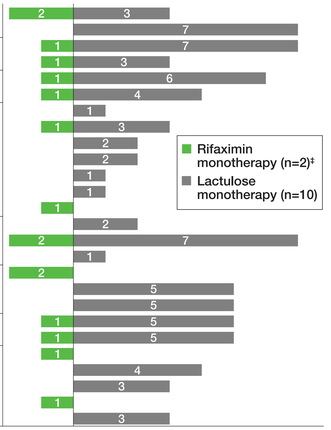
Table 2. Most Common Adverse Events

	Patients, n (%)	
Adverse Event	**Rifaximin monotherapy (n=125)**	**Lactulose monotherapy (n=145)**
≥1 AE	105 (84.0)	126 (86.9)
≥1 drug-related AE	8 (6.4)*	35 (24.1)
≥1 serious AE	44 (35.2)	60 (41.4)
Discontinuation due to an AE	25 (20.0)†	57 (39.3)
Most common (≥6.7%) AEs		
Nausea	17 (13.6)	21 (14.5)
Fatigue	16 (12.8)	18 (12.4)
Peripheral edema	20 (16.0)	13 (9.0)
Constipation	18 (14.4)	10 (6.9)
Urinary tract infection	14 (11.2)	14 (9.7)
Diarrhea	6 (4.8)‡	21 (14.5)
Headache	9 (7.2)	17 (11.7)
Insomnia	14 (11.2)	11 (7.6)
Ascites	9 (7.2)	15 (10.3)
Muscle spasms	10 (8.0)	10 (6.9)
Vomiting	6 (4.8)	14 (9.7)
Abdominal pain	8 (6.4)	11 (7.6)
Anemia	12 (9.6)	6 (4.1)
Asthenia	6 (4.8)	12 (8.3)

Results between the 2 groups were not statistically different unless otherwise indicated; P values calculated using Fisher's exact test. *P<0.0001 vs. lactulose. †P<0.001 vs. lactulose; patients with an AE leading to study discontinuation may have chosen termination due to an AE, breakthrough hepatic encephalopathy, or liver transplant. ‡P=0.008 vs. lactulose.
AE = adverse event.

- Of those who died during the study, only 1 patient (in lactulose group) had a baseline Child-Pugh class C, and 2 patients (1 in each group) had a baseline Model for End-Stage Liver Disease score of ≥19 (**Figure 2**)

Figure 2. Baseline Characteristics in the Mortality Population (n=12)*



*Through follow-up (14 ± 2 days after end of treatment). †At screening. ‡Both patients were from the phase 4 trial.
MELD = Model for End-Stage Liver Disease; OHE = overt hepatic encephalopathy.

CONCLUSIONS

- Rifaximin treatment (eg, monotherapy) was well tolerated and associated with significantly fewer episodes of OHE recurrence than lactulose monotherapy
- Rifaximin treatment may confer a survival benefit in patients with cirrhosis and a history of OHE
- Overall, these data suggest that rifaximin monotherapy may be an appropriate management approach to reduce the risk of OHE recurrence in select patient populations with cirrhosis and a history of OHE episodes

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