POSTER NUMBER
4192

Lower 6-Month All-Cause Mortality Rates With Rifaximin Monotherapy Versus Lactulose Monotherapy in Patients With Cirrhosis and a History of Overt Hepatic Encephalopathy

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INTRODUCTION

- Hepatic encephalopathy (HE) is associated with a poor prognosis,[1] and data suggest that rifaximin use may improve survival[2-4]
- Lactulose monotherapy is recommended as secondary prophylaxis after an initial episode of overt HE (OHE)[5,6]
- 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[5,6]
- Nonadherence to lactulose therapy can precipitate recurrence of HE[7-8]
- Potential barriers to lactulose adherence include[9,10]:
  - Gastrointestinal (GI) adverse effects (eg, diarrhea, nausea, and vomiting)
    - These can lead to dehydration or electrolyte imbalances, which are also precipitating factors of OHE[10,11]
  - 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
- A previous analysis showed that rifaximin monotherapy reduced the risk of a breakthrough OHE episode by 60% versus lactulose monotherapy during 6 months of treatment, with a number needed to treat (NNT) of 4 (hazard ratio [HR], 0.40; 95% CI, 0.26-0.62; *P*<0.001)[12]

AIM

- To compare the rate of all-cause mortality in patients with cirrhosis and a history of OHE treated with rifaximin monotherapy versus lactulose monotherapy

METHODS

- Data were pooled post hoc from 2 randomized trials (one phase 3 double-blind trial[13] and one phase 4 open-label trial[14]) of adults who had cirrhosis and a history of OHE during the previous 6 months and were currently in OHE remission (Conn score ≤1; Table 1)

Table 1. Summary of Key Inclusion and Exclusion Criteria for 2 Trials

Criteria	Phase 3 Trial[13]	Phase 4 Trial[14]
Inclusion criteria	• Aged ≥18 y • ≥2 episodes of OHE (Conn score ≥2) during previous 6 mo • Currently in HE remission (Conn score ≤1) • MELD score ≤25	• Aged ≥18 y • ≥1 episode of OHE (Conn score ≥2) during previous 6 mo • Currently in HE remission (Conn score ≤1)

Table 1. Summary of Key Inclusion and Exclusion Criteria for 2 Trials (Cont.)

Criteria	Phase 3 Trial[13]	Phase 4 Trial[14]
Exclusion criteria	• Current GI bleeding or GI hemorrhage requiring hospitalization and transfusion of ≥2 units of blood ≤3 months before screening • Chronic renal insufficiency (creatinine >2.0 mg/dL) • Chronic respiratory insufficiency • Anemia (hemoglobin <8 g/dL) • Hypovolemia or electrolyte abnormality – Serum sodium <125 mmol/L – Serum calcium >10 mg/dL (2.5 mmol/L) – Potassium <2.5 mmol/L • Intercurrent infection • Active SBP • Portosystemic shunt or TIPS placement ≤3 months before screening • Liver transplantation anticipated ≤1 month after screening	• Current GI bleeding or GI hemorrhage requiring hospitalization and transfusion of ≥2 units of blood ≤3 months before screening • Renal insufficiency requiring dialysis • Chronic respiratory insufficiency • Anemia (hemoglobin <8 g/dL) • Hypovolemia or electrolyte abnormality – Serum sodium <125 mmol/L – Serum calcium >10 mg/dL – Potassium <2.5 mmol/L • Current infection for which oral or parenteral antibiotics are being used • Positive stool test for *Clostridioides difficile* toxin at screening • Active SBP or requires daily prophylactic antibiotics

GI = gastrointestinal; HE = hepatic encephalopathy; MELD = Model for End-Stage Liver Disease; OHE = overt hepatic encephalopathy; SBP = spontaneous bacterial peritonitis; TIPS = transjugular intrahepatic portosystemic shunt.

Treatment and Assessments

- Data were analyzed for patients who received rifaximin 550 mg twice daily (BID; ie, no concomitant lactulose [phase 3 or 4 trials]) or lactulose (titrated to 2-3 soft stools/day) plus placebo (ie, lactulose monotherapy [phase 3 trial]) for up to 6 months*
- In the phase 3 trial, assessments occurred on Day 0 (±1); Days (±2) 7, 14, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, and 168; and during the follow-up visit (14±2 days after the end of treatment)
- In the phase 4 trial, assessments occurred on Day 1; Days (±2) 28, 56, 84, 112, 140, and 168; and during the follow-up visit (14±2 days after the end of treatment)
- Survival data were determined using Kaplan-Meier methodology, HR estimates were obtained using a Cox proportional hazards model with effect for treatment, and *P* values were based on the score statistic unless otherwise indicated

*In the phase 3 trial, rifaximin 550 mg BID or placebo was administered with optional lactulose; in the phase 4 trial, rifaximin 550 mg BID or rifaximin 550 mg BID plus lactulose was administered. Only patients receiving rifaximin alone or lactulose plus placebo ("lactulose alone") were included in the current analysis.

RESULTS

- A total of 270 patients were treated with rifaximin monotherapy (n=125) or lactulose monotherapy (n=145; Table 2)

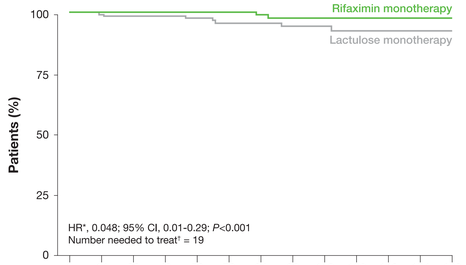
Table 2. Demographic and Baseline Disease Characteristics

Characteristic	Rifaximin Monotherapy (n=125)	Lactulose Monotherapy (n=145)
Age, y		
Mean (SD)	58.2 (9.5)	56.6 (9.3)
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)
Asian	2 (1.6)	7 (4.8)
Other	2 (1.6)	7 (4.8)
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)
Baseline Conn score, n (%)		
0	86 (68.8)	98 (67.6)
1	39 (31.2)	47 (32.4)
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.

- There was a significantly lower mortality rate in the rifaximin monotherapy group compared with the lactulose monotherapy group during 6 months of treatment (1.6% vs 4.8% [Day 168]; *P*<0.001), with an NNT of 19 (Figure 1; HR, 0.048; 95% CI, 0.01-0.29)

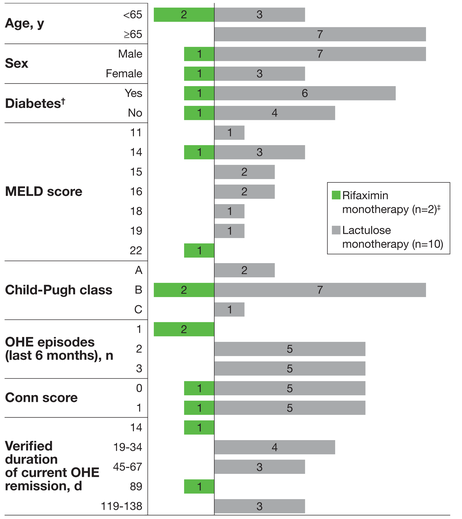
Figure 1. Time To All-Cause Mortality*



*HR for the risk of all-cause mortality in the rifaximin group compared with the lactulose group. †Rifaximin group versus lactose group.
HR = hazard ratio.

- Study discontinuation was higher in the lactulose monotherapy group (62.1%) compared with the rifaximin monotherapy group (36.0%), most commonly due to a breakthrough HE episode (46.2% for lactulose monotherapy and 21.6% for rifaximin monotherapy)
- Through follow-up (14±2 days after end of treatment), mortality was reported in 1.6% of patients in the rifaximin monotherapy group and 6.9% in the lactulose monotherapy group (Figure 2)
- Of those who died during the study, only 1 patient (in lactulose group) met criteria for Child-Pugh class C at baseline, 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) may confer a survival benefit in patients with cirrhosis and a history of OHE
- Rifaximin monotherapy may be an appropriate management approach in select patient populations

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ACKNOWLEDGMENTS: The trials and current analyses were supported by Salix Pharmaceuticals. Technical editorial and medical writing assistance was provided under direction of the authors by Mary Beth Moncrief, PhD, Synchrony Medical Communications, LLC, West Chester, PA. Funding for this assistance was provided by Salix Pharmaceuticals.

DISCLOSURES: JSB and RSR report being clinical trial investigators for Salix Pharmaceuticals. CA, ZH, and RJI are employees of Salix Pharmaceuticals or its affiliates. KVK reports having received grant/research/clinical trial support (paid to institution) from 89bio, Corcept Therapeutics, CymaBay Therapeutics, GENFIT, Gilead, GSK, Hanmi Pharmaceutical, Intercept Pharmaceuticals, Madrigal Pharmaceuticals, Mirum, Novo Nordisk, NGM Bio, Pfizer, Pliant Therapeutics, Terns Pharmaceuticals, and Viking Therapeutics; having served as a consultant/advisory board member for 89bio, CymaBay Therapeutics, Enanta Pharmaceuticals, GENFIT, Gilead, HighTide Therapeutics, Inipharm, Intercept Pharmaceuticals, Madrigal Pharmaceuticals, Mirum, NGM Bio, Pfizer, and Salix Pharmaceuticals; having served on speakers' bureaus for AbbVie, Gilead, and Intercept Pharmaceuticals; and having stock options in Inipharm.

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Research funded by: Salix Pharmaceuticals