Rifaximin and Lactulose Combination Therapy Versus Lactulose Alone for Prevention of Overt Hepatic Encephalopathy Recurrence: A Pooled Analysis of Two Randomized Trials

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INTRODUCTION

- Prognosis of patients with cirrhosis worsens with transition from the compensated to the 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]
  - Preventing or minimizing the occurrence of complications of cirrhosis is critical in the management of patients with cirrhosis[2]
- Overt HE is a common neurologic complication in patients with cirrhosis, with clinical manifestations ranging from personality and/or behavioral changes, asterixis, and time disorientation to confusion and somnolence, and, in the most severely affected, coma[3]
- HE-related US hospitalizations have increased 33% from 2005 to 2014[4]
  - A US claims database analysis reported that patients with decompensated cirrhosis are hospitalized a mean of 2.4 times annually, with an average length of stay of ~7 days[5]
- Rifaximin 550 mg (Xifaxan® [rifaximin] tablets, Salix Pharmaceuticals, Bridgewater, NJ) is a nonsystemic oral agent indicated in the United States for reducing the risk of overt HE recurrence in adults (1 tablet twice daily)[6]
- Practice guidelines from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver state that rifaximin is effective as add-on therapy to lactulose for preventing recurrence of overt HE[3]

AIM

- To examine the efficacy and safety of rifaximin plus lactulose versus lactulose alone as prophylaxis in patients with cirrhosis and a history of overt HE

METHODS

Study Design and Patient Population

- Pooled analysis of 1 double-blind phase 3 trial and 1 open-label phase 4 trial
- Trials included adults with cirrhosis with a history of overt HE during the previous 6 months who were currently in overt HE remission (Conn score ≤1)
- Patients were randomly assigned to receive rifaximin 550 mg twice daily or placebo for up to 6 months
- Lactulose use (titrated to produce 2–3 soft stools per day) was allowed (phase 3 study) or required (treatment arm of phase 4 study)

Assessments

- The time to onset of an overt HE episode (Conn score ≥2; primary endpoint in each study) and time to first HE-related hospitalization (secondary endpoint in each study) were determined
  - Time to either event was defined as the duration between the date of the first dose of study treatment to the date of the event (ie, first overt HE episode, first HE-related hospitalization)
- Analysis of efficacy outcomes was conducted in the intention-to-treat (ITT) population (ie, patients who received ≥1 dose of study treatment); the safety population included all patients in the ITT population (phase 3 trial also required ≥1 post-baseline safety assessment)
- A Cox proportional-hazards model was used with effect for treatment to estimate hazard ratios for breakthrough HE and first HE-related hospitalization, with corresponding *P* values based on the score statistic
- Kaplan-Meier methods were used to estimate the time to breakthrough HE and time to first HE-related hospitalization

RESULTS

Demographics and Baseline Characteristics

- 381 patients were included in the pooled analysis and received rifaximin plus lactulose (n=236) or placebo plus lactulose (ie, lactulose alone; n=145)
- Demographic and baseline disease characteristics were generally comparable between the 2 groups (**Table 1**)

Table 1. Demographic and Baseline Characteristics

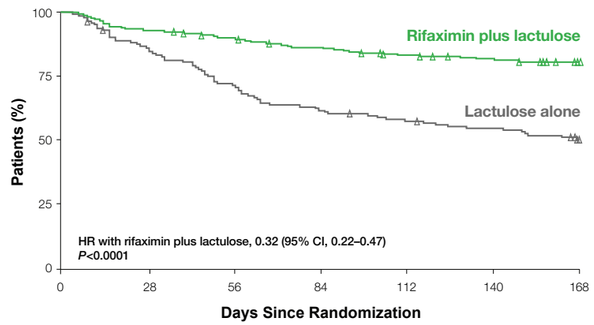
Characteristic	Rifaximin Plus Lactulose (N=236)	Lactulose Alone (n=145)
Age, y, mean (SD)	56.9 (9.7)	56.6 (9.3)
Male sex, n (%)	139 (58.9)	99 (68.3)
Race*, n (%)		
White	206 (87.3)	126 (86.9)
Black	12 (5.1)	5 (3.4)
Asian	5 (2.1)	7 (4.8)
Other†	12 (5.1)	7 (4.8)
Baseline MELD score, mean (SD)	12.5 (3.5)	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 0, n (%)	159 (67.4)	98 (67.6)
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.
†Includes individuals identifying as American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, and other unspecified races.
MELD = Model End-Stage Liver Disease; SD = standard deviation.

Efficacy Outcomes

- Significantly fewer patients treated with rifaximin plus lactulose experienced a breakthrough overt HE episode compared with those treated with lactulose alone during a 6-month period (19.1% vs 49.0%, respectively; *P*<0.0001)
  - Patients receiving rifaximin plus lactulose had a 68% reduction in the risk of a breakthrough overt HE event during 6 months of treatment compared with lactulose alone (hazard ratio [HR], 0.32; 95% confidence interval [CI], 0.22–0.47; **Figure 1**)

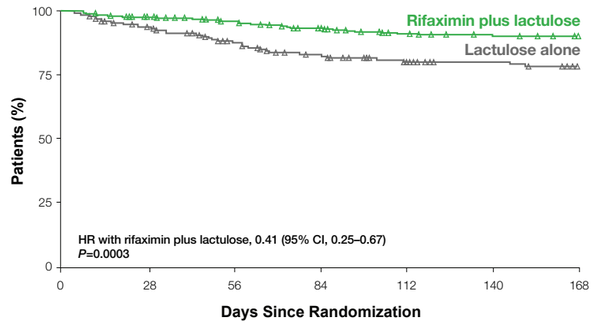
Figure 1. Time to First Breakthrough Overt HE Episode



Δ = censored observation(s); CI = confidence interval; HE = hepatic encephalopathy; HR = hazard ratio.

- In addition, significantly fewer patients treated with rifaximin plus lactulose experienced an overt HE-related hospitalization (11.9%) compared with those treated with lactulose alone (23.4%) during 6 months of treatment, demonstrating a 59% reduction in risk (HR, 0.41; 95% CI, 0.25–0.67; *P*=0.0003; **Figure 2**)

Figure 2. Time to First Overt HE-Related Hospitalization



Δ = censored observation(s); CI = confidence interval; HE = hepatic encephalopathy; HR = hazard ratio.

Safety Outcomes

- Rifaximin plus lactulose was generally well tolerated (**Table 2**)
  - The most common adverse events in the rifaximin plus lactulose group were peripheral edema, HE, nausea, and ascites
  - Fewer patients in the rifaximin plus lactulose group (19.5%) discontinued from the study due to an adverse event versus lactulose alone group (39.3%)
  - The mortality rate during the studies was similar in the rifaximin plus lactulose (5.1%) and lactulose alone (6.9%) groups

Table 2. Summary of Adverse Events

Adverse Event, n (%)	Rifaximin Plus Lactulose (n=236)	Lactulose Alone (n=145)
Any AE	188 (79.7)	126 (86.9)
Any drug-related AE	39 (16.5)	35 (24.1)
Discontinuation due to an AE	46 (19.5)	57 (39.3)
Any serious AE	85 (36.0)	60 (41.4)
Death	12 (5.1)	10 (6.9)
Most common AEs*		
Peripheral edema	35 (14.8)	13 (9.0)
HE	32 (13.6)	45 (31.0)
Nausea	31 (13.1)	21 (14.5)
Ascites	29 (12.3)	15 (10.3)
Diarrhea	28 (11.9)	21 (14.5)
Fatigue	26 (11.0)	18 (12.4)
Insomnia	24 (10.2)	11 (7.6)
Dizziness	23 (9.7)	13 (9.0)
Muscle spasms	23 (9.7)	10 (6.9)
Abdominal pain	20 (8.5)	11 (7.6)
Dyspnea	19 (8.1)	7 (4.8)
Headache	18 (7.6)	17 (11.7)
Constipation	18 (7.6)	10 (6.9)
Abdominal distension	17 (7.2)	12 (8.3)
Pruritus	17 (7.2)	9 (6.2)
Urinary tract infection	16 (6.8)	14 (9.7)
Vomiting	16 (6.8)	14 (9.7)
Cough	15 (6.4)	11 (7.6)
Anxiety	15 (6.4)	7 (4.8)
Depression	15 (6.4)	6 (4.1)
Anemia	13 (5.5)	6 (4.1)
Nasopharyngitis	12 (5.1)	10 (6.9)

*Any AE reported in ≥5.0% of patients in rifaximin plus lactulose group.
AE = adverse event; HE = hepatic encephalopathy.

CONCLUSIONS

- **Rifaximin plus lactulose was efficacious for the reducing of risk of overt HE recurrence and HE-related hospitalization during a 6-month period in patients with cirrhosis and a history of overt HE**
- **Rifaximin plus lactulose should be considered for any patient with cirrhosis with a history of overt HE or who has been hospitalized due to an episode of overt HE**

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DISCLOSURES: KTW reports serving as a speaker for Salix Pharmaceuticals. JSB reports being a consultant for Salix Pharmaceuticals. ZH and RJI report being employees of Salix Pharmaceuticals or its affiliates. AJS reports having stock options in Genfit; being the president of Sanyal Biotechnology; and serving as a consultant to AbbVie, AstraZeneca, Bristol-Myers Squibb Company, DURECT Corporation, Eli Lilly and Company, Enanta Pharmaceuticals, Inc., Galmed Pharmaceuticals Ltd., GENFIT, Gilead Sciences, Inc., Ikaria, Immuron Ltd, Intercept Pharmaceuticals, Inc., Merck & Co., Inc., Nitto Denko Corporation, Novartis, Salix Pharmaceuticals, and Zafgen, Inc.

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