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

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INTRODUCTION

- Rifaximin (Xifaxan®) is indicated for the reduction in risk of overt hepatic encephalopathy (OHE) recurrence in adults
- Practice guidelines recommend rifaximin as an add-on therapy to lactulose for prevention of OHE recurrence[1]
- Diabetes mellitus is a common comorbidity in patients with cirrhosis, and limited published data suggest that comorbid diabetes in patients with cirrhosis may impact the effectiveness of some HE therapies[2,3]

AIM

- To evaluate the efficacy and safety of rifaximin plus lactulose versus lactulose alone in patients with cirrhosis, with or without diabetes

METHODS

Study Design and Patient Population

- Data were pooled from 2 randomized studies (phase 3 randomized, double-blind trial[4] and a phase 4 open-label clinical trial) and included 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 diabetes (yes/no)

Treatment and Assessments

- In the phase 3 trial, rifaximin 550 mg twice daily (BID) 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 the current analysis), rifaximin 550 mg BID plus lactulose (titrated to 2-3 soft stools/day) was administered for 6 months*
- Placebo plus lactulose treatment was defined as "lactulose alone"
- Outcomes assessed included time to onset of OHE episode (Conn score ≥2) and time to first 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

RESULTS

- 135 patients with cirrhosis had comorbid diabetes and 246 patients did not have diabetes at baseline (**Table 1**)
  - At baseline, 78.5% of patients with diabetes had mean MELD scores of 11-24 (median, 13) and 69.1% without diabetes had MELD scores 11-24 (median, 12)

Table. Demographic and Baseline Disease Characteristics

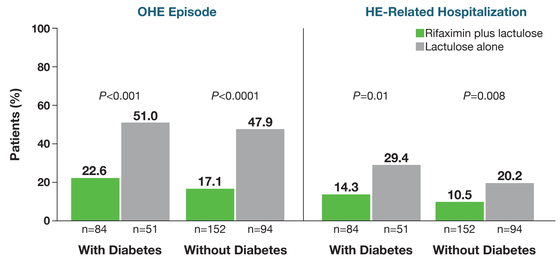
Characteristic	Baseline Diabetes (n=135)		No Baseline Diabetes (n=246)	
	Rifaximin Plus Lactulose (n=84)	Lactulose Alone (n=51)	Rifaximin Plus Lactulose (n=152)	Lactulose Alone (n=94)
MELD				
Mean (SD)	12.7 (3.3)	13.3 (3.6)	12.4 (3.6)	12.6 (3.9)
Median (range)	13 (6-21)	14 (7-23)	12 (6-24)	12 (6-23)
Child-Pugh class, n (%)				
A	28 (33.3)	16 (31.4)	52 (34.2)	33 (35.1)
B	47 (56.0)	27 (52.9)	77 (50.7)	40 (42.6)
C	4 (4.8)	3 (5.9)	16 (10.5)	10 (10.6)
Missing	5 (6.0)	5 (9.8)	7 (4.6)	11 (11.7)
Duration of current OHE remission, d, median	62.0	64.0	53.0	56.0
OHE episodes during previous 6 mo, n (%)				
1-2	61 (72.6)	31 (60.8)	122 (80.3)	68 (72.3)
≥3	18 (21.4)	19 (37.3)	28 (18.4)	26 (27.7)
Missing	5 (6.0)	1 (2.0)	2 (1.3)	0

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

*The rifaximin alone arm was not included in the current pooled analysis.

- Significantly fewer patients treated with rifaximin plus lactulose had an OHE episode compared with lactulose alone during 6 months for those with diabetes (22.6% vs 51.0%; *P*<0.001) and for those without diabetes (17.1% vs 47.9%; *P*<0.0001; **Figure 1**)

Figure 1. Percentage of Patients With an OHE Episode or HE-Related Hospitalization During 6 Months of Treatment



HE = hepatic encephalopathy; OHE = overt hepatic encephalopathy.

- Patients treated with rifaximin plus lactulose had a 64% reduction in risk of OHE recurrence versus lactulose alone (HR, 0.36; number needed to treat [NNT]=3.5 [**Figure 2A**]) during 6 months of treatment among those with diabetes, whereas patients without diabetes had a 70% reduction in risk of OHE recurrence (HR, 0.30; NNT=3.3 [**Figure 2B**])
- Furthermore, significantly fewer patients treated with rifaximin plus lactulose had an HE-related hospitalization compared with lactulose alone among those with diabetes (14.3% vs 29.4%; *P*=0.01) and without diabetes (10.5% vs 20.2%; *P*=0.008; **Figure 1**)
- Patients treated with rifaximin plus lactulose had a 60% reduction in risk of first HE-related hospitalization during 6 months compared with lactulose alone among those with diabetes (HR, 0.40; NNT=6.6 [**Figure 3A**]) and a 59% reduction in risk among those without diabetes (HR, 0.41; NNT=10.3 [**Figure 3B**])
- When comparing the subgroup with diabetes to the group without diabetes, treatment with rifaximin plus lactulose showed similar positive outcomes for rate of OHE episodes (*P*=0.31, with vs without diabetes) and HE-related hospitalizations (*P*=0.34, with vs without diabetes)
- Addition of rifaximin to lactulose was generally well tolerated, regardless of baseline diabetes status (**Table 2**)

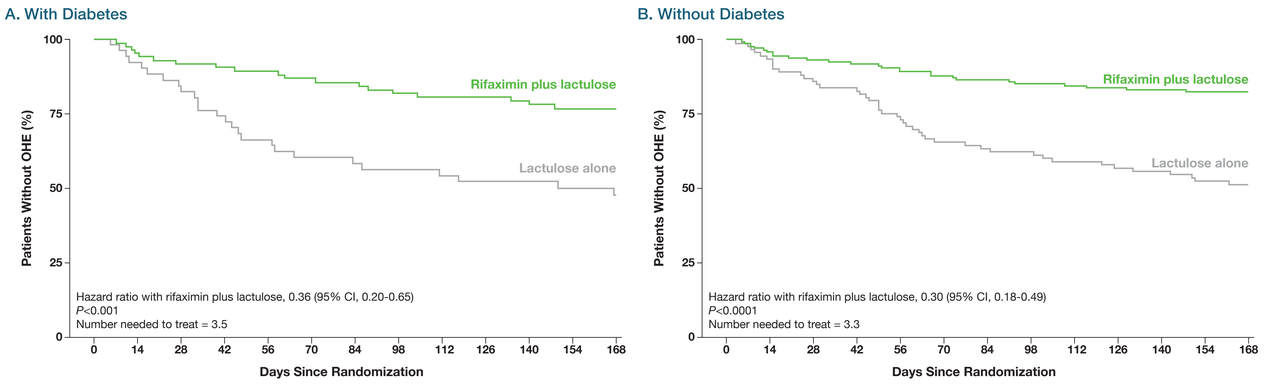
Table 2. Summary of Adverse Events

Patients With an Adverse Event, n (%)	Baseline Diabetes (n=135)		No Baseline Diabetes (n=246)	
	Rifaximin Plus Lactulose (n=84)	Lactulose Alone (n=51)	Rifaximin Plus Lactulose (n=152)	Lactulose Alone (n=94)
Any AE	74 (88.1)	45 (88.2)	114 (75.0)	81 (86.2)
Any serious AE	36 (42.9)	31 (60.8)	49 (32.2)	29 (30.9)
Most common gastrointestinal-related AEs*				
Abdominal discomfort	5 (6.0)	0	2 (1.3)	3 (3.2)
Abdominal distension	6 (7.1)	5 (9.8)	11 (7.2)	7 (7.4)
Abdominal pain	8 (9.5)	5 (9.8)	12 (7.9)	6 (6.4)
Abdominal pain, upper	3 (3.6)	3 (5.9)	7 (4.6)	5 (5.3)
Ascites	14 (16.7)	7 (13.7)	15 (9.9)	8 (8.5)
Constipation	9 (10.7)	2 (3.9)	9 (5.9)	8 (8.5)
Diarrhea	8 (9.5)	8 (15.7)	20 (13.2)	13 (13.8)
Flatulence	2 (2.4)	0	7 (4.6)	5 (5.3)
Nausea	15 (17.9)	8 (15.7)	16 (10.5)	13 (13.8)
Vomiting	6 (7.1)	6 (11.8)	10 (6.6)	8 (8.5)

*>5.0% of patients in any treatment group, ordered alphabetically.
AE = adverse event.

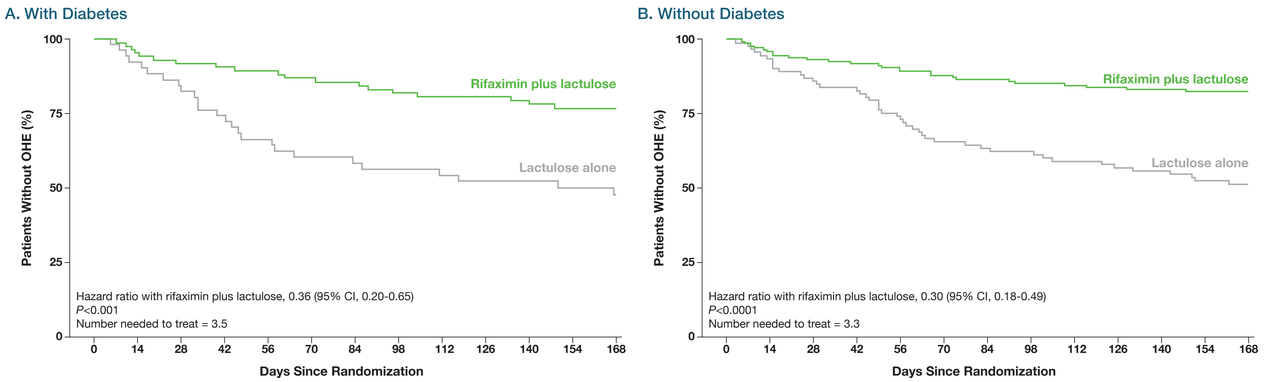
RESULTS

Figure 2. Time to First Breakthrough OHE Episode in Patients With (A) or Without (B) Baseline Diabetes



OHE = overt hepatic encephalopathy.

Figure 3. Time to First HE-Related Hospitalization in Patients With (A) or Without (B) Baseline Diabetes



HE = hepatic encephalopathy.

CONCLUSIONS

- Rifaximin plus lactulose was more efficacious than lactulose alone for reducing the risk of OHE recurrence and HE-related hospitalization in adults, regardless of diabetes status
- Thus, both groups (with/without diabetes) could benefit from the addition of rifaximin to lactulose therapy for reducing the risk of OHE recurrence
- Also, although the sample size was small, comorbid diabetes in patients with cirrhosis does not appear to negatively impact rifaximin effectiveness

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