Identification of Overt Hepatic Encephalopathy Precipitating Factors: a Pooled Analysis of 3 Clinical Trials of Rifaximin Plus Lactulose

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INTRODUCTION

- The shift from the compensated phase of cirrhosis, with favorable prognosis, to the decompensated phase is associated with onset of complications (eg, hepatic encephalopathy [HE]) and a poor prognosis[1]
- Rifaximin (Targaxan/Xifaxan) is indicated in multiple countries for reducing the risk of overt HE (OHE) recurrence in adults; The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) practice guideline recommends rifaximin as an add-on therapy to lactulose for prevention of OHE recurrence[2]
- OHE events have been linked to several precipitating factors, including constipation, dehydration, electrolyte disorders, gastrointestinal bleeding, infections, and lactulose nonadherence[2-4]

AIM

- To summarize precipitating factors associated with breakthrough OHE events in patients who received rifaximin plus lactulose or lactulose alone during 3 clinical trials

METHODS

Study Design and Patient Population

- Data were pooled post hoc from 3 clinical trials
  - 6-month, phase 3, randomized, double-blind, placebo-controlled trial (NCT00298038)[5]
  - 24-month, phase 3, open-label maintenance trial (NCT00686920)[6]
  - 6-month, phase 4, randomized, open-label trial (NCT01842581)
- Adults with cirrhosis who had a history of OHE, were currently in OHE remission (Conn score <2 or ≤2[6]), and were treated with either rifaximin 550 mg twice daily plus lactulose or lactulose alone were included in the analysis
- During the trials, investigators were asked to record any identified contributing factors or precipitating events for each OHE episode
- Analyses were conducted in the safety population (all patients randomly assigned to treatment who ingested ≥1 dose of study drug)
- *P* values were determined using the Fisher exact test

RESULTS

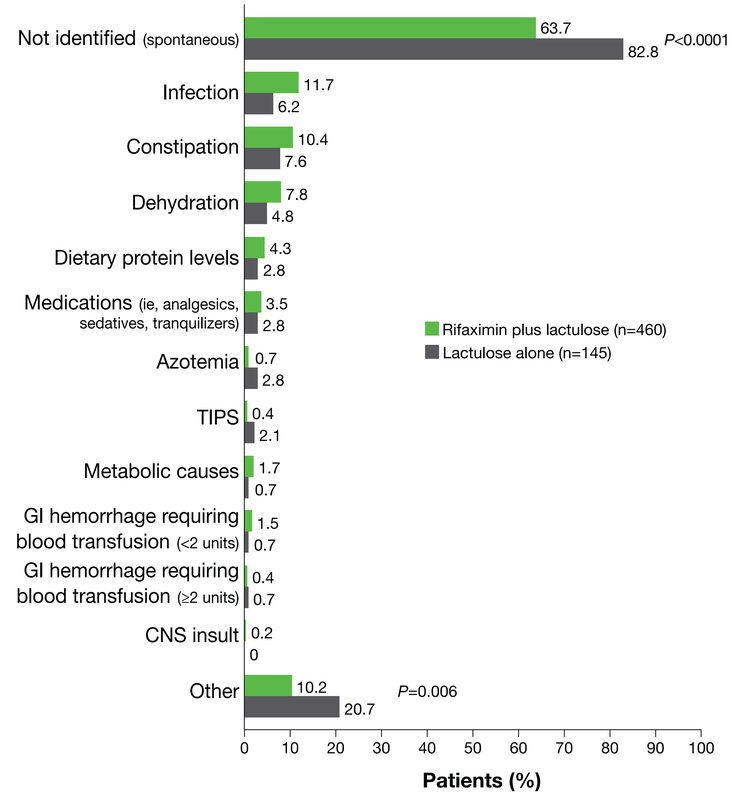
- A total of 605 patients were included in the analysis (rifaximin plus lactulose [n=460]; lactulose alone [n=145])
- Most baseline demographic and disease characteristics were generally comparable between the 2 treatment groups (**Table**)
- Overall, commonly identified precipitating factors were infection, constipation, and dehydration, each observed in a comparable percentage of patients in each treatment group (*P*≥0.05; **Figure**)
  - However, precipitating factors were not identified (ie, spontaneous events) in a majority of patients in the rifaximin plus lactulose and lactulose alone groups (63.7% vs 82.8%, respectively; *P*<0.0001)

Table. Demographics and Baseline Disease Characteristics (Safety Population)

Characteristic	Rifaximin Plus Lactulose (n=460)	Lactulose Alone (n=145)
Age, y, mean (SD)	57.1 (9.3)	56.6 (9.3)
Age group, n (%)		
<55 y	179 (38.9)	54 (37.2)
≥55 y	281 (61.1)	91 (62.8)
Male sex, n (%)	278 (60.4)	99 (68.3)
Race, n (%)		
Black	20 (4.3)	5 (3.4)
White	414 (90.0)	126 (86.9)
MELD score*, mean (SD)	12.7 (3.8)	12.9 (3.8)
MELD score category*, n (%)		
≤10	133 (28.9)	39 (26.9)
11-18	287 (62.4)	92 (63.4)
19-24	34 (7.4)	13 (9.0)
≥25	2 (0.4)	0
Conn score, mean (SD)	0.4 (0.5)	0.3 (0.5)
Mean number of HE episodes during previous 6 mo (SD)†	2.1 (1.3)	2.5 (0.9)

*Missing data for 4 patients in rifaximin plus lactulose group and 1 patient in lactulose alone group. †Missing data for 8 patients in rifaximin plus lactulose group and 1 patient in lactulose alone group. HE = hepatic encephalopathy; MELD = Model End Stage Liver Disease; SD = standard deviation.

Figure. Precipitating Factors of Breakthrough OHE Events



CNS = central nervous system; GI = gastrointestinal; OHE = overt hepatic encephalopathy; TIPS = transjugular intrahepatic portosystemic shunt.

- Results were generally similar when data were analyzed by sex (male or female) or age (<55 years; ≥55 years; data not shown)

CONCLUSIONS

- **The AASLD/EASL guideline recommends that OHE precipitating factors be identified and corrected to improve treatment outcomes[2]**
- **In this analysis, in both treatment groups (rifaximin plus lactulose and lactulose alone), infection, constipation, and dehydration were the most commonly identified precipitating factors for OHE events in patients with a history of OHE**
- **In most cases, no specific OHE precipitating factor was identified; therefore, empiric therapy should be promptly initiated, while contributing factors are being identified**
- **Prevention or early identification of OHE precipitating factors is an important component of an overall disease management strategy to reduce the risk of OHE recurrence and HE-related hospitalizations**

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