POSTER NUMBER

SAT517

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

Arun B. Jesudian, MD[1]; Arun J. Sanyal, MD[2]; Robert S. Brown, Jr., MD, MPH[1]; Zeev Heimanson, PharmD[3]; Robert J. Israel, MD[3]; Jasmohan S. Bajaj, MD[2,4]

[1]Weill Cornell Medicine, New York, NY, USA; [2]Virginia Commonwealth University, Richmond, VA, USA; [3]Salix Pharmaceuticals, Bridgewater, NJ, USA; [4]McGuire VA Medical Center, Richmond, VA, USA

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

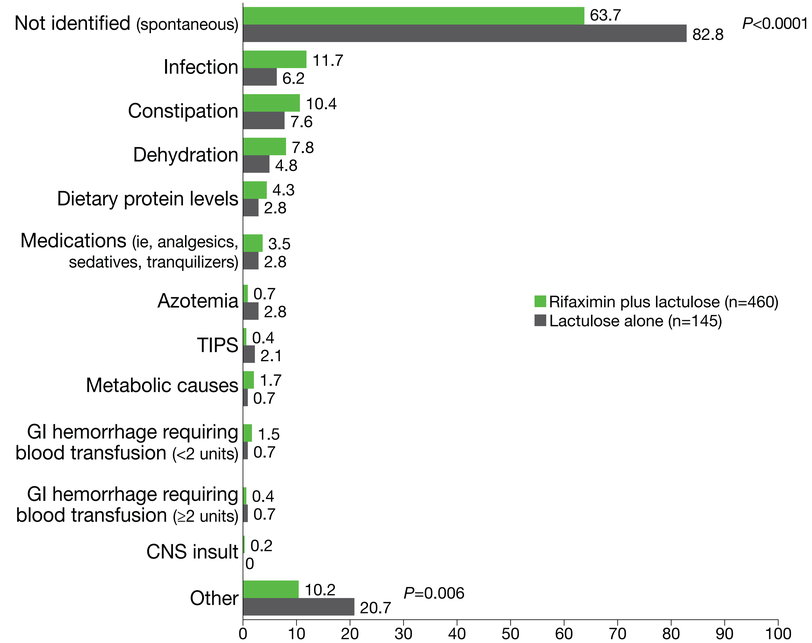
- A total of 605 patients were included in the analysis (rifaximin plus lactulose [n=460]; lactulose alone [n=145])
- Most baseline demographic and disease characteristics were generally comparable between the 2 treatment groups (**Table**)
- Overall, commonly identified precipitating factors were infection, 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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ACKNOWLEDGMENTS: The trials and current analyses were supported by Salix Pharmaceuticals. Technical editorial and medical writing assistance were provided under direction of the authors by Mary Beth Moncrief, PhD, and Sophie Bolick, PhD, Synchrony Medical Communications, LLC, West Chester, PA. Funding for this assistance was provided by Salix Pharmaceuticals.

DISCLOSURES: ABJ reports being a consultant for and receiving speaker fees from Salix Pharmaceuticals. AJS reports receiving research funding (paid to his institution) from Boehringer Ingelheim, Bristol-Myers Squibb, Conatus Pharmaceuticals Inc., Cumberland Pharmaceuticals Inc, Echosens, Gilead Sciences, Inc, Immuron, Intercept Pharmaceuticals, Inc, Mallinckrodt Pharmaceuticals, Merck & Co, Inc, Novartis, and Sequana Therapeutics, Inc; serving as a consultant for ARTham Therapeutics, AstraZeneca, Bird Rock Bio, Blade, Conatus Pharmaceuticals Inc., Echosens, Eli Lilly, Gilead Sciences, Inc, Glympse, HemoShear, MedImmune (AstraZeneca), NASH Pharmaceuticals Inc, Novartis, Novo Nordisk, Pfizer Inc, ProSciento, Inc, Salix Pharmaceuticals, Sanofi, Terns Pharmaceuticals, and Teva Pharmaceutical Industries Ltd; serving as a scientific advisor for Albireo Pharma, Inc, AstraZeneca, and MedImmune; ownership of Sanyal Biotechnology; being a stock shareholder of DURECT Corp, Exhalenz, Galmed Pharmaceuticals Ltd, Genfit, Indalo Therapeutics, and Tiziana Life Sciences plc; and research collaborations with CymaBay, LabCorp, and Second Genome. RSB Jr. reports being a consultant for and receiving research support from Salix Pharmaceuticals. ZH and RJI are employees of Salix Pharmaceuticals or its affiliates. JSB reports being a consultant for Salix Pharmaceuticals.

The International Liver Congress™ 2022 (ILC 2022): Annual Meeting of the European Association for the Study of the Liver • June 22–26, 2022 • London, United Kingdom

Research funded by: Salix Pharmaceuticals