POSTER NUMBER
1774

Precipitating Factors of Overt Hepatic Encephalopathy Occurrence: an Analysis of 3 Rifaximin Clinical Trials

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INTRODUCTION

- Hepatic encephalopathy (HE) is a common and debilitating neurologic complication of cirrhosis[1] and is a frequent cause of hospitalization in individuals with cirrhosis[2-4]
- Rifaximin, a nonsystemic oral antibiotic, is indicated in the United States for reduction in risk of overt HE (OHE) recurrence in adults[5]
  - The efficacy and safety of rifaximin 550 mg twice daily for the prevention of OHE recurrence have been well established in clinical trials[6-8]
- The occurrence/recurrence of OHE episodes has been associated with several precipitating factors, including dehydration, constipation, infections, acute renal failure, and lactulose nonadherence[9,10]

OBJECTIVE

- To summarize precipitating factors associated with breakthrough OHE events in patients with cirrhosis recorded during 3 clinical trials

METHODS

- Data were pooled for 3 trials of adults with cirrhosis who had a history of OHE and were in OHE remission at the time of the study (Table 1)
- During these studies, rifaximin 550 mg was administered twice daily; rifaximin- and placebo-treated patients may have received concomitant lactulose (Table 1)

Table 1. Trial Summaries

Study	Study Design	Key Inclusion Criteria		Treatment*	Treatment Duration, mo
RFHE3001 (NCT00298038)[6]	Randomized, double-blind, placebo-controlled	• Adults aged ≥18 y • History of ≥2 OHE episodes	• Currently in OHE remission† • MELD score ≤25	Rifaximin (n=140) Placebo (n=159)	6
RFHE3002 (NCT00686920)[7]	Open-label maintenance‡	• Adults aged ≥18 y • History of OHE episodes	• Currently in OHE remission§	Rifaximin (n=322)	24
RFHE4044 (NCT01842581)	Randomized, open-label, active-controlled	• Adults aged ≥18 y • History of ≥1 OHE episode	• Currently in OHE remission†	Rifaximin without lactulose (n=113) Rifaximin + lactulose (n=108)	6

*Patients in RFHE3001 and RFHE3002 were permitted to take concomitant lactulose during the study; in RFHE4044, patients were randomly assigned to receive rifaximin alone (ie, no lactulose) or rifaximin plus lactulose (self-titrated to produce 2-3 soft stools/day).
†Conn score <2. ‡Patients from RFHE3001 were permitted to enroll. §Conn score ≤2.
MELD = Model for End-stage Liver Disease; OHE = overt hepatic encephalopathy.

- For each breakthrough OHE episode, investigators were asked to record contributing factors or precipitating events, if one (or more) could be identified
- Patients participating in both the double-blind, randomized controlled trial and maintenance study were counted as separate patients in the current analysis
- Data were summarized using descriptive statistics

RESULTS

- The current analysis included 842 adults (rifaximin group [n=683]; placebo group [n=159]) with a history of OHE episodes (Table 2)

Table 2. Demographics and Baseline Characteristics

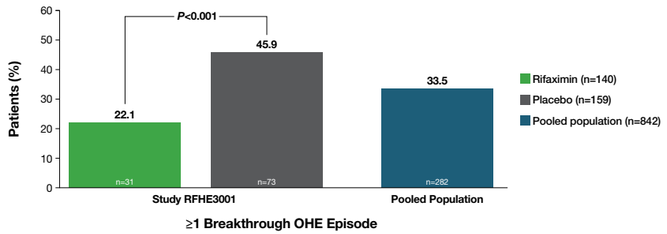
Parameter	Placebo* (n=159)	All Rifaximin (n=683)	Total Population (n=842)
Age, y, mean	56.8	55.5–58.4†	55.5–58.4†
Male sex, n (%)	107 (67.3)	410 (60.0)	517 (61.4)
Race, n (%)			
White	139 (87.4)	611 (89.5)	750 (89.1)
Black	5 (3.1)	33 (4.8)	38 (4.5)
Asian	8 (5.0)	15 (2.2)	23 (2.7)
Other/Unknown	7 (4.4)	24 (3.5)	31 (3.7)
Conn score, n (%)			
0	107 (67.3)	458 (67.1)	565 (67.1)
1	52 (32.7)	213 (31.2)	265 (31.5)
2	0	12 (1.8)	12 (1.4)
Concomitant lactulose use, n (%)	145 (91.2)	518 (75.8)	663 (78.7)
Prior HE episodes, n (%)‡			
1	0	247 (36.2)	247 (29.3)
2	111 (69.8)	260 (38.1)	371 (44.1)
3	35 (22.0)	88 (12.9)	123 (14.6)
≥4	12 (7.5)	69 (10.1)	81 (9.6)
Unknown	1 (0.6)	19 (2.8)	20 (2.4)

*Data from study RFHE3001.[6] †Range of means reported across the 3 trials. ‡During the previous 6 months for studies RFHE3001 and RFHE3002 and the previous 12 months for RFHE4044.
HE = hepatic encephalopathy.

RESULTS

- During the 3 trials, breakthrough OHE episodes were experienced by approximately one-third of the 842 rifaximin- or placebo-treated patients (Figure 1)
  - In RFHE3001 (double-blind, placebo-controlled study), breakthrough OHE events occurred significantly less often in the rifaximin group compared with the placebo group during 6 months of treatment (hazard ratio, 0.42; 95% confidence interval, 0.28–0.64; $P<0.001$)[6]

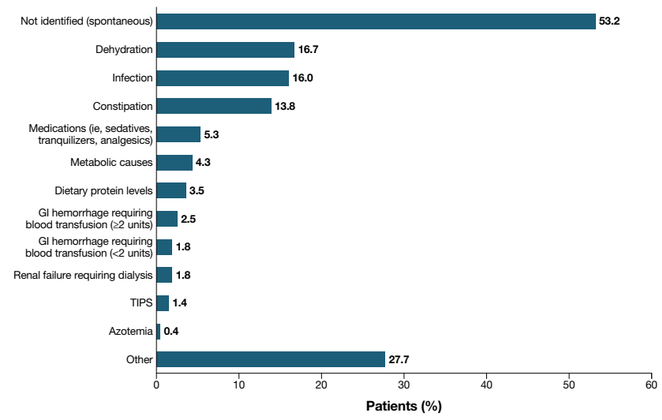
Figure 1. Breakthrough OHE Episodes (Study RFHE3001 and Pooled Population)



OHE = overt hepatic encephalopathy.
Data for Study RFHE3001 from Bass NM, et al. *N Engl J Med.* 2010;362(12):1071-1081.[6]

- For the 282 rifaximin- or placebo-treated patients with ≥1 breakthrough OHE episode during the 3 studies, the most common precipitating factors were dehydration, infection, and constipation (Figure 2)
  - No precipitating factor(s) were identified for an OHE episode for more than half of the patients (ie, spontaneous event)

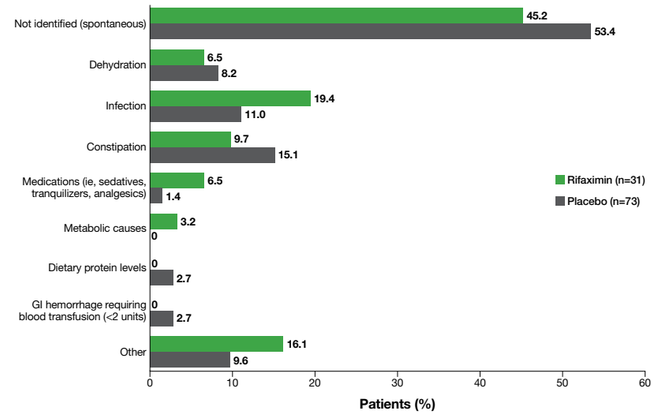
Figure 2. Precipitating Factors of Breakthrough OHE Events in Patients With ≥1 Breakthrough OHE Episode in Pooled Population (n=282)*



*Rifaximin- or placebo-treated patients.
GI = gastrointestinal; OHE = overt hepatic encephalopathy; TIPS = transjugular intrahepatic portosystemic shunt.

- In Study RFHE3001, there were some differences between the 2 treatment groups in the frequency of precipitating factors for OHE (Figure 3)

Figure 3. Precipitating Factors of Breakthrough OHE Events During Treatment With Rifaximin Versus Placebo (Study RFHE3001)*



*Patients with ≥1 breakthrough OHE episode. No patient in either treatment group had a GI hemorrhage requiring blood transfusion ≥2 units, renal failure requiring dialysis, transjugular intrahepatic portosystemic shunt, or azotemia recorded as precipitating factors.
GI = gastrointestinal; OHE = overt hepatic encephalopathy.

CONCLUSIONS

- **In this pooled analysis, the most commonly identified precipitating factors for breakthrough overt HE events in patients with cirrhosis and a history of overt HE were dehydration, infection, and constipation**
- **Because a cause was not identified in the majority of breakthrough OHE cases, empiric therapy should be promptly initiated in the clinic while precipitating factors are being identified**
- **Prevention or early identification of precipitating factors is an important part of an overall 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, Synchrony Medical Communications, LLC, West Chester, PA. Funding for this assistance was provided by Salix Pharmaceuticals.

DISCLOSURES: SLF reports serving on the speakers' bureau for AbbVie, Gilead Sciences, Inc., Intercept Pharmaceuticals, Inc., and Salix Pharmaceuticals; and receiving research support from DURECT Corporation and Gilead Sciences, Inc. ZH is an employee of Salix Pharmaceuticals. RJI is an employee of Salix Pharmaceuticals or its affiliates. ABJ reports serving as a consultant for and on the speakers' bureau for Salix Pharmaceuticals.

AASLD The Liver Meeting Digital Experience™ 2020 • November 13–16, 2020

Research funded by: Salix Pharmaceuticals