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# Lactulose Withdrawal Can Potentiate Breakthrough Overt Hepatic Encephalopathy in Patients Controlled With Rifaximin Plus Lactulose Therapy: a Post Hoc Analysis of a Randomized Controlled Trial

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## INTRODUCTION

- Hepatic encephalopathy (HE) is a recurrent complication of cirrhosis[1]
- Rifaximin 550 mg is a nonsystemic antibiotic indicated in multiple countries as twice-daily (BID) therapy for the prevention of overt HE recurrence in adults[2]
  - In a phase 3, randomized, double-blind study, rifaximin 550 mg BID for 6 months reduced the risk of overt HE recurrence and risk of HE-related hospitalization versus placebo (91% of patients in each group were on concomitant lactulose)[3]
  - An open-label study affirmed that a reduction in HE-related hospitalizations was maintained during long-term treatment with rifaximin (≥2 years)[4]
- Guidelines from the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommend prophylaxis to prevent HE recurrence in patients who have had an episode of overt HE[1]
  - Lactulose for prevention of HE recurrence after an initial HE episode is recommended, with rifaximin as add-on therapy after a second HE episode is observed
  - A 2019 systematic review supported that concomitant long-term treatment with rifaximin plus lactulose was more efficacious in reducing the risk of overt HE recurrence and HE-related hospitalization versus lactulose alone[5]
- However, given the potential issues with adherence and potential adverse effects (eg, bloating, nausea) with lactulose therapy,[6,7] a study was conducted to evaluate rifaximin alone versus rifaximin + lactulose therapy in patients with a history of overt HE
  - Based on the clinical trial design, patients may have had alterations (eg, withdrawal or addition) of HE prophylactic medications prior to randomization

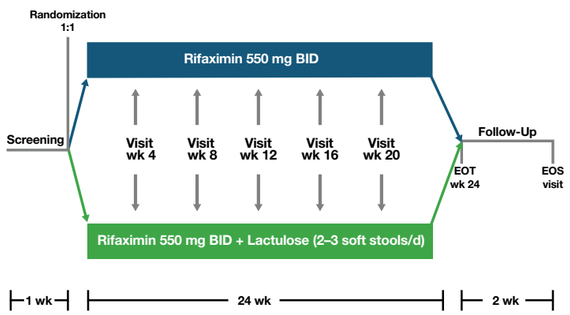
## AIM

- To explore the impact of HE medication changes necessitated by trial design on HE recurrence over 6 months

## METHODS

- The study was a randomized, multicenter, open-label, phase 4 trial of rifaximin alone versus rifaximin + lactulose (ClinicalTrials.gov identifier: NCT01842581; Figure 1)

### Figure 1. Study Design




BID = twice daily; EOS = end of study; EOT = end of treatment.

- Adults with cirrhosis, a history of ≥1 overt HE episode (Conn score ≥2) during the previous 6 months, and current HE remission (Conn score ≤1) were eligible for inclusion
- Exclusion criteria included current gastrointestinal bleeding, anemia (hemoglobin <8 g/dL), renal insufficiency requiring routine dialysis, active spontaneous bacterial peritonitis, or need for daily antibiotic prophylaxis
- HE prophylactic medications were withdrawn from patients at least 1 day prior to random assignment to open-label rifaximin 550 mg BID or rifaximin 550 mg BID + lactulose (self-titrated to 2-3 soft stools/d) for 24 weeks (Figure 2)

## METHODS

### Figure 2. Possible HE Medication Changes Upon Randomization


*HE prophylaxis medication changes upon randomization; per protocol.
HE = hepatic encephalopathy.

- The protocol-defined primary efficacy endpoint was time to first breakthrough overt HE episode (Conn score ≥2)
- HE events were captured up to time of last patient contact, and data were analyzed post hoc based on HE medication withdrawal prior to randomization

## RESULTS

- Demographics and baseline characteristics were generally similar between the rifaximin alone group (n=113) and the rifaximin + lactulose group (n=108; Table 1)

### Table 1. Demographics and Baseline Characteristics

| Parameter | Rifaximin Alone (n=113) | Rifaximin + Lactulose (n=108) |
|---|---|---|
| Age, y, mean (SD) | 58.1 (9.5) | 58.8 (9.5) |
| Male sex, n (%) | 69 (61.1) | 70 (64.8) |
| Race, n (%) | | |
| White | 102 (90.3) | 99 (91.7) |
| Black | 7 (6.2) | 6 (5.6) |
| Other/Unknown | 4 (3.5) | 3 (2.8) |
| Child-Pugh classification | | |
| A | 46 (40.7) | 42 (38.9) |
| B | 61 (54.0) | 62 (57.4) |
| C | 6 (5.3) | 4 (3.7) |
| MELD score, mean (SD) | 11.9 (3.6) | 11.8 (3.2) |
| Conn score, n (%) | | |
| 0 | 78 (69.0) | 74 (68.5) |
| 1 | 35 (31.0) | 34 (31.5) |

MELD = Model for End-Stage Liver Disease; SD = standard deviation.

- >70% of patients across treatment arms had their prior HE medications removed 1 day prior to randomization
- At randomization, a greater percentage of patients assigned to the rifaximin + lactulose group had rifaximin and/or lactulose added; conversely, a greater percentage of patients assigned to the rifaximin alone group had lactulose withdrawn (Table 2)
  - In the rifaximin alone group, 67.3% of patients had lactulose withdrawn versus 0% in the rifaximin + lactulose group

### Table 2. HE Prophylaxis Medication Changes*

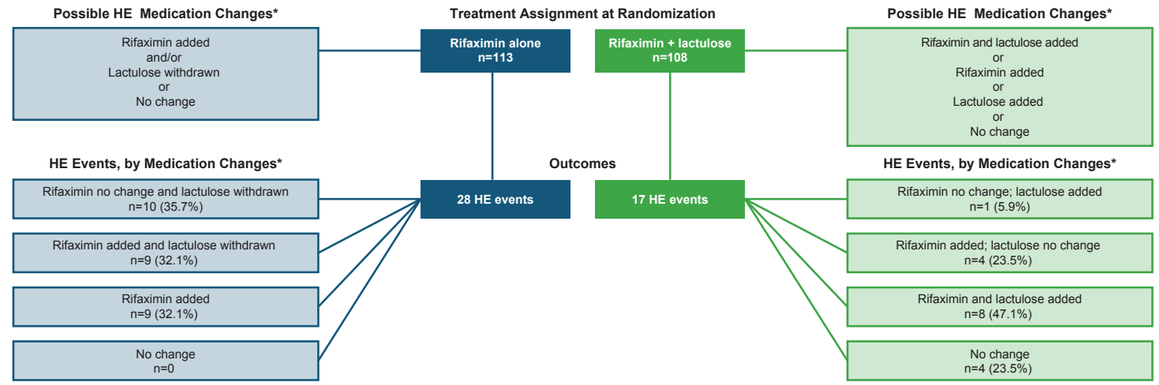
| | Patients, n (%) | |
|---|---|---|
| HE Medication Changes | Rifaximin Alone (n=113) | Rifaximin + Lactulose (n=108) |
| Rifaximin added | 73 (64.6) | 81 (75.0) |
| Lactulose added | – | 39 (36.1) |
| Rifaximin and lactulose added | – | 31 (28.7) |
| Lactulose withdrawn | 76 (67.3) | – |
| No changes | 9 (8.0) | 19 (17.6) |

*HE prophylaxis medication changes upon randomization; per protocol. Patients may have had >1 medication change, thus values total >100%.
HE = hepatic encephalopathy.

## RESULTS

- Breakthrough overt HE events occurred more often in the rifaximin alone group (n=28) compared with the rifaximin + lactulose group (n=17; Figure 3)
  - None of the 9 patients in the rifaximin alone group who were taking rifaximin prior to randomization (ie, no treatment change) had an overt HE event
- Breakthrough overt HE events in the rifaximin alone group occurred most frequently in patients who had lactulose withdrawn at randomization (19/28 [67.9%]), and the rate (67.9%) was higher than that observed for patients in the rifaximin + lactulose group who continued lactulose (8/17 [47.1%]; Figure 3)
- In addition, time to first overt HE breakthrough event data showed that the rifaximin alone group had >2 times more overt HE events versus the rifaximin + lactulose group (17 [15.0%] vs 7 [6.5%]) during the first 56 days after randomization

### Figure 3. Overt HE Events Subgrouped by HE Medication Changes at Randomization*




*HE prophylaxis medication changes upon randomization; per protocol.
HE = hepatic encephalopathy.

- In the rifaximin + lactulose group, the greatest percentage of patients with overt HE events were those with a history of HE who were not receiving any HE prophylaxis (lactulose or rifaximin) at study entry (47.1%; Figure 3)
  - The lack of HE prophylaxis at study entry in patients who had a history of HE conflicts with AASLD/EASL practice guidelines, which recommend prophylaxis (lactulose; rifaximin add-on therapy) for prevention of HE recurrence in patients with a history of overt HE[1]
  - Notably, this percentage (47.1%) was higher versus patients who were on 1 prophylactic therapy (monotherapy) prior to study entry and had a second therapy prescribed (lactulose added [5.9%] or rifaximin added [23.5%])
    - One hypothesis is that for patients at risk (ie, history of overt HE), the lack of institution of prophylactic therapy for prevention of overt HE recurrence after that first HE episode may limit the effectiveness of therapeutics added later in the progression of cirrhosis; therefore, early adoption of HE prophylactic therapies after the first overt HE episode is critical to minimize patient risk for additional HE episodes

## CONCLUSIONS

- **Guidelines recommend rifaximin as an effective add-on therapy to lactulose for the prevention of overt HE recurrence**
- **Lactulose and rifaximin may play a synergistic role in the prevention of overt HE recurrence**
- **Withdrawal of lactulose at randomization was associated with a higher risk of overt HE recurrence in patients tolerating combination therapy in this study and may have affected study outcomes in the rifaximin alone group**

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