Rifaximin Is Safe and Well Tolerated for Long-term Maintenance of Remission From Overt Hepatic Encephalopathy

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BACKGROUND & AIMS: **Rifaximin is a gut-selective, oral antimicrobial agent shown to reduce the recurrence of overt hepatic encephalopathy (HE) and HE-related hospitalizations in a 6-month, randomized, controlled trial (RCT). We performed a phase 3, open-label maintenance study to assess the safety and rate of hospitalization with long-term rifaximin use.**

METHODS: **We conducted a 24-month, open-label maintenance study of rifaximin (550 mg, twice daily) in patients with HE who participated in the previous RCT of rifaximin or new patients enrolled from March 2007 to December 2010. Safety was assessed (adverse events, clinical laboratory parameters) for the integrated population of all patients, who were given rifaximin 550 mg twice daily (all-rifaximin population, N = 392). Safety and hospitalization data were compared between the group given placebo in the original RCT (n = 159) and those given rifaximin (n = 140).**

RESULTS: **In the all-rifaximin population, the median exposure to rifaximin was 427.0 days (range, 2–1427 d), with 510.5 person-years of exposure. The profile and rate of adverse events with long-term rifaximin treatment were similar to those of the original RCT. There was no increase in the rate of infections, including with *Clostridium difficile*, or development of bacterial antibiotic resistance. Rates of hospitalizations with long-term rifaximin administration remained low: the HE-related hospitalization rate, normalized for exposure (0.21; all-rifaximin population), was similar to that of the rifaximin group in the original RCT (0.30), and lower than that for the placebo group (0.72).**

CONCLUSIONS: **Long-term treatment (≥24 mo) with rifaximin (550 mg, twice daily) appears to provide a continued reduction in the rate of HE-related and all-cause hospitalization, without an increased rate of adverse events. ClinicalTrials.gov number: NCT00686920.**

Keywords: Xifaxan; Cirrhosis; Chronic Liver Disease; Antimicrobial Agent.

Hepatic encephalopathy (HE) is a serious and potentially progressive neurologic syndrome in patients with cirrhosis. The neuropsychiatric symptoms and neuromuscular dysfunction associated with HE significantly contribute to the clinical and socioeconomic burden of chronic liver disease for patients and their caregivers.[1,2] HE frequently results in hospitalizations[3] and is associated with decreased survival in patients with cirrhosis.[4,5] Prevention of HE episodes may improve outcomes for patients while awaiting transplantation and improve post-transplant function.[4,5] A long-term therapeutic intervention to prevent recurrent HE is needed to decrease health care burden, improve quality of life, and improve outcomes for chronically ill patients.

Historically, lactulose and lactitol (available outside of the United States), and antibiotics have been used as short-term overt HE treatments.[6,7] The presumed mechanism of action is a reduction in the burden of neurotoxins derived from both intestinal enterocyte metabolism (via glutaminase) and gut bacterial metabolism that may contribute to altered mental status; these toxins accumulate as a result of liver dysfunction and portosystemic shunting in patients with cirrhosis and portal hypertension.[8] Lactulose therapy can prevent recurrent HE[9]; however, long-term use is limited by

Abbreviations used in this paper: AE, adverse event; HE, hepatic encephalopathy; OLM, open-label maintenance study; PYE, person-years of exposure; RCT, randomized controlled trial.

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numerous adverse effects, often resulting in nonadherence to therapy.[10]

Rifaximin (Xifaxan; Salix Pharmaceuticals, Inc, Raleigh, NC) is an oral antimicrobial agent with broad-spectrum activity that is gut-selective and nonsystemic.[11] Rifaximin appears to have a low level of selection for resistant bacterial mutants[12] and may not confer the same risks as those associated with systemic antibiotics. In a randomized, double-blind trial, rifaximin therapy significantly reduced the risk of overt HE recurrence and HE-related hospitalizations during a 6-month period in patients with cirrhosis and a recent history of recurrent, overt HE.[13] The safety profile was favorable and indistinguishable from that of placebo. Nevertheless, theoretical concerns remain regarding the safety and durability of treatment response during long-term antibiotic use.

The objectives of this open-label study were to examine the effect of long-term (≥24 mo) rifaximin administration on safety, survival, underlying disease, and rate of hospitalizations in patients with cirrhosis and recurrent HE.

Methods

Patients

Males and females 18 years of age and older were eligible if they had a history of overt HE episodes with documented severity of Conn score of 2 or higher within 12 months before screening, and a Conn score of 2 or less at enrollment. Patients from a previous randomized controlled trial (RCT) (ClinicalTrials.gov number: NCT00298038) were permitted to enroll. Exclusion criteria included history of allergy to rifampin or rifaximin, renal insufficiency (serum creatinine level, >2.0 mg/dL), severe anemia (hemoglobin level, <8 g/dL), clinically significant hypovolemia or any electrolyte abnormality that could affect mental function (eg, serum sodium level, <125 mEq/L; serum calcium level, >10 mg/dL), severe hypokalemia (serum potassium level, <2.5 mEq/L), intestinal obstruction, active inflammatory bowel disease, diagnosis of human immunodeficiency virus, history of active tuberculosis, or current spontaneous bacterial peritonitis. The study protocol and the informed consent form were approved by the institutional review boards of each center. The trial complied with the Declaration of Helsinki. All enrolled patients or their legally authorized representatives provided informed consent. Patients were enrolled from March 2007 to December 2010.

Study Design, Intervention, and Assessments

This study was a phase 3, multicenter, open-label maintenance study (OLM) (ClinicalTrials.gov number: NCT00686920) evaluating oral rifaximin 550 mg administered twice daily for 24 months or more. Concomitant therapy with lactulose was optional. Clinic visits occurred at 1 and 3 months, and then every 3 months until the end of treatment, followed by a 2-week posttreatment clinic visit. Patients also were monitored by telephone 2 weeks after beginning rifaximin, and then every 6 weeks after the third month until the end of treatment.

The primary objective was to evaluate the long-term safety of rifaximin 550 mg twice daily. Adverse events (AEs) were assessed during each clinic visit and telephone interview, vital sign measurements, hematology, blood chemistry, urinalysis, and coagulation tests were conducted during each clinic visit, and a physical examination was conducted during the end-of-treatment visit and during clinic visits as needed to evaluate patient symptoms. Data on infections were captured from the AE database. Data on *Clostridium difficile* infections were investigated further to evaluate the clinical context, nature, and outcome of the infection. Data on hospitalizations were collected prospectively as part of the primary objective to analyze safety. Hospitalization data were investigated further and compared post hoc to assess the rate of HE-related and all-cause hospitalizations. Overall, the inclusion/exclusion criteria and safety evaluations and definitions were consistent with those in the RCT clinical trial,[13] with the exception of enrollment of patients with Conn scores of 2 in the OLM.

Statistical Analyses

The planned sample size for the OLM was approximately 300 patients. All analyses were performed for the safety population, defined as all patients who received 1 or more doses of study medication and had 1 or more postbaseline safety assessments.

Data were analyzed for all patients treated with rifaximin 550 mg twice daily during either the OLM or the previously published RCT[13] (all-rifaximin population) and for a subset of this population: patients who had received placebo during the RCT[13] and received rifaximin during the OLM, plus patients who only participated in the OLM (new-rifaximin population). Differences in demographics and baseline characteristics were determined using the Fisher exact test or the *t* test. Nonstatistical comparisons to historical data from the placebo control group and rifaximin group from the previously published RCT[13] were included, based on methodology and recommendations from regulatory guidance and published literature.[14–16] This historical RCT and current OLM included similar enrollment criteria and were supported by the same organization and investigators. In addition, demographic and baseline characteristics of the historical placebo and rifaximin groups were similar to those for the OLM population, and many of the patients in the placebo arm of the RCT continued in the OLM.

All continuous and categoric variables were summarized using descriptive statistics. Adherence was determined at each clinic visit and was calculated as follows: ([number of tablets dispensed – number of tablets