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Rifaximin Safety Profile in Irritable Bowel Syndrome

Leonard B. Weinstock, MD[1,2]; Mark Pimentel, MD[3]; Zeev Heimanson, PharmD[4]; Anthony Lembo, MD[5]

[1]Washington University School of Medicine, St. Louis, MO; [2]Specialists in Gastroenterology, LLC, St. Louis, MO; [3]Cedars-Sinai Medical Center, Los Angeles, CA; [4]Salix Pharmaceuticals, Bridgewater, NJ; [5]Beth Israel Deaconess Medical Center, Boston, MA

BACKGROUND

- Rifaximin is a nonsystemic, gastrointestinal (GI)-targeted antibiotic indicated for the treatment of irritable bowel syndrome (IBS) with diarrhea in adults[1*]
  - Rifaximin 550 mg is administered 3 times daily (TID) for 2 weeks and patients who experience symptom recurrence may be retreated for up to 2 additional courses[1]
- Phase 3 trials have demonstrated the efficacy of single[2] and repeated courses[3] of rifaximin in the treatment of diarrhea-predominant IBS (IBS-D)
  - In two identically designed, randomized, double-blind, placebo-controlled trials, a 2-week course of rifaximin 550 mg TID provided adequate relief of global IBS symptoms versus placebo during ≥2 of the first 4 weeks post-treatment (P<0.001; pooled), and response was durable (eg, through ≥10 weeks post-treatment)[2]
- Some antibiotics have been associated with an increased risk of GI-related adverse events (AEs), hepatoxicity, and opportunistic infections (eg, *Clostridium difficile*)[4-6]

OBJECTIVE

- To conduct a pooled analysis of three large studies to further characterize the GI-, hepatic-, and infection-related safety profile of rifaximin for IBS-D at the indicated dosage (550-mg tablet TID for 2 weeks)

METHODS

- Pooled post hoc safety analysis of three phase 3, randomized, double-blind, placebo-controlled clinical trials of rifaximin 550 mg for the treatment of adults with IBS-D (**Table 1**)
  - In all three trials, patients received at least one course of rifaximin 550 mg or placebo TID for 2 weeks
  - At 10 weeks post-treatment, patients in Study 3 received an additional 2-week course of rifaximin 550 mg or placebo TID

Table 1. Phase 3 Clinical Studies

Study	Study Design	Treatment	Post-Treatment Follow-Up (wk)
Study 1 (TARGET 1)[2]	R, PBO	Rifaximin 550 mg or placebo TID for 2 weeks	10
Study 2 (TARGET 2)[2]	R, PBO	Rifaximin 550 mg or placebo TID for 2 weeks	10
Study 3 (TARGET 3)[3]	R, PBO	Responders to open-label rifaximin 550 mg TID for 2 weeks, who had recurrence within 18 weeks, entered a randomized, placebo-controlled phase and received 2 courses of rifaximin 550 mg or placebo TID for 2 weeks; courses 1 and 2 were separated by 10 weeks	Course 1: 10* Course 2: 8*

*The first course (2 weeks) was followed by a 10-week treatment-free period, a second course (2 weeks), and an 8-week treatment-free period.
IBS-D = diarrhea-predominant irritable bowel syndrome; PBO = placebo-controlled; R = randomized; TARGET = Targeted, nonsystemic Antibiotic Rifaximin Gut-selective Evaluation of Treatment for IBS-D; TID = three times daily.

METHODS

- AEs were determined during treatment and post-treatment follow-up (**Table 1**)
- Patients who received ≥1 dose of double-blind study medication and had ≥1 postbaseline safety assessment were included in the analyses

RESULTS

- 952 patients in the rifaximin group (mean age, 46.6 y; 71.8% female; 87.8% white) and 942 patients in the placebo group (70.7% female; 89.6% white) were included
- For the overall evaluation period, the AE profile for rifaximin-treated patients was generally comparable to that of placebo-treated patients (**Table 2**)
  - Few patients discontinued therapy due to AEs in both groups and fewer patients in the rifaximin versus placebo group reported serious or severe AEs

Table 2. Adverse Events Overview

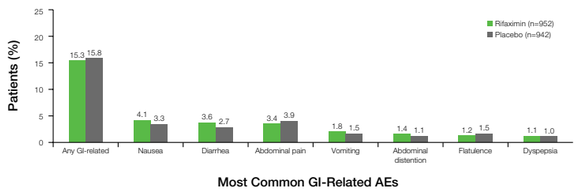
Patients With an AE, n (%)	Rifaximin (n=952)	Placebo (n=942)
Any AE*	480 (50.4)	477 (50.6)
AEs leading to study discontinuation	9 (0.9)	9 (1.0)
Drug-related AEs	81 (8.5)	109 (11.6)
Serious AEs	14 (1.5)†	19 (2.0)‡
AE intensity	n=480	n=477
Mild	210 (22.1)	211 (44.2)
Moderate	230 (24.2)	207 (43.4)
Severe	39 (4.1)	59 (6.3)
Not reported	1 (0.1)	0

*Patients who experienced an AE classified with the same preferred term more than once were only counted once for the summary of that event, using the event with the most severe intensity or closest relationship to study drug.
†Only 1 serious AE (alcohol withdrawal syndrome), occurring in the rifaximin group, was considered by investigators to be related to the study drug. The patient had completed treatment at the onset of the AE and remained in the study.
‡2 serious AEs, occurring in the placebo group (1 event of abdominal pain and 1 event of bipolar I disorder), were considered by investigators to be related to the study drug.
AE = adverse event.

- Overall, the most common AEs in the rifaximin group compared with placebo were upper respiratory tract infection (4.9% vs 5.0%), headache (4.4% vs 5.4%), nausea (4.1% vs 3.3%), and diarrhea (3.6% vs 2.7%)
- A similar percentage of patients with any GI-related AEs for rifaximin versus placebo were comparable and the most common GI-related AEs in both groups were nausea, diarrhea, and abdominal pain (**Figure 1**)
  - Constipation was lower in the rifaximin (0.7%) versus placebo (1.6%) group

RESULTS

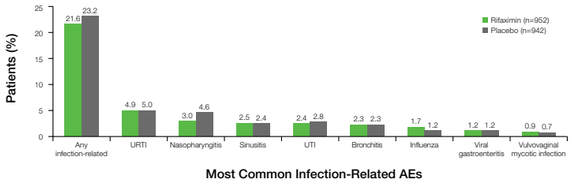
Figure 1. Most Common GI-Related AEs*



*>1% of patients in rifaximin group.
AE = adverse event; GI = gastrointestinal.

- For rifaximin versus placebo, liver chemistry AEs occurred with similar frequency
  - Increased alanine aminotransferase levels (1.6% vs 1.2%)
  - Increased aspartate aminotransferase levels (1.3% vs 1.0%)
- Hepatobiliary AEs were infrequent (rifaximin, 0.1%; placebo, 0.3%)
  - One AE of hepatic steatosis in the rifaximin group; one AE each of acute cholecystitis, biliary colic, and cholecystitis in the placebo group
- Infection-related AEs occurred in a similar percentage in rifaximin and placebo groups and the most common infection-related AEs reported were upper respiratory tract infection, nasopharyngitis, and sinusitis (**Figure 2**)

Figure 2. Most Common Infection-Related AEs*



*≥0.9% of patients in rifaximin group.
AE = adverse event; URTI = upper respiratory tract infection; UTI = urinary tract infection.

RESULTS

- No patients in the rifaximin group and 3 (0.3%) patients in the placebo group reported a Staphylococcal abscess or infection; 3 patients in each group reported cellulitis (0.3%)
- One patient in the rifaximin group experienced recurrent *C difficile* colitis, which resulted in study discontinuation
  - *C difficile* infection was not considered by the investigator to be treatment-related, but likely occurred because the patient had received a 10-day cefdinir course for treatment of a urinary tract infection

CONCLUSION

- **The frequency of general, GI-, hepatic-, and infection-related AEs with rifaximin was generally comparable with that of placebo in adults with IBS-D**
- **These data support the overall favorable safety and tolerability profile of rifaximin**

REFERENCES

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DISCLOSURES

LW reports serving as a consultant and on the speakers' bureau for Salix Pharmaceuticals. MP reports serving as a consultant for and receiving research grants from Salix Pharmaceuticals. Additionally, Cedars-Sinai Medical Center has a licensing agreement with Salix Pharmaceuticals. ZH reports being an employee of Salix Pharmaceuticals. AL reports serving as a consultant for Salix Pharmaceuticals.

*Rifaximin is also indicated for reducing the risk of overt hepatic encephalopathy recurrence in adults (550 mg twice daily) and treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli* in children aged ≥12 years and adults.

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