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Infection-Related Safety Profile of Rifaximin Repeat Treatment for Diarrhea-Predominant Irritable Bowel Syndrome

William D. Chey, MD[1]; Anthony Lembo, MD[2]; Ray A. Wolf, PharmD[3]

[1]University of Michigan School of Medicine, Ann Arbor, MI, USA; [2]Beth Israel Deaconess Medical Center, Boston, MA, USA; [3]Salix, a Division of Valeant Pharmaceuticals North America LLC, Bridgewater, NJ, USA

INTRODUCTION

- Irritable bowel syndrome (IBS) is characterized by abdominal pain or discomfort that is associated with altered defecation and a change in bowel habits[1]
- Alterations in gut microbiota, such as those observed in patients with diarrhea-predominant IBS (IBS-D),[2] may play a role in the pathophysiology of IBS[3] and suggest the therapeutic potential of antimicrobial therapies, such as antibiotics
  - Use of traditional antibiotics has been associated with microbial antibiotic resistance,[4] adverse events (AEs),[4] and increased risk of *Clostridium difficile* infection[5]
- Rifaximin is a nonsystemic antibiotic approved in May 2015 by the US Food and Drug Administration for the treatment of IBS-D in adults[6]
  - Data from two phase 3, 12-week, single-course trials of rifaximin 550 mg 3 times daily (TID) for 2 weeks reported a similar incidence of infection-related AEs between rifaximin and placebo[7]; however, infection-related incidence with repeated courses of rifaximin is unknown
- Results of TARGET 3, a large, randomized, placebo-controlled trial, demonstrated the favorable efficacy and overall safety and tolerability of repeat treatment of rifaximin for IBS-D[8]

AIM

- To examine the infection-related safety profile of rifaximin during repeat therapy (up to three 2-week courses) in patients with IBS-D who participated in the TARGET 3 trial

METHODS

Patient Population

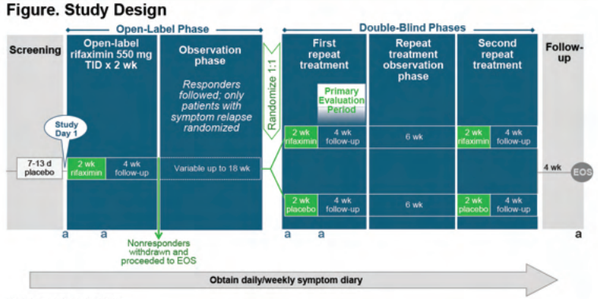
- Adults diagnosed with IBS-D (based on Rome III criteria) who had mean symptom severity scores of ≥3 for IBS-related abdominal pain (0 = no pain, 10 = worst possible pain you can imagine) and bloating (0 = not at all, 6 = a very great deal), and stools for ≥2 days per week that met criteria for Bristol Stool Scale (BSS) type 6 (loose) or type 7 (watery) consistency during a screening phase
- Excluded were patients with inflammatory bowel disease; those taking antidiarrheals, antispasmodics, narcotics, drugs indicated for IBS, or probiotics; and those who had taken antibiotics within 14 days of providing written informed consent

Study Design

- Phase 3, randomized double-blind (DB) phase, placebo-controlled, multicenter, multinational trial (Figure)

METHODS

Figure. Study Design



[a]Stool sample collection.
EOS = end of study.

- Eligible patients received open-label (OL) rifaximin 550 mg TID for 2 weeks followed by a 4-week follow-up period to determine response
  - Response was defined as meeting weekly response criteria for abdominal pain (≥30% improvement from baseline in mean weekly pain score) and stool consistency (≥50% decrease from baseline in number of days/week with BSS type 6 or 7 stool consistency) for ≥2 of 4 weeks during follow-up
  - Patients who responded to OL rifaximin but experienced symptom relapse (loss of response for abdominal pain or stool consistency criteria for ≥3 weeks of a consecutive, rolling 4-week period) during the 18-week observation phase were randomly assigned to receive two 2-week courses of DB placebo or rifaximin 550 mg TID, with courses separated by 10 weeks
  - During the DB phase, all patients, regardless of response or relapse status after the first repeat treatment, received a second repeat treatment with the same treatment assigned at randomization
- Safety assessments (eg, AEs, clinical laboratory tests, vital sign measurements) were evaluated during the OL phase (24 weeks) and the DB phase with follow-up (22 weeks)

RESULTS

- Of the 2583 patients enrolled in the study, 2579 received OL rifaximin (Table 1)
- 2438 patients were evaluable for efficacy; of these, 1074 (44.1%) responded to rifaximin
  - 636 of the patients who responded to OL rifaximin experienced symptom relapse during the 18-week observation phase and entered the DB phase (placebo, n = 308; rifaximin n = 328; Table 1)

RESULTS

Table 1. Patient Demographics

Characteristic		Open-Label Population: Rifaximin 550 mg TID (N = 2579)	Double-Blind Population: Rifaximin 550 mg TID (n = 328)	Double-Blind Population: Placebo (n = 308)
Age, y, mean (SD)		46.4 (13.7)	47.9 (14.2)	45.6 (13.8)
Sex, n (%)	Male	819 (31.8)	106 (32.3)	89 (28.9)
	Female	1760 (68.2)	222 (67.7)	219 (71.1)
Race, n (%)	White	2155 (83.6)	273 (83.2)	262 (85.1)
	Black	289 (11.2)	37 (11.3)	31 (10.1)
	Other	135 (5.2)	18 (5.5)	15 (4.9)
Duration since first onset of IBS symptoms, y, mean (SD)		10.9 (10.8)	11.4 (11.0)	11.2 (10.9)
Number of daily bowel movements, mean (SD)		3.9 (2.2)	3.8 (2.1)	3.7 (2.1)
Days with BSS stool type 6 or 7 in a week, mean (SD)		4.9 (1.8)	4.9 (1.8)	5.0 (1.7)
Days with stool urgency in a week, mean (SD)		5.9 (1.7)	5.9 (1.7)	5.8 (1.7)

BSS = Bristol Stool Scale; IBS = irritable bowel syndrome; SD = standard deviation; TID = 3 times daily.

- 80 patients in the OL phase (3.1%) and 3 patients in the DB phase (placebo, n = 2 [0.6%]; rifaximin, n = 1 [0.3%]) discontinued the study because of an AE
- The overall incidence of infection-related AEs was slightly higher in the DB phase (19.2%) than in the OL (11.9%) phase; however, in the DB phase, rates were similar between placebo (19.8%) and rifaximin (18.6%)
- The most common infection-related AEs in the OL and DB phases were upper respiratory tract infection, nasopharyngitis, and urinary tract infection (Table 2)
- Vulvovaginal mycotic infection, which occurred in 5 patients (0.2%) during the OL phase, was the only infection-related AE occurring in ≥2 patients that was considered by the investigators to be drug-related in either the OL or DB phase
- Hospitalization for *C difficile* colitis occurred in 1 patient 37 days after repeat treatment with rifaximin
  - This patient tested negative for *C difficile* Toxins A and B at study entry and had a medical history of *C difficile* infections
  - *C difficile* infection symptoms (eg, severe diarrhea, dehydration, lower abdominal cramping, weakness) began after the completion of a 10-day course of cefdinir for the treatment of a urinary tract infection
  - Event resolved after 4 weeks of treatment with oral vancomycin

RESULTS

Table 2. Infection-Related Adverse Events

Adverse event, n (%)[a]	Open-Label Population: Rifaximin 550 mg TID (N = 2579)	Double-Blind Population: Rifaximin 550 mg TID (n = 328)	Double-Blind Population: Placebo (n = 308)
Any infection-related adverse event	380 (11.9)	61 (18.6)	61 (19.8)
Upper respiratory tract infection	41 (1.6)	12 (3.7)	8 (2.6)
Urinary tract infection	35 (1.4)	11 (3.4)	15 (4.9)
Nasopharyngitis	36 (1.4)	10 (3.0)	9 (2.9)
Bronchitis	15 (0.6)	9 (2.7)	5 (1.6)
Influenza	33 (1.3)	7 (2.1)	2 (0.6)
Sinusitis	34 (1.3)	7 (2.1)	7 (2.3)
Viral gastroenteritis	14 (0.5)	4 (1.2)	3 (1.0)

[a]≥1% of patients in either population.
TID = 3 times daily.

CONCLUSIONS

- There were no specific trends in infection-related AEs observed with the nonsystemic antibiotic rifaximin
- There was no increased risk of infection-related AEs during up to 3 treatment courses of rifaximin 550 mg TID for 2 weeks for patients with IBS-D

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