POSTER NUMBER

Su1194

Efficacy of Rifaximin in Patients With Diarrhea-Predominant Irritable Bowel Syndrome and Prior Use of IBS Medications

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INTRODUCTION

- Antidiarrheal (eg, loperamide) and antispasmodic (eg, dicyclomine) therapies are frequently used to manage symptoms of irritable bowel syndrome with diarrhea (IBS-D)[1,2]
  - These agents generally only target individual symptoms (eg, diarrhea for antidiarrheals; cramping/pain for antispasmodics)
- Rifaximin, a nonsystemic antibiotic, is indicated in the United States for the treatment of adults with IBS-D[3]
- Randomized, phase 3, double-blind, placebo-controlled studies have demonstrated the efficacy of single[4] and repeat[5] 2-week courses of rifaximin for the treatment of IBS-D
  - In 2 identically designed studies, a significantly greater percentage of patients receiving a single course of rifaximin 550 mg three times daily (TID) for 2 weeks experienced improvement in both daily abdominal pain and stool consistency, daily abdominal pain alone, and daily stool consistency alone versus placebo during ≥2 of the first 4 weeks post-treatment (P<0.001, for all comparisons; pooled data); improvements were observed during the entire 3 months of the studies[4]
  - In a repeat treatment study, up to three 2-week courses of rifaximin were efficacious and well tolerated in patients with IBS-D[5]
- The effects of prior IBS treatments on the efficacy of repeat treatment with rifaximin are unknown

AIM

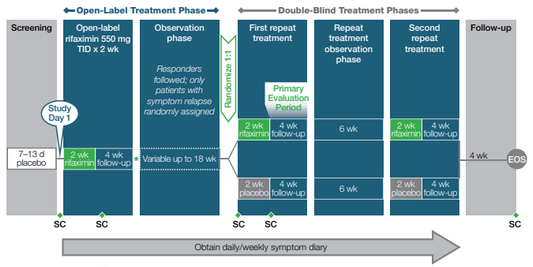
- To examine the effect of prior IBS medication use on the efficacy of rifaximin by performing a post hoc analysis of a previously published repeat treatment phase 3 study[5]

METHODS

Study Design and Patients[5]

- Phase 3, randomized, double-blind, placebo-controlled trial
- Adults with IBS-D meeting Rome III criteria with mean daily abdominal pain score ≥3 (range, 0-10), bloating score ≥3 (range, 0-6), and ≥2 days/week with Bristol Stool Scale (BSS) type 6 or 7 (mushy/watery) stool during a placebo-screening phase (**Figure 1**)

Figure 1. Study Design



[1]Nonresponders withdrawn and proceeded to EOS.
EOS = end of study; SC = stool sample collection; TID = three times daily.
Adapted with permission from Lembo A, et al. *Gastroenterology*. 2016;151:1113-1121.[5] © Elsevier.

METHODS

- Patients who responded to a 2-week course of open-label rifaximin 550 mg TID and who then experienced recurrence of symptoms during an 18-week treatment-free observation phase were randomly assigned to receive 2 courses of double-blind rifaximin 550 mg TID or placebo for 2 weeks; each course was separated by 10 weeks
- The most frequently used IBS medications reported in the open-label population were loperamide and dicyclomine; therefore, patients with a prior medical history of treatment with loperamide or dicyclomine were included in the current analyses

Assessments

- Primary endpoint (per protocol; primary evaluation period): percentage of responders after first repeat treatment, defined as patients simultaneously achieving weekly response for abdominal pain (≥30% decrease 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) during ≥2 of the first 4 weeks post-treatment
- Individual components of the primary endpoint were also evaluated
  - Abdominal pain responder: patient with ≥30% decrease from baseline in mean weekly pain score during ≥2 of the first 4 weeks post-treatment
  - Stool consistency responder: patient with ≥50% decrease from baseline in number of days/week with BSS type 6 or 7 stool during ≥2 of the first 4 weeks post-treatment
- Safety assessments included monitoring of adverse events, vital signs, and clinical laboratory tests
- P values were obtained using the Cochran-Mantel-Haenszel method

RESULTS

- Analysis included 155 patients with prior loperamide use (rifaximin [n=79]; placebo [n=76]) and 68 with prior dicyclomine use (rifaximin [n=31]; placebo [n=37]; **Table 1**)

Table 1. Demographics and Baseline Disease Characteristics

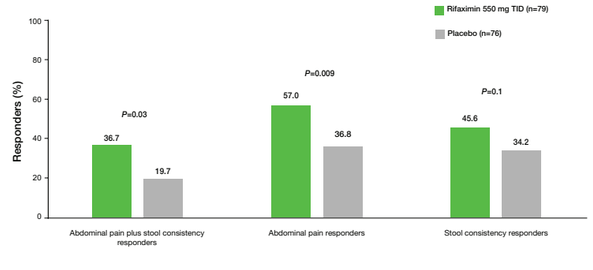
Characteristic	Prior Loperamide Use		Prior Dicyclomine Use	
	Rifaximin 550 mg TID (n=79)	Placebo (n=76)	Rifaximin 550 mg TID (n=31)	Placebo (n=37)
Age, y, mean (SD)	46.6 (15.3)	46.7 (14.4)	48.1 (13.0)	42.3 (14.3)
Female, n (%)	57 (72.2)	52 (68.4)	22 (71.0)	29 (78.4)
Race, n (%)				
White	69 (87.3)	69 (90.8)	24 (77.4)	32 (86.5)
Black	8 (10.1)	5 (6.6)	3 (9.7)	3 (8.1)
Other	2 (2.5)	2 (2.6)	4 (12.9)	2 (5.4)
Average daily score, mean (SD)				
Abdominal pain	4.7 (2.2)	4.6 (2.3)	4.5 (1.9)	4.5 (2.2)
Bloating	3.7 (1.4)	3.7 (1.5)	3.4 (1.2)	3.3 (1.2)
IBS symptoms	3.7 (1.4)	3.7 (1.4)	3.5 (1.1)	3.4 (1.3)
Number of daily bowel movements, mean (SD)	3.7 (2.5)	4.0 (2.5)	2.8 (1.6)	3.1 (1.5)
Days with BSS type 6/7 stool in a week, mean (SD)	4.3 (2.1)	4.5 (2.1)	3.9 (1.4)	4.5 (2.0)

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

- A significantly greater percentage of patients in the prior loperamide group treated with rifaximin were responders for abdominal pain plus stool consistency (P=0.03) and the individual component of abdominal pain (P=0.009) versus placebo (**Figure 2**)
  - A greater percentage of stool consistency responders were observed with rifaximin versus placebo, but this difference was not significant (P=0.1)

RESULTS

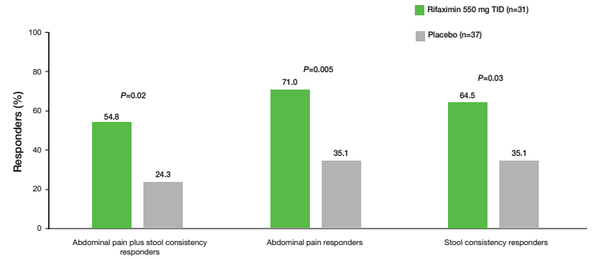
Figure 2. Response in Patients With Prior Loperamide Use



TID = three times daily.

- A significantly greater percentage of patients in the prior dicyclomine group who received rifaximin were responders for both abdominal pain plus stool consistency (P=0.02) and the individual components of abdominal pain (P=0.005) and stool consistency (P=0.03) versus placebo (**Figure 3**)

Figure 3. Response in Patients With Prior Dicyclomine Use



TID = three times daily.

- Significantly greater percentage of pain responders was observed at 10 weeks post-treatment (repeat treatment observation phase) for rifaximin versus placebo in the loperamide group (40.5% vs 22.4%, respectively; P=0.02) and dicyclomine group (48.4% vs 8.1%, respectively; P=0.0006)
- Rifaximin treatment was well tolerated in both the prior loperamide and dicyclomine groups (**Table 2**)

Table 2. Summary of Adverse Events

AE, n (%)	Prior Loperamide Use		Prior Dicyclomine Use	
	Rifaximin (n=79)	Placebo (n=76)	Rifaximin (n=31)	Placebo (n=37)
Any AE	57 (72.2)	45 (59.2)	15 (48.4)	28 (75.7)
Discontinuation due to AE	0	0	0	1 (2.7)
Most common AEs*				
UTI	6 (7.6)	7 (9.2)	2 (6.5)	5 (13.5)
Increased blood CPK	5 (6.3)	0	1 (3.2)	0
Influenza	5 (6.3)	2 (2.6)	0	1 (2.7)
URTI	3 (3.8)	3 (3.9)	2 (6.5)	4 (10.8)
Sinusitis	3 (3.8)	3 (3.9)	1 (3.2)	6 (16.2)
Anxiety	3 (3.8)	1 (1.3)	0	1 (2.7)
Arthralgia	3 (3.8)	2 (2.6)	0	0
Hypertension	3 (3.8)	2 (2.6)	0	2 (5.4)
Increased ALT	3 (3.8)	1 (1.3)	0	0
Increased AST	3 (3.8)	1 (1.3)	0	0
Increased GGT	3 (3.8)	0	0	0

*≥3 patients in prior loperamide rifaximin-treated group or ≥3 patients in of prior dicyclomine rifaximin-treated group. AEs ordered by total number reported in the 2 rifaximin groups, then alphabetical.
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = γ-glutamyl transferase; URTI = upper respiratory tract infection; UTI = urinary tract infection.

CONCLUSIONS

- **Repeat rifaximin treatment was efficacious and well tolerated in improving abdominal pain and stool consistency in patients with IBS-D with prior antidiarrheal or antispasmodic use**

REFERENCES: **1.** Chey WD, et al. *JAMA*. 2015;313(9):949-958. **2.** Sayuk GS, et al. *Am J Gastroenterol*. 2017;112(6):892-899. **3.** Xifaxan® (rifaximin) tablets, for oral use [package insert]. Bridgewater, NJ: Salix Pharmaceuticals; 2018. **4.** Pimentel M, et al. *N Engl J Med*. 2011;364(1):22-32. **5.** Lembo A, et al. *Gastroenterology*. 2016;151(6):1113-1121.

ACKNOWLEDGMENTS: The trial and current analyses were supported by Salix Pharmaceuticals. Technical editorial and medical writing assistance was provided under direction of the authors by Sophie Bolick, PhD, Synchrony Medical Communications, LLC, West Chester, PA. Funding for this support was provided by Salix Pharmaceuticals.

DISCLOSURES: AL, SR, and AR report being a consultant for Salix Pharmaceuticals. ZH is an employee of Salix Pharmaceuticals. MP reports being a consultant for and has received research grants from Salix Pharmaceuticals. Additionally, Cedars-Sinai Medical Center has a licensing agreement with Salix Pharmaceuticals.

Research funded by: Salix Pharmaceuticals