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Impact of Colonoscopy Timing on Rifaximin in Patients With Irritable Bowel Syndrome With Diarrhea

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INTRODUCTION

- Adequate bowel cleansing is important for successful colonoscopy, facilitating the detection and removal of precancerous lesions and diagnosis of other gastrointestinal symptoms[1]
- Bowel preparations for colonoscopy have been associated with transient alterations of the gut microbiota[2-4]
- Although the pathophysiology of irritable bowel syndrome (IBS) is unclear, alterations in the gut microbiota may play a role in its etiology and/or clinical symptoms[5]
- Rifaximin, a nonsystemic antibiotic indicated for the treatment of adults with IBS with diarrhea (IBS-D),[6] is thought to transiently modulate the gut microbiota[7]
  - Rifaximin is administered as short course (2 weeks) of therapy for IBS-D[6]
- Given the lack of data on whether bowel preparations may impact the gut microbiota in patients with IBS-D, an exploratory analysis was conducted to assess if near-term bowel preparation administration might impact rifaximin treatment outcomes in IBS-D

OBJECTIVE

- To evaluate the effect of time since colonoscopy on response to rifaximin in patients with IBS-D

METHODS

- Post hoc analysis of adults with IBS-D[8] who participated in two identically designed, phase 3, randomized, placebo-controlled studies (TARGET 1 and 2)[9]
  - Inclusion criteria included documented history of colonoscopy <2 years prior to enrollment for IBS evaluation or IBS symptoms, or undergoing colonoscopy within 30 days of signed consent
- Patients were randomly assigned to receive rifaximin 550 mg three times daily or placebo for 2 weeks
- Patients meeting weekly response criteria for both abdominal pain (≥30% decrease from baseline in mean weekly pain score [range, 0 (not at all) to 6 (a very great deal)]) and stool consistency (weekly average stool consistency score <4; range, 1 [very hard] to 5 [watery]) during ≥2 of the first 4 weeks post-treatment were considered composite responders
  - Responders for the individual components of abdominal pain severity and stool consistency were also determined
- Data were analyzed in an intent-to-treat population defined as all patients who received ≥1 dose of study drug
- Data were grouped by time from colonoscopy to start of treatment (≤60 days or >60 days), and analyzed using last observation carried forward methodology

RESULTS

- A total of 839 (rifaximin, n=408; placebo, n=431) and 418 patients (rifaximin, n=215; placebo, n=203) had undergone colonoscopy ≤60 days and >60 days prior to receiving their first dose of treatment, respectively (Table)
  - Patients receiving rifaximin or placebo in both colonoscopy-timing groups had comparable average daily abdominal pain severity scores, average number of daily bowel movements, and average daily stool consistency scores at baseline

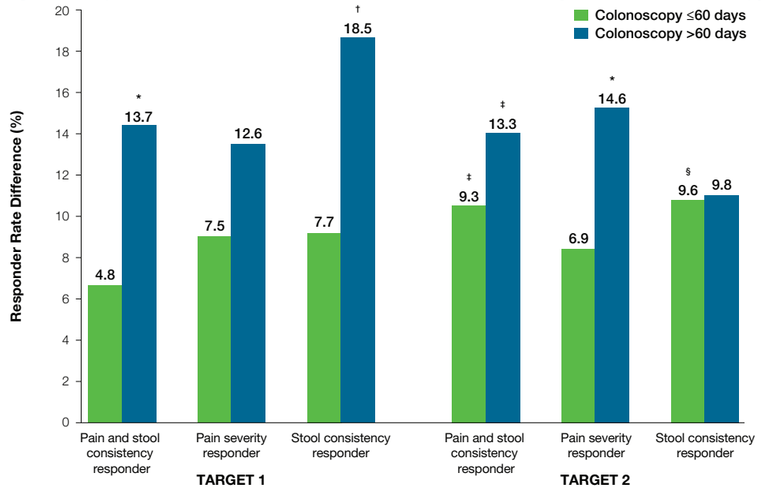
Table. Demographics and Baseline Characteristics

	TARGET 1				TARGET 2			
	Colonoscopy ≤60 days		Colonoscopy >60 days		Colonoscopy ≤60 days		Colonoscopy >60 days	
Characteristic	Rifaximin 550 mg (n=199)	Placebo (n=208)	Rifaximin 550 mg (n=109)	Placebo (n=106)	Rifaximin 550 mg (n=209)	Placebo (n=223)	Rifaximin 550 mg (n=106)	Placebo (n=97)
Age, y, mean (SD)	44.7 (14.5)	45.1 (14.5)	48.7 (15.5)	46.2 (14.8)	44.0 (13.9)	46.7 (14.2)	49.5 (13.1)	45.3 (15.3)
Female, n (%)	147 (73.9)	137 (65.9)	87 (79.8)	85 (80.2)	143 (68.4)	155 (69.5)	84 (79.2)	70 (72.2)
Race, n (%)								
White	181 (91.0)	182 (87.5)	99 (90.8)	98 (92.5)	182 (87.1)	210 (94.2)	100 (94.3)	92 (94.8)
Black	14 (7.0)	23 (11.1)	10 (9.2)	7 (6.6)	17 (8.1)	9 (4.0)	4 (3.8)	5 (5.2)
Other	4 (2.0)	3 (1.4)	0	1 (0.9)	10 (4.8)	4 (1.8)	2 (1.9)	0
Duration since first onset of IBS symptoms, y, mean (SD)	11.8 (10.0)	11.0 (11.1)	11.7 (11.0)	12.2 (13.4)	11.2 (9.9)	12.1 (10.2)	10.0 (10.9)	11.1 (10.8)
Average daily abdominal pain/ discomfort score, mean (SD)	3.2 (0.7)	3.2 (0.7)	3.3 (0.7)	3.2 (0.7)	3.3 (0.7)	3.3 (0.7)	3.3 (0.7)	3.2 (0.8)
Average daily bowel movements, mean (SD)	2.8 (1.3)	2.9 (1.3)	3.0 (1.4)	3.1 (1.6)	2.9 (1.3)	2.9 (1.5)	3.2 (2.0)	3.2 (1.5)
Average daily stool consistency score, mean (SD)	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)

IBS = irritable bowel syndrome; SD = standard deviation.

- Differences in responder rates between rifaximin and placebo were observed in colonoscopy-timing subgroups (≤60 days or >60 days), with the largest treatment differences seen in the group with colonoscopy >60 days (Figure 1)
  - Although numeric responder rates differences were apparent, no significant between-group differences for colonoscopy ≤60 days versus >60 days were observed for the individual studies (data not shown)

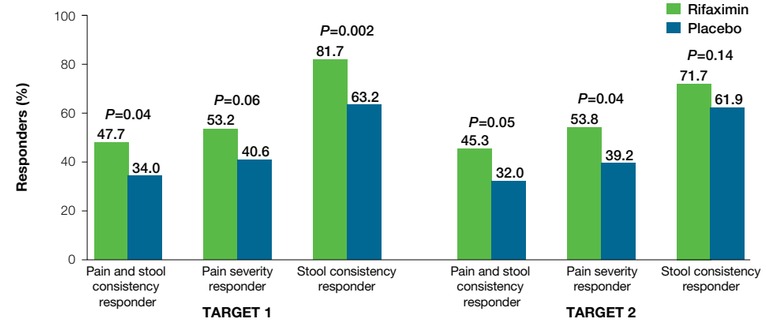
Figure 1. Responder Rate Differences Between Rifaximin and Placebo by Time Since Colonoscopy



*P=0.04 (rifaximin vs placebo). †P=0.002 (rifaximin vs placebo). ‡P=0.05 (rifaximin vs placebo). §P=0.03 (rifaximin vs placebo).

- As noted above, higher percentages of responders were reported in the rifaximin group versus placebo group for patients who had undergone colonoscopy >60 days prior, with statistical significance observed for several assessments (Figure 2)

Figure 2. Percentage of Responders in Group Who had Colonoscopy >60 Days Prior to Starting Treatment



- For patients who had a colonoscopy ≤60 days prior to starting treatment:
  - In TARGET 1, a greater percentage of patients treated with rifaximin versus placebo were composite (45.7% vs 40.9%; *P*=0.32), abdominal pain severity (50.3% vs 42.8%; *P*=0.13), or stool consistency (77.4% vs 69.7%; *P*=0.08) responders in this colonoscopy timing subgroup
  - In TARGET 2, a greater percentage of patients treated with rifaximin versus placebo were responders, although differences were smaller: composite (47.4% vs 38.1%; *P*=0.05), abdominal pain severity (51.7% vs 44.8%; *P*=0.16), and stool consistency (75.1% vs 65.5%; *P*=0.03) in this colonoscopy timing subgroup

CONCLUSIONS

- **Differences in the percentages of responders for rifaximin versus placebo were greatest in the group of adults with IBS-D who underwent colonoscopy >60 days from the start of treatment**
- **This may be related in part to the re-establishment of IBS-related gut microbiota dysbiosis and further research is warranted**

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