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A Pooled Analysis of Two Phase 3, Placebo-Controlled Studies Assessing the Impact of Colonoscopy Timing on Rifaximin Efficacy in Irritable Bowel Syndrome With Diarrhea

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BACKGROUND

- Use of bowel cleansing preparations prior to colonoscopy has been shown to be associated with transient alterations in gut microbiota[1-4]
- The pathophysiology of irritable bowel syndrome (IBS) remains to be fully elucidated; however, alterations in the gut microbiota may be involved in IBS etiology and/or clinical symptoms[5]
- The nonsystemic antibiotic rifaximin 550 mg (Xifaxan®, Salix Pharmaceuticals, Bridgewater, New Jersey, USA) is approved in the United States and Canada for the treatment of adults with IBS with diarrhea (IBS-D)[6]
  - Rifaximin 550 mg three times daily (TID) is administered as a short-course (2-weeks) of therapy, with up to 2 additional 2-week courses to manage symptom recurrence, as needed
- Data are lacking on whether bowel preparations may impact the gut microbiota in patients with IBS-D; therefore, an exploratory analysis was conducted to assess if bowel preparations administered prior to colonoscopy might impact rifaximin treatment outcomes in patients with IBS-D

OBJECTIVE

- To examine the effect of colonoscopy timing on response to rifaximin in adults with IBS-D

METHODS

- Data were pooled from 2 identically designed, phase 3, randomized, double-blind studies (TARGET 1 and 2)[7]
- Studies included adults with IBS (Rome II criteria) who had a documented history of colonoscopy <2 years prior to enrollment or who were undergoing colonoscopy within 30 days of written consent
  - Patients had average daily abdominal pain and bloating scores between 2 and 4.5 on a 7-point scale (range, 0 [not at all] to 6 [a very great deal]) and average daily stool consistency ≥3.5 on a 5-point scale (range, 1 [very hard] to 5 [watery])
- Patients were randomly assigned to receive a 2-week course of rifaximin 550 mg TID or placebo followed by a 10-week treatment-free follow-up period
- Efficacy responders were defined as patients meeting response criteria for both abdominal pain (defined as ≥30% improvement from baseline in weekly average abdominal pain score) and stool consistency (weekly mean stool consistency score <4) during ≥2 of the first 4 weeks post-treatment (composite endpoint)
  - Responders for the individual components of abdominal pain severity and stool consistency were also determined
- Post hoc analyses used last observation carried forward methodology and included all patients who received ≥1 dose of study drug, subgrouped by time between colonoscopy (≤60 days or >60 days) and treatment assigned

RESULTS

- Overall, 839 patients underwent colonoscopy ≤60 days and 418 patients underwent colonoscopy >60 days prior to receiving their first dose of study medication (Table 1)
  - The majority of patients were female, and the mean duration since first onset of IBS symptoms was comparable between the 2 colonoscopy subgroups for both rifaximin and placebo
  - Mean daily disease characteristics at baseline (eg, abdominal pain severity, number of daily bowel movements, stool consistency) were similar for patients receiving rifaximin or placebo in both colonoscopy subgroups

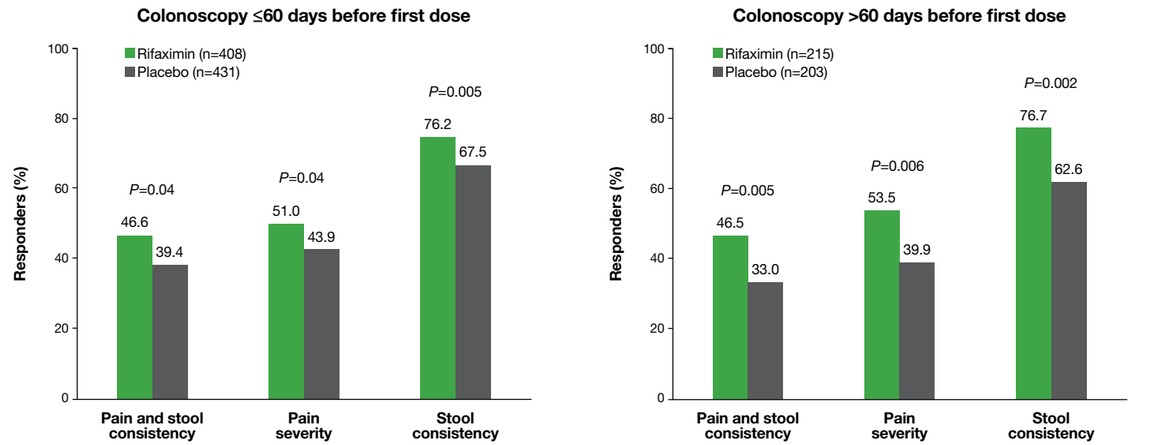
Table 1. Demographic and Baseline Disease Characteristics

	Colonoscopy ≤60 days		Colonoscopy >60 days	
Characteristic	Rifaximin (n=408)	Placebo (n=431)	Rifaximin (n=215)	Placebo (n=203)
Age, y				
Mean	44.3 (14.2)	45.9 (14.4)	49.1 (14.4)	45.8 (15.0)
Range	19–88	18–82	18–86	18–82
Female sex, n (%)	290 (71.1)	292 (67.7)	171 (79.5)	155 (76.4)
White race, n (%)	363 (89.0)	392 (91.0)	199 (92.6)	190 (93.6)
BMI, kg/m^2, mean (SD)	29.1 (7.1)	28.9 (6.6)	29.6 (6.5)	28.6 (6.9)
Duration since first onset of IBS symptoms, y, mean (SD)	11.5 (9.9)	11.6 (10.6)	10.8 (11.0)	11.7 (12.2)
Daily abdominal pain score, mean (SD)*	3.3 (0.7)	3.3 (0.7)	3.3 (0.7)	3.2 (0.7)
Daily bowel movements, mean (SD)	2.9 (1.3)	2.9 (1.4)	3.1 (1.7)	3.1 (1.6)
Daily stool consistency score, mean (SD)†	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)
Daily IBS symptom score, mean (SD)‡	3.4 (0.7)	3.4 (0.7)	3.4 (0.7)	3.4 (0.7)

*Responses to the question "In regards to your specific IBS symptom of abdominal pain and discomfort, on a scale of 0-6, how bothersome were your IBS-related abdominal pain and discomfort today?" were 0 = not at all, 1 = hardly, 2 = somewhat, 3 = moderately, 4 = a good deal, 5 = a great deal, and 6 = a very great deal.
†Responses to the question "What was the overall stool form of your bowel movements today?" were 1 = very hard, 2 = hard, 3 = formed, 4 = loose, and 5 = watery.
‡Responses to the question "In regards to all your symptoms of IBS, on a scale of 0-6, how bothersome were your symptoms of IBS today?" were 0 = not at all, 1 = hardly, 2 = somewhat, 3 = moderately, 4 = a good deal, 5 = a great deal, and 6 = a very great deal.
BMI = body mass index; IBS = irritable bowel syndrome; SD = standard deviation.

- For both the ≤60-day and >60-day colonoscopy subgroups, a significantly greater percentage of rifaximin-treated patients were responders for the composite endpoint (abdominal pain and stool consistency) compared with placebo-treated patients (Figure)

Figure. Percentage of Responders to Rifaximin Versus Placebo, by Time Since Colonoscopy



- In addition, significant differences favoring rifaximin versus placebo were observed for the individual components of abdominal pain and stool consistency in both colonoscopy subgroups (Figure)
- Treatment differences in the percentage of responders (rifaximin vs placebo) were larger in the >60-day colonoscopy subgroup (Table 2)
  - However, these differences did not differ significantly from those observed in the ≤60-day colonoscopy subgroup

Table 2. Responder Rate Differences Between Rifaximin and Placebo, by Time Since Colonoscopy

	Responder rate difference (%)*		
Endpoint	Colonoscopy ≤60 days	Colonoscopy >60 days	*P* value†
Abdominal pain and stool consistency responders	7.1	13.5	0.27
Abdominal pain responders	7.1	13.6	0.28
Stool consistency responders	8.7	14.2	0.31

*Rifaximin minus placebo.
†Colonoscopy ≤60 days vs >60 days.

CONCLUSIONS

- **In this pooled analysis, a 2-week course of rifaximin in adults with IBS-D had significantly greater efficacy versus placebo regardless of whether colonoscopy occurred ≤60 days or >60 days before start of treatment**
- **Treatment differences between rifaximin and placebo were larger in the >60-day subgroup, which may be due, in part, to re-establishment of IBS-related gut microbiota dysbiosis; further research is warranted**

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