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Analysis of Potential Predictors of Symptom Recurrence in Patients Treated With Rifaximin for Diarrhea-Predominant Irritable Bowel Syndrome (IBS-D)

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BACKGROUND

- Irritable bowel syndrome (IBS) is characterized by recurrent abdominal pain associated with defecation or a change in bowel habits; consequently management strategies should be developed based on symptoms and symptom severity[1]
- Rifaximin is a nonsystemic antibiotic that was approved in 2015 for the treatment of diarrhea-predominant IBS (IBS-D) in adults
- Three phase 3 trials have demonstrated the safety and efficacy of rifaximin in IBS-D[2,3]
  - A 2-week course of rifaximin 550 mg 3 times daily (TID) provided durable (eg, through ≥10 weeks post-treatment) improvement in IBS symptoms[2,3]
- However, the patient demographics or baseline disease characteristics that might predict symptom recurrence in patients who respond to rifaximin therapy is unknown

AIM

- To identify potential predictors of symptom recurrence in patients responding to open-label rifaximin during a repeat treatment trial

METHODS

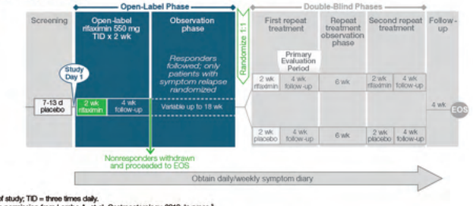
Patient Population

- Eligible patients ≥18 years of age with IBS-D (Rome III criteria) with average symptom severity scores of ≥3 for IBS-related abdominal pain during a placebo-screening phase (scale, 0–10; 0 = no pain, 10 = worst possible pain) and ≥3 for bloating (scale 0–6; 0 = not at all, 6 = a very great deal), and had ≥2 days per week with Bristol Stool Scale (BSS) type 6 (loose) or 7 (watery) stool
  - Exclusion criteria included use of antidiarrheals, antispasmodics, narcotics, drugs indicated for IBS (eg, alosetron, lubiprostone), probiotics, or antibiotics within 14 days of the study

Study Design

- After completing a placebo-screening phase, eligible patients entered an open-label treatment phase in which they received rifaximin 550 mg TID for 2 weeks, followed by a 4-week post-treatment period to assess response (Figure)
  - A responder was defined as a patient meeting weekly response criteria for both 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) for at least 2 of 4 weeks following treatment
- Responders continued in a treatment-free observation phase lasting up to 18 weeks or until symptom relapse occurred
  - Relapse was defined as loss of response for either abdominal pain (<30% decrease from baseline in mean weekly pain score) or stool consistency (<50% decrease from baseline in number of days/week with BSS type 6 or 7 stool) for at least 3 weeks of a consecutive, rolling 4-week period

Figure. Study Design



EOS = end of study; TID = three times daily.
Adapted with permission from Lembo A, et al. *Gastroenterology*. 2016. In press.[3]

- Factors evaluated were age (<65; ≥65 y); sex; country; years since onset of IBS symptoms (<5; 5–10; 11–20; >20); mean daily score for abdominal pain (≤5; >5), stool consistency (≤5; >5), bloating (≤4; >4), and IBS symptoms (≤4; >4); number of daily bowel movements (≤4; >4); days per week with BSS type 6 or 7 stool (≤4; >4); days per week with bowel movement urgency (≤4; >4); and prohibited medication use (yes/no)
- Data were analyzed using univariate and stepwise logistic regression modeling (entry/stay significance level of 0.1)

RESULTS

- Among the 2579 patients with IBS-D who received rifaximin 550 mg TID (Table 1), 2438 were evaluable for efficacy
  - Of these patients, 1074 (44.1%) were responders and entered the observation phase (up to 18 weeks)

Table 1. Demographics and Baseline Characteristics

Characteristic	Rifaximin 550 mg TID (N=2579)
Age, y, mean (SD)	46.4 (13.7)
Male:Female (%)	31.8:68.2
Race, n (%)	
White	2155 (83.6)
Black	289 (11.2)
Other	135 (5.2)
Duration since first onset of IBS symptoms, y, mean (SD)	10.9 (10.8)
Daily symptom score, mean (SD)[a]	
Abdominal pain	5.5 (1.7)
Bloating	4.1 (0.9)
Stool consistency	5.6 (0.8)
IBS symptoms	4.2 (0.9)
Number of daily bowel movements, mean (SD)	3.9 (2.2)
Days with BSS type 6 or 7 stool in a week, mean (SD)	4.9 (1.8)
Days with bowel movement urgency in a week, mean (SD)	5.9 (1.7)
Country	
United States	2567 (99.5)
United Kingdom	12 (0.5)

[a]Scale score ranges: abdominal pain (scale 0–10), bloating (scale 0–6), stool consistency (BSS scale 1–7), IBS symptoms (scale 0–6).
BSS = Bristol Stool Scale; IBS = irritable bowel syndrome; SD = standard deviation; TID = three times daily.
Data from Lembo A, et al. *Gastroenterology*. 2016. In press.[3]

- During the 18-week treatment-free observation phase, 692 (64.4%) of the 1024 patients experienced symptom relapse

Predictors of Relapse

- No demographic or baseline factors predicted recurrence of abdominal pain or changes in stool consistency (Table 2)
- However, a greater percentage of patients with symptom recurrence used prohibited medications versus patients without recurrence (21.7% [150/692] vs 1.8% [7/382]; Table 3); this was identified as a predictor using univariate (Table 2) and stepwise logistic regression modeling (Table 4)

RESULTS

Table 2. Baseline Factors Contributing to IBS-D Symptom Relapse[a] After Initial Response to Rifaximin (n=1074)[b]

Factor	Odds Ratio (95% CI)	*P* Value
Age (<65; ≥65 y)	0.86 (0.56–1.31)	0.5
Sex	0.91 (0.70–1.19)	0.5
Duration since first onset of IBS symptoms (<5; 5–10; 11–20; >20 y)	0.96 (0.86–1.08)	0.5
Mean daily abdominal pain score (≤5; >5)	0.99 (0.77–1.28)	>0.9
Mean daily stool consistency score (BSS, ≤5; >5)	0.92 (0.67–1.26)	0.6
Mean daily bloating score (≤4; >4)	1.13 (0.88–1.46)	0.3
Mean daily IBS symptoms score (≤4; >4)	1.04 (0.81–1.33)	0.8
Number of daily bowel movements (≤4; >4)	1.13 (0.88–1.47)	0.3
Days with BSS type 6/7 stool in a week (≤4; >4)	1.14 (0.88–1.48)	0.3
Days with bowel movement urgency in a week (≤4; >4)	0.81 (0.59–1.13)	0.2
Country	0.91 (0.08–10.03)	0.9
Use of prohibited medications	0.07 (0.03–0.15)	<0.001

[a]Relapse defined as <30% decrease from baseline in mean weekly pain score or <50% decrease from baseline in number of days/week with BSS type 6 or 7 stool for at least 3 weeks of a consecutive, rolling 4-week period.
[b]Unadjusted logistic regression model tested the effect of a single covariate in each model.
BSS = Bristol Stool Scale; CI = confidence interval; IBS = irritable bowel syndrome; IBS-D = diarrhea-predominant irritable bowel syndrome.

Table 3. Most Common Prohibited Medications[a]

Medication	Patients, n (%) With Recurrence (n=692)	Patients, n (%) Without Recurrence (n=382)
Psychoanaleptics	64 (9.2)	1 (0.3)
Citalopram	15 (2.2)	0
Sertraline	13 (1.9)	0
Drugs for acid-related disorders	45 (6.5)	4 (1.0)
Omeprazole	23 (3.3)	2 (0.5)
Psycholeptics	38 (5.5)	3 (0.8)
Alprazolam	12 (1.7)	2 (0.5)
Systemic antibacterials	36 (5.2)	4 (1.0)
Azithromycin	11 (1.6)	2 (0.5)

[a]≥5% of patients in either group, for any medication class.

Table 4. Predictors of Relapse (Stepwise Logistic Regression)

Factor	Odds Ratio (95% CI)	*P* Value[a]
Overall[b]		
Use of prohibited medications	0.07 (0.03–0.15)	<0.001
Abdominal pain[c]		
Duration of onset of first IBS symptoms (<5; 5–10; 11–20; >20 y)	1.2 (1.1–1.3)	0.003
Mean daily stool consistency score (BSS, ≤5; >5)	0.8 (0.5–1.0)	0.09
Stool consistency[d]		
Use of prohibited medications	0.2 (0.2–0.4)	<0.001

[a]0.1 was used as the enter/stay probability for the stepwise selection.
[b]Relapse defined as <30% decrease from baseline in mean weekly pain score or <50% decrease from baseline in number of days/week with BSS type 6 or 7 stool for at least 3 weeks of a consecutive, rolling 4-week period.
[c]Relapse defined as <30% decrease from baseline in mean weekly pain score for at least 3 weeks of a consecutive, rolling 4-week period.
[d]Relapse defined as <50% decrease from baseline in number of days/week with BSS type 6 or 7 stool for at least 3 weeks of a consecutive, rolling 4-week period.
BSS = Bristol Stool Scale; CI = confidence interval; IBS = irritable bowel syndrome.

- When analyzing the individual components of relapse, some potential predictive factors for relapse were identified (Table 5)
  - Using stepwise logistic regression (Table 4), predictors of recurrence in abdominal pain were duration since first onset of IBS symptoms and mean daily stool consistency score; a predictor of recurrence in stool consistency (loose/watery) was prohibited medication use

Table 5. Baseline Factors Contributing to IBS-D Abdominal Pain[a] or Stool Consistency[b] Relapse After Initial Response[c] to Rifaximin (n=1074)[d]

Factor	Abdominal Pain Relapse: Odds Ratio (95% CI)	Abdominal Pain Relapse: *P* Value	Stool Consistency Relapse: Odds Ratio (95% CI)	Stool Consistency Relapse: *P* Value
Age (<65; ≥65 y)	1.50 (0.96–2.36)	0.1	0.67 (0.45–1.00)	0.05
Sex	1.12 (0.85–1.46)	0.4	0.87 (0.68–1.13)	0.3
Duration since first onset of IBS symptoms (<5; 5–10; 11–20; >20 y)	1.20 (1.07–1.35)	0.002	0.93 (0.84–1.04)	0.2
Mean daily abdominal pain score (≤5; >5)	0.82 (0.63–1.07)	0.1	0.88 (0.68–1.12)	0.3
Mean daily stool consistency score (BSS, ≤5; >5)	0.73 (0.52–1.01)	0.1	0.91 (0.67–1.23)	0.5
Mean daily bloating score (≤4; >4)	0.77 (0.60–1.00)	0.046	1.07 (0.84–1.36)	0.6
Mean daily IBS symptoms score (≤4; >4)	0.88 (0.68–1.14)	0.3	0.89 (0.70–1.14)	0.4
Number of daily bowel movements (≤4; >4)	0.77 (0.59–1.00)	0.046	1.05 (0.82–1.35)	0.7
Days with BSS type 6/7 stool in a week (≤4; >4)	0.81 (0.62–1.05)	0.1	1.12 (0.87–1.43)	0.4
Days with bowel movement urgency in a week (≤4; >4)	1.09 (0.78–1.52)	0.6	0.70 (0.50–0.97)	0.03
Country	1.01 (0.09–11.2)	>0.9	0.42 (0.04–4.65)	0.5
Use of prohibited medications	0.96 (0.67–1.37)	0.8	0.24 (0.17–0.36)	<0.001

[a]Relapse defined as <30% decrease from baseline in mean weekly pain score for at least 3 weeks of a consecutive, rolling 4-week period.
[b]Relapse defined as <50% decrease from baseline in number of days/week with BSS type 6 or 7 stool for at least 3 weeks of a consecutive, rolling 4-week period.
[c]Initial responders to primary endpoint (abdominal pain and stool consistency).
[d]Unadjusted logistic regression model tested the effect of a single covariate in each model.
BSS = Bristol Stool Scale; CI = confidence interval; IBS = irritable bowel syndrome; IBS-D = diarrhea-predominant irritable bowel syndrome.

CONCLUSION

- No baseline demographics or disease characteristics (ie, excluding prohibited medication use) were identified as predictors of symptom recurrence after rifaximin response, except for duration since first IBS symptoms and stool consistency in patients with abdominal pain recurrence
- Further research is needed to identify predictors of symptom recurrence in patients with IBS-D

REFERENCES: **1.** Lacy BE, et al. *Gastroenterology*. 2016;150:1393-1407. **2.** Pimentel M, et al. *N Engl J Med*. 2011;364:22-32. **3.** Lembo A, et al. *Gastroenterology*. 2016. In press.

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