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A Randomized Double-Blind Placebo-Controlled Trial of Rifaximin in Patients with Abdominal Bloating and Flatulence

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AIMS: To study the efficacy of rifaximin, a nonabsorbable antibiotic, in relieving chronic functional symptoms of bloating and flatulence.

METHODS: Randomized double-blind placebo-controlled trial consisting of three 10-day phases: baseline (phase 1), treatment with rifaximin 400 mg b.i.d. or placebo (phase 2), and post-treatment period (phase 3). Primary efficacy variable was subjective global symptom relief at the end of each phase. A symptom score was calculated from a symptom diary. Lactulose H_2-breath test (LHBT) was performed at baseline and end of study.

RESULTS: One hundred and twenty-four patients were enrolled (63 rifaximin and 61 placebo). Baseline characteristics were comparable and none had an abnormal baseline LHBT. Rome II criteria were met in 58.7% and 54.1%, respectively. At the end of phase 2, there was a significant difference in global symptom relief with rifaximin *versus* placebo (41.3% *vs* 22.9%, $p = 0.03$). This improvement was maintained at the end of phase 3 (28.6% *vs* 11.5%, $p = 0.02$). Mean cumulative and bloating-specific scores dropped significantly in the rifaximin group ($p < 0.05$). Among patients with IBS, a favorable response to rifaximin was noted (40.5% *vs* 18.2%; $p = 0.04$) persisting by the end of phase 3 (27% *vs* 9.1%; $p = 0.05$). H_2-breath excretion dropped significantly among rifaximin responders and correlated with improvement in bloating and overall symptom scores ($p = 0.01$). No adverse events were reported.

CONCLUSIONS: Rifaximin is a safe and effective treatment for abdominal bloating and flatulence, including in IBS patients. Symptom improvement correlates with reduction in H_2-breath excretion. Future trials are needed to examine the efficacy of long-term or cyclic rifaximin in functional colonic disorders.

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INTRODUCTION

The irritable bowel syndrome (IBS), characterized by altered bowel habits and abdominal discomfort in the absence of organic disease, is the most common digestive disease with a variable prevalence of 3–20% (1–3). It has been estimated that IBS accounts for 12% of visits to primary care physicians and 28% of referrals to gastroenterologists with significant health and economic consequences (4–6). A national, cross-sectional, telephone survey of households in the United States suggested that chronic symptoms of abdominal bloating and pain affect 15.9% and 25.8% of adults, respectively (7). Although the vast majority of these individuals suffer from functional gastrointestinal disorders, they may or may not be diagnosed as having IBS when complex diagnostic criteria are used. In fact, it has been argued that the Rome II criteria, albeit useful in patient selection for research, are too restrictive in clinical practice (2, 8–10).

The pathophysiology of IBS remains poorly understood, although various mechanisms, including altered gut flora and/or small bowel bacterial overgrowth, have been suggested to play a role in the development of gas-related symptoms. Based on these putative pathophysiologic mechanisms, a number of treatments have been suggested. However, only few have been shown in randomized controlled trials to yield sufficient relief of symptoms in the majority of patients. Further, no treatment has been shown to date to be clearly effective in primarily relieving the common—and often most disturbing—symptoms of bloating, gaseous distension, and flatulence.

Rifaximin is a rifamycine derivative highly active against enteric bacteria, including anaerobes (11, 12). Due to the lack of intestinal absorption, rifaximin has no systemic side effects and is therefore suitable for chronic use. Administration of

Drs. Sharara and Aoun contributed equally to this manuscript.

rifaximin was shown to be effective in short-term treatment of small intestinal bacterial overgrowth (13), and in managing intestinal gas production and related symptoms in open-label trials involving patients with functional abdominal symptoms and uncomplicated diverticular disease (14, 15).

The aims of this study were (i) to verify whether patients complaining of intestinal gas-related symptoms suffer from early exaggerated release of hydrogen during bacterial carbohydrate fermentation suggesting small bowel bacterial overgrowth; (ii) to examine the effect of short-term administration of rifaximin on gas-related symptoms (bloating, abdominal distension, and flatulence); (iii) and to attempt to correlate symptom improvement with diminution in hydrogen excretion.

PATIENTS AND METHODS

Figure 1 shows the general design of the study which included three phases of 10 days each: a baseline period of symptom recording (phase 1), the actual treatment phase (phase 2), and a post-treatment symptom recording period (phase 3). Study subjects were recruited by advertisements and announcements posted in clinics and pharmacies. A preliminary phone interview was conducted in order to recruit patients that fit the inclusion criteria which consisted of greater than 12-wk history of bloating and/or excessive flatulence and any of the following: chronic abdominal pain or discomfort, disturbances in bowel movements including feeling of incomplete evacuation, or abnormal stool consistency. Exclusion criteria were age below 18 yr, allergy to rifaximin and use of antibiotics, probiotics, or any drug that could influence bowel function for 1 month prior to entering the study, known lactose intolerance, or any evidence of advanced organic or psychiatric disease that may impact on the patient's compliance or adherence to the study protocol.

In order to rule out any organic disease, all records of previous medical investigations relating to the patient's complaint were carefully reviewed. In addition, patients with a history of

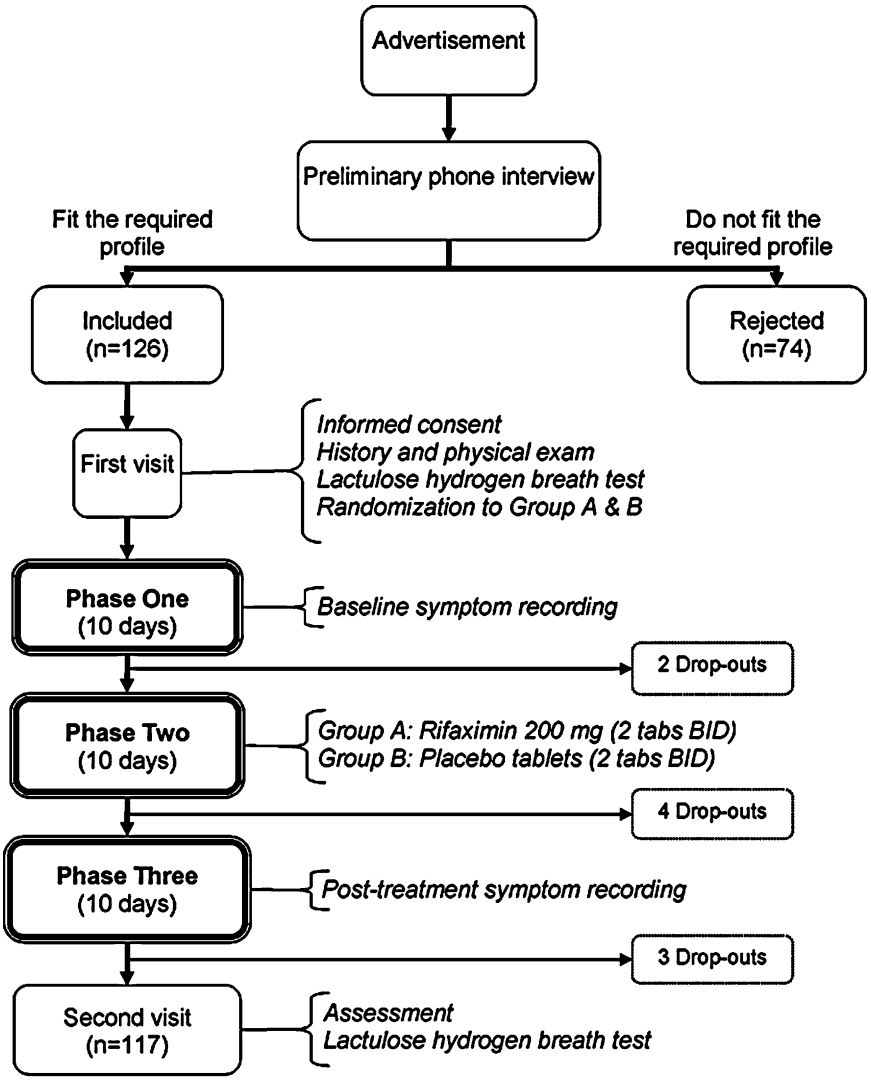

Figure 1. Study design and patient group assignment.

bloody stools or melena, nocturnal or constitutive symptoms such as fever and weight loss were excluded. Further and to avoid referral bias, subjects were not recruited from specialty gastroenterology clinics at the American University of Beirut Medical Center. Patients who fit the study profile were instructed to present for a first appointment to the Gastrointestinal Unit at the American University of Beirut Medical Center after fasting for 12 h. Smoking and physical exercise were not allowed on the day of the examination. Upon presentation, patients were again informed of the details of the study. Written informed consent was obtained and baseline lactulose hydrogen breath test (LHBT) was performed as follows: after measuring a baseline breath sample, subjects ingested 15 mL of lactulose (Duphalac, Solvay pharmaceuticals, NL-Weesp, The Netherlands). Breath samples were then measured at 15-minute intervals for 180 minutes. Samples were analyzed for hydrogen using HBT Sleuth machine (Breathe E-Z Systems Inc., Shawnee Mission, KS, USA) and results were expressed as parts per million (ppm). A normal LHBT was defined as the absence of an early rise in hydrogen excretion of >20 ppm within the first 90 minutes (16–19). A subsequent gradual rise in hydrogen was considered physiologic, given the nonabsorbable nature of lactulose, its expected colonic fermentation, and the normal orocecal transit time in humans of 90–100 minutes (16, 20, 21). Every subject received a patient diary form for symptom recording. They were instructed to fill in the diary on a daily basis throughout the three phases of the trial. The symptoms evaluated included abdominal pain, distension, number of bowel movements, stools consistency, and feeling of incomplete evacuation. Patients were asked to grade each symptom using a 4-point Likert scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe). The information collected from this diary was used to derive a daily symptom score. A composite score was derived for every 10-day phase by adding up the individual daily scores (maximum score = 150).

All subjects were randomized by an independent investigator using a computer-generated random numbers table. The randomization key was kept under lock until the completion of the study. Patients were given verbal and written instructions on the study timetable and on how to fill the symptom score diary. Study drugs were provided in opaque envelopes with group A receiving rifaximin (Normix, Alfa Wassermann, Bologna, Italy) 200 mg tablets, two tablets twice daily for 10 days and group B receiving a similar regimen of matching placebo tablets. Subjects were given an appointment for a follow-up visit at the end of phase 3, during which the diaries were collected and a second LHBT was performed. The study of the main efficacy variable was the subjective feeling of global symptom improvement as reported by the subjects on three occasions, once at the end of each phase in response to the following question: "Do you consider that your symptoms have improved since starting the study drug?" A positive reply to the question was considered a positive response. Secondary end points studied included changes in the LHBT and in the composite 10-day symptom score described above. Response in these secondary end points was defined as a statistically significant drop in the baseline composite score and in the late (plateau) phase of the LHBT. Patient follow-up between phases was by telephone calls. Compliance was checked by pill count. The trial was approved by the Institutional Research Board of the American University of Beirut Medical Center.

Sample size calculation was estimated based on the assumption of a 50% response to rifaximin *versus* a 25% response to placebo using the z-statistic to compare dichotomous variables with $\alpha = 0.05$ (2-tailed) and $\beta = 0.20$. The estimated sample size was 58 patients per arm. The data were entered and analyzed using SPSS version 11.5. Frequency tables and cross-tabulations were derived in order to depict any associations between the different variables. Analysis of the primary end point (global symptom relief) was done according to intent-to-treat (ITT) basis. The paired samples *t*-test and the independent samples *t*-test were used to compare the symptom score means and hydrogen breath test results. The latter were done for paired results and hence are considered per-protocol analyses. Correlation between drop in bloating and overall symptom scores with drop in LHBT at 180 minutes was done using the bivariate Pearson correlation coefficient (r). The 180 minutes time point was chosen as the peak value and best representative of the late plateau phase of the LHBT. A p value at or below 0.05 was considered as the cut-off point for statistical significance.

RESULTS

A total of 200 phone interviews were conducted. Seventy-four cases did not fit the inclusion profile. The remaining 126 were given an appointment for a first visit. Overall, nine patients dropped out of the study for different personal and time reasons: two dropped before starting the medication (during phase 1), four during phase 2, and three never showed up for the follow-up visit (Fig. 1). None of the seven individuals who dropped out of the trial during or after the active treatment phase (phase 2) reported any side effects related to the study medication(s). The ITT population consisted of 124 patients. The per-protocol population (*i.e.*, patients having paired symptom scores and LHBT) consisted of 110 patients.

The random assignment of cases into each arm resulted in 63 patients on rifaximin in group A and 61 patients on placebo in group B. Baseline characteristics of both groups were comparable (Table 1). The mean age for individuals in group A was 42.6 ± 12.1 yr *versus* 39.6 ± 10.9 yr for those in group B. There was a slight majority of females in both groups (52.4% in group A and 57.4% in group B). Most patients have been suffering from their symptoms for more than 1 yr (range 7 months to 6 yr). All patients suffered from gas-related symptoms (*i.e.*, bloating and/or excessive flatulence). The majority had been investigated by their primary care physician including history, physical examination, and stool studies that did not reveal any abnormality. Similarly, 21/63 patients (33.3%)

Table 1. Patient Characteristics

	Group A (n = 63)	Group B (n = 61)	*p* Value
Age	42.2 ± 11.4	38.9 ± 10.6	NS
Gender M:F	30:33	26:35	NS
Duration of symptoms (yr)	2.0 ± 1.4	2.2 ± 1.4	NS
Rome II criteria satisfied	37 (58.7%)	33 (54.1%)	NS
Abdominal pain	51 (81.0%)	49 (80.3%)	NS
Bloating/distension	56 (88.9%)	57 (93.4%)	NS
Excessive flatulence	42 (66.7%)	46 (75.4%)	NS
Disturbance in BM	30 (47.6%)	30 (49.2%)	NS
Baseline LHBT (ppm)	6.2 ± 2.2	6.4 ± 2.5	NS

LHBT = lactulose hydrogen breath test; ppm = parts per million; BM = bowel movements.

in group A and 24/61 (39.3%) in group B had previously underwent endoscopic procedures that turned out negative. The Rome II criteria for diagnosing IBS were met in 37/63 (58.7%) and 33/61 (54.1%) of patients, respectively. Of these, 20%, 38.3%, and 41.7% suffered from diarrhea-predominant, constipation-predominant, and alternating diarrhea and constipation, respectively. Patients who did not fit the Rome II criteria reported normal bowel habits and lack of relief of their gas-related symptoms with defecation.

Only one patient from each group reported an improvement in the overall severity of their symptoms during the pretreatment observation phase (at the end of phase 1). By the end of phase 2, a significant difference in the subjective feeling of symptom relief was noted with 26/63 (41.3%) of patients in the rifaximin group reporting a decrease in the overall severity of symptoms *versus* 14/61 (22.9%) in the placebo group B ($p = 0.03$). This symptomatic improvement was also maintained by the end of phase 3 in the rifaximin group (18/63 [28.6%] *vs* 7/61 [11.5%], $p = 0.02$) (Fig. 2A). A subgroup analysis of patients with IBS satisfying the Rome II criteria showed a favorable response to rifaximin over placebo at the end of phase 2 with 15/37 *versus* 6/33 (40.5% *vs* 18.2%, $p = 0.04$), a difference that remained significant by the end of phase 3 (10/37 [27%] *vs* 3/33 [9.1%], $p = 0.05$) (Fig. 2B). In patients in whom the Rome II criteria were unmet, the response rates at the end of phase 2 were 11/26 (42.3%) in the rifaximin group compared to 8/28 (28.6%) ($p =$ NS).

The mean baseline symptom scores during phase 1 were not different between groups (112.3 ± 9.4 for the rifaximin group and 112.5 ± 11.8 for the placebo group). The scores dropped significantly in the rifaximin group after treatment (at the end of phase 2) to a mean of 104.9 ± 11.4 *versus* 109.8 ± 12.5 for the placebo group (mean δ 7.6 ± 4.72 *vs* 2.7 ± 1.8). The drop was significantly more pronounced in the rifaximin arm when compared to placebo ($p = 0.03$). A mild increase was observed in the symptom score at the end of phase 3 (106.4 ± 12.1 *vs* 111.4 ± 13.2 for the rifaximin and placebo group, respectively). The paired samples *t*-test used to compare the mean scores for phase 1 and 3 revealed a significant drop for patients on rifaximin ($p < 0.01$) but not for those on placebo ($p = 0.125$). Similarly, bloating scores dropped in the rifaximin group from 24.4 ± 2.3 at baseline to 20.8 ± 2.6 at the end of phase 2, and to 21.5 ± 2.7 at the end of phase 3 ($p = 0.01$ for both *vs* baseline). In contrast, bloating scores did not change significantly with placebo (23.8 ± 2.5 at baseline to 22.5 ± 3.4 for phase 2 and 23.1 ± 3.1 for phase 3, $p =$ NS for both). These differences were also significant between groups at both phases (20.8 ± 2.6 *vs* 22.5 ± 3.4 for phase 2 [$p = 0.02$] and 21.5 ± 2.7 *vs* 23.1 ± 3.1 for phase 3 [$p = 0.03$]).

None of the patients had an abnormal baseline LHBT (this was also compared with LHBT performed on 10 healthy volunteers; data not shown). Paired LHBT was available on 110 patients. The mean baseline hydrogen breath test was 6.2 ± 2.2 ppm for group A and 6.4 ± 2.5 ppm for group B ($p = 0.37$). Repeat LHBT 10 days after the assigned treatment showed a decrease in the hydrogen excretion levels in the rifaximin group; however, this drop was not statistically significant when compared to baseline and to patients on placebo (Fig. 3). However, a subgroup analysis of patients responding to rifaximin *versus* nonresponders in the same group showed a statistically significant drop among responders in correlation with drop in bloating-specific and overall symptom scores

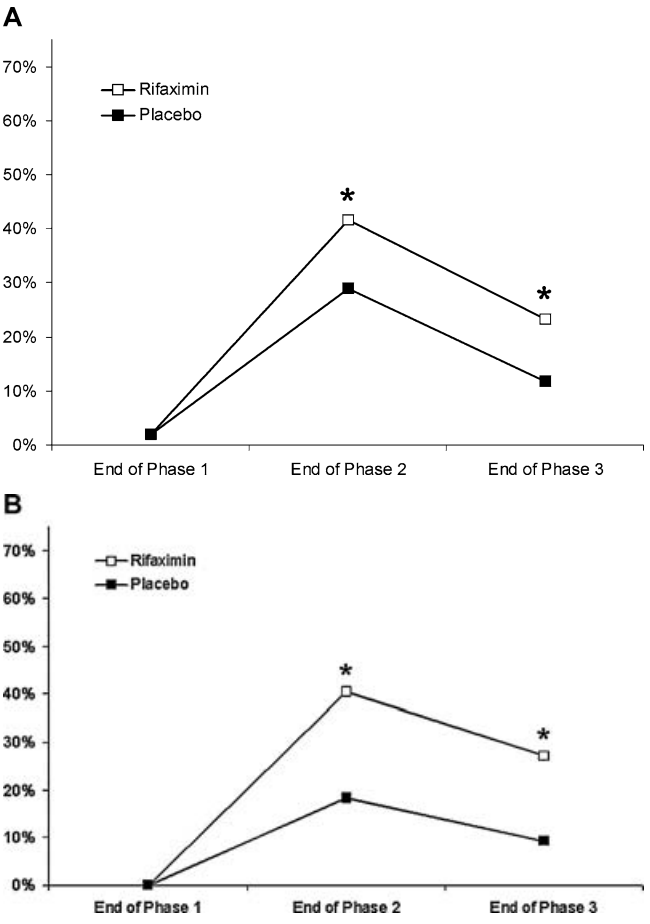

Figure 2. Subjective global relief at the end of each phase of the study in (*A*) overall study population, and (*B*) patients with irritable bowel syndrome ($^*p \leq 0.05$).

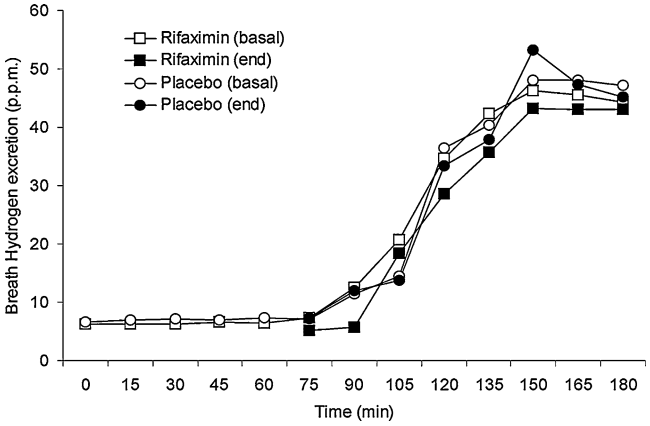

Figure 3. Baseline and post-treatment lactulose breath hydrogen excretion in both study groups (shown are mean values).

($p = 0.01$ for both) (Figs. 4 and 5). There was no correlation between change in LHBT and symptom or bloating scores in the rifaximin nonresponders or the placebo group. Finally, compliance with the assigned therapy was excellent (within two pill count in 96% of patients) and there were no adverse effects related to the treatment reported in either group.

DISCUSSION

In this double-blind, randomized controlled trial, rifaximin was found to be superior to placebo in the relief of symptoms of abdominal bloating, distension, and flatulence. This benefit was also evident in patients suffering from these functional symptoms and fulfilling the Rome II criteria for IBS. The relief of symptoms in the rifaximin arm correlated with a significant decline in hydrogen excretion suggesting that the beneficial effect is likely related to the antibacterial effect on the colonic microflora.

Our study is the first of its kind to primarily address the common complaints of bloating, abdominal distension, and flatulence in the community regardless of whether these subjects fit the strict and complex criteria used in IBS studies. We found that about 50–60% of these individuals have *bona fide* IBS leaving a good number of community subjects suffering from chronic functional gas-related symptoms that would normally be excluded from IBS studies because of adherence to complex diagnostic criteria. These symptoms are common and often more disturbing to patients—as well as arguably harder to treat—than the associated diarrhea or constipation component of IBS. In our study, patients with functional colonic symptoms showed improved response to rifaximin in the relief of their chronic gas-related symptoms although this effect was more pronounced in IBS patients. The therapeutic gain achieved over placebo was observed early after treatment, and was sustained during phase 3 of post-treatment observation. The lack of a precipitous drop in the global relief of symptoms from phase 2 to 3 (Fig. 2)

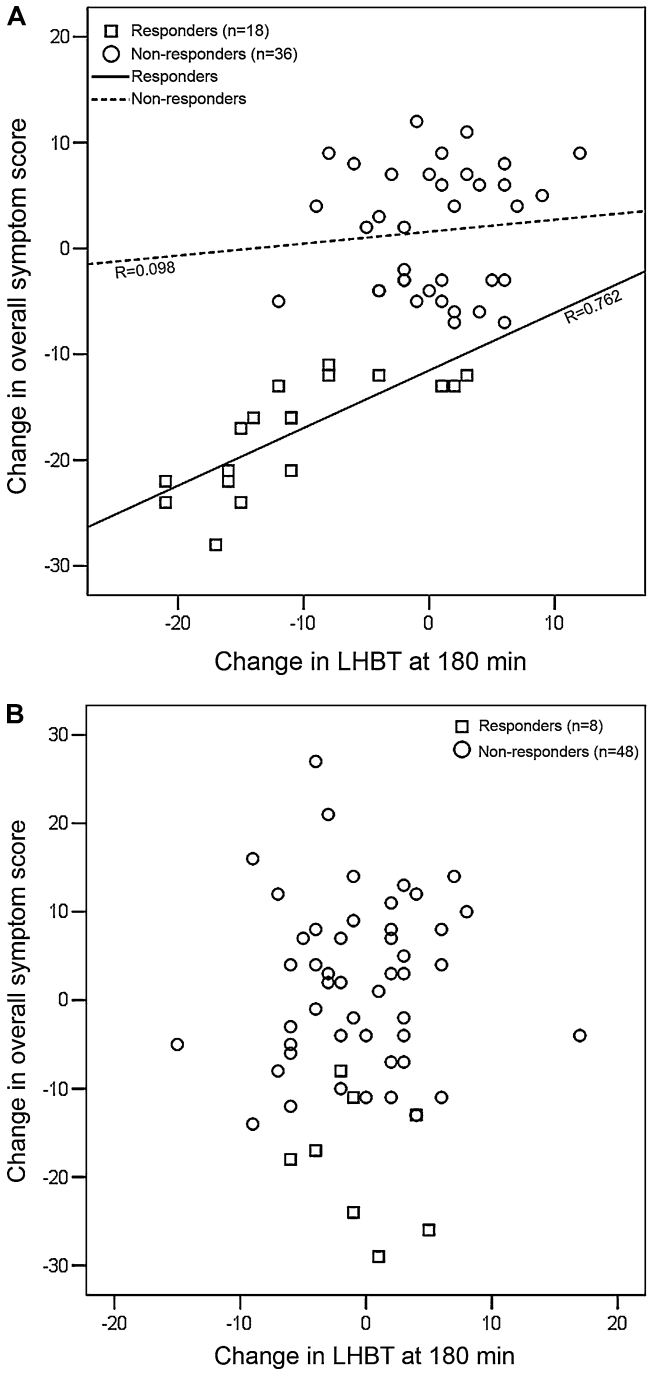

Figure 4. Scatter plot of change in overall symptom score *versus* change in LHBT results at 180 minutes for (*A*) rifaximin and (*B*) placebo-treated patients at the end of phase 3.

suggests a true response to diminution of hydrogen excretion as a result of reduced colonic fermentation. The latter is in line with the antibacterial effect of rifaximin and the fact that bacterial colonic flora is felt to reconstitute as early as 2–3 wk following nonabsorbable antibiotic therapy (22, 23).

Pimentel *et al.* have suggested that an abnormal LHBT is common in subjects with IBS (84% compared to 20% in

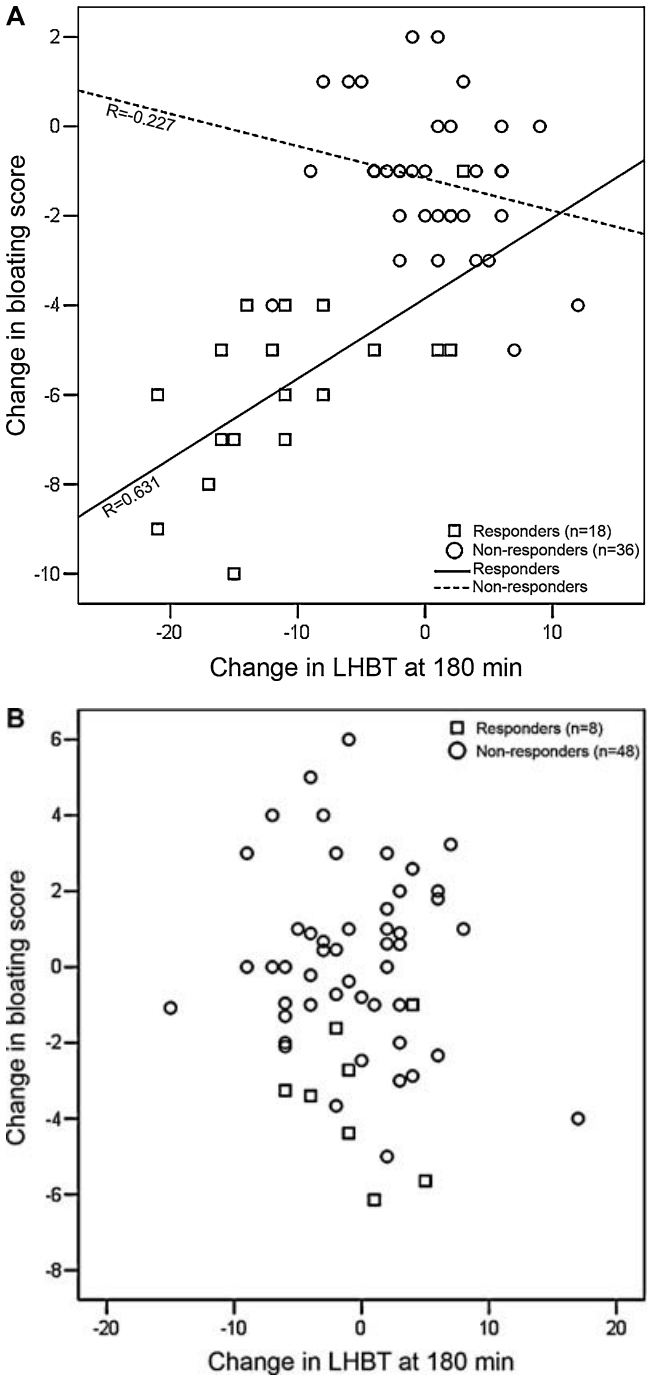

Figure 5. Scatter plot of change in bloating score *versus* change in LHBT results at 180 minutes for (*A*) rifaximin and (*B*) placebo-treated patients at the end of phase 3.

healthy controls) and may be indicative of small bowel bacterial overgrowth (24). Further, they have shown that oral neomycin leads to a significant reduction in IBS symptoms in 35% of these patients compared to 11.4% for placebo (24). It has been argued, however, that the limited symptom responses and their rapid recurrence reported in that study do not necessarily imply small bowel bacterial overgrowth, rather an antimicrobial effect on pathogenic organisms in the colon that theoretically reconstitute quickly upon cessation of antibiotic therapy (25). Our results support the latter opinion as our study subjects suffering from chronic gas-related symptoms—with or without IBS—did not have an abnormal baseline LHBT to indicate small bowel bacterial overgrowth. It is important to note that we did not measure the production of other gases, such as methane, in our patients. It is conceivable that a small group of our patients may suffer from excess methane production and may have responded to the rifaximin treatment accordingly (14, 26). It is, however, unlikely that such exclusively methanogenic patients were unequally distributed in the study groups during randomization.

The evidence that altered gut flora plays a pathogenic role in gas-related functional symptoms in IBS is based on the findings that hydrogen production by enteric bacteria after lactulose is increased in IBS patients (24, 27) and on improved symptomatology in some patients following therapies that modify gut flora such as probiotics or antibiotics such as metronidazole and neomycin (24, 28–31). Moreover, it has been suggested that the fecal microbial flora in patients with IBS shows a decrease of coliforms, lactobacilli, and, to a lesser extent, bifidobacteria, as compared to control healthy individuals (29, 32). Although theoretically appealing, the use of antibiotics in patients with IBS and gas-related abdominal symptoms is limited by their potential side effects, the risk of development of bacterial resistance, and their untested long-term clinical efficacy.

Rifaximin, a rifamycine derivative with broad-spectrum bactericidal activities, is currently approved in the United States for the treatment and prevention of travelers' diarrhea. It is an oral nonabsorbable antibiotic devoid of any side effects and may hence be suitable for chronic administration. Di Stefano *et al.* compared rifaximin to activated charcoal in 34 patients with functional abdominal symptoms, showing a significant reduction in hydrogen breath excretion and in overall severity of symptoms (based on a non-validated symptom score) (14). In particular, a significant reduction in the mean number of flatus episodes and in mean abdominal girth in the rifaximin arm was noted. Latella *et al.* studied the efficacy of cyclic long-term administration of rifaximin (400 mg twice daily for 7 days every month for 1 yr) in a large series of patients with uncomplicated diverticular disease of the colon (15). The patients were randomized to receive the non-digestible fiber glucomannan alone or in combination with rifaximin. After 12 months, the group treated with the fiber and rifaximin combination showed significantly fewer symptoms in term of abdominal pain or discomfort, bloating, tenesmus, diarrhea, and abdominal tenderness as well as a lower global symptomatic score. However, these symptoms are not widely accepted as attributable to what the authors call uncomplicated diverticular disease and may arguably be part and parcel of functional abdominal complaints commonly noted in the community.

The effect of intermittent high-dose rifaximin (1800 mg/day in three treatment periods of 10 days, each followed by 25 days of wash-out) on enteric bacteria (enterococci, coliforms, lactobacilli, bifidobacteria, Bacteroides spp., and *Clostridium perfringens*) was studied in patients with ulcerative colitis (22). After each wash-out period, concentrations of the bacteria tested returned to initial values, suggesting that the administration of high doses of rifaximin does not significantly modify the colonic microflora. Rifaximin-resistant isolates were found, mostly in Bifidobacteria. Other studies have shown that rifaximin did not select for significant resistance in the Gram-negative and Gram-positive intestinal flora during therapy (11, 12, 23, 33, 34) and have documented rapid disappearance from the intestinal tract of bacteria resistant to rifaximin upon wash-out of therapy (23). Given its exceptional safety profile, efficacy, and low risk of significant bacterial resistance, rifaximin fits the optimal profile for an antibiotic-based cyclic treatment of chronic gas-related symptoms.

Our results show an advantage for rifaximin in patient overall-assessment of response and in a cumulative and a bloating-specific patient symptom score. The use of overall satisfactory relief from symptoms as the primary end point is, however, more important because of the wide and varied symptomatology of IBS and functional abdominal symptoms, and the varying importance that patients place on particular symptoms. This helps to overcome inherent disadvantages of symptom score systems, which measure the physical experience of individual symptom response but do not address the impact of this on global well-being. To our knowledge, this is the first study to show a direct correlation between improvement in bloating and overall symptom scores, and diminution in colonic hydrogen gas production after oral lactulose as a result of targeted therapy, in this case rifaximin. It is noteworthy that this correlation remained evident at the end of phase 3, a full 10 days after completion of rifaximin therapy. Why some patients have a salutary diminution in H_2 production in response to rifaximin while others do not remains, however, unclear.

The limitations of this study include the somewhat inhomogeneous patient population (IBS and non-IBS patients), the short duration of therapy and follow-up, and the relatively small number of patients achieving a positive response making analysis of predictors of response and relationship to colonic hydrogen gas production of limited power. The above notwithstanding, this study supports a modest but significant effect of rifaximin in the short-term management of gas-related abdominal symptoms. Breath hydrogen testing may be useful to monitor the effect of treatment and possibly predict its efficacy in individual patients. Further studies are, however, needed to identify the specific colonic flora associated with these symptoms and the role of probiotics and antibiotics in this disorder. The efficacy of long-term or cyclic use of rifaximin, as primary or adjuvant therapy in this patient population deserves further investigation.

STUDY HIGHLIGHTS

What is Current Knowledge

- No treatment has been shown to date to be clearly efficacious in primarily relieving the common symptoms of bloating, gaseous distension, and flatulence.
- It is unclear if patients complaining of intestinal gas-related symptoms have small bowel bacterial overgrowth as suggested by early exaggerated release of hydrogen during bacterial carbohydrate fermentation.

What Is New Here

- In this double-blind, randomized controlled trial, rifaximin was superior to placebo in the relief of symptoms of abdominal bloating, distension, and flatulence.
- Patients suffering from chronic gas-related symptoms-with or without irritable bowel syndrome did not have evidence of small bowel bacterial overgrowth.

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