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Clinical trial: the combination of rifaximin with partially hydrolysed guar gum is more effective than rifaximin alone in eradicating small intestinal bacterial overgrowth

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SUMMARY

Background
Abnormal intestinal clearance is involved in the pathogenesis of small intestinal bacterial overgrowth (SIBO). It is known that partially hydrolysed guar gum affects intestinal motility. Eradication therapy of SIBO is based on antibiotic treatment: no data are available on the role of fibre supplementation in eradicating SIBO.

Aim
To assess whether the combination of partially hydrolysed guar gum and rifaximin is more effective than rifaximin alone in the treatment of SIBO.

Methods
A 50 g-glucose breath test was given to 500 consecutive patients. Patients with a positive glucose breath test and predisposing conditions to SIBO entered into the study, and were randomized to receive rifaximin 1200 mg/day or rifaximin 1200 mg/day plus partially hydrolysed guar gum 5 g/day for 10 days. Patients completed a symptom questionnaire and glucose breath test both in basal condition and 1 month after withdrawal of therapy.

Results
Seventy-seven patients had SIBO. Eradication rate of SIBO was 62.1% in the rifaximin group (both on per-protocol and intention-to-treat analyses), and 87.1% (per-protocol, $P = 0.017$) and 85.0% (intention-to-treat, $P = 0.036$) in the rifaximin-plus-partially hydrolysed guar gum group. Clinical improvement was observed in 86.9% and 91.1% of eradicated cases in rifaximin and rifaximin-plus-partially hydrolysed guar gum groups respectively ($P = 0.677$).

Conclusion
The combination of rifaximin with partially hydrolysed guar gum seems to be more useful in eradicating SIBO compared with rifaximin alone.

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INTRODUCTION

Small intestinal bacterial overgrowth (SIBO) is a condition mainly characterized by diarrhoea, bloating, flatulence and abdominal pain due to an abnormal amount of bacteria in the small intestine.[1–4] Gastric acid production, anatomical integrity of intestinal wall and peristaltic motility are main factors in preserving the fine equilibrium between host and bacteria. Therefore, predisposing conditions that alter the above-mentioned mechanisms could heighten the number of bacteria in the small intestine and lead to the development of this syndrome. Furthermore, it has been proposed that gut microflora could play a role in the modulation of some inflammatory diseases. This was suggested by the higher incidence of SIBO among patients with rheumatoid arthritis[5] and non-alcoholic steatohepatitis[6] and by improvement of Rosacea after eradicating SIBO.[7] Although severe forms presenting remarkable malabsorption can be seen occasionally, a majority of clinical manifestations of SIBO are generally mild and make it hardly distinguishable from other conditions such as irritable bowel syndrome (IBS) or lactose intolerance. This difficulty is clearly underlined by the heterogeneous results of several studies that reported IBS comorbidity with SIBO ranging widely from 10% to 80%.[8–13]

The presence of at least 10^5 CFU/mL in jejunal aspirate culture is considered the gold standard test to diagnose SIBO, especially when colonic-type bacteria are isolated.[1–4, 14] However, hydrogen breath tests are commonly used in clinical practice, being more acceptable to patients and giving quicker information to the clinician.[15] Among them, glucose breath test (GBT) has proved to have the highest accuracy in diagnosing SIBO.[14, 16] Once the bacterial overgrowth is diagnosed, it can be successfully treated by locally active non-absorbable antibiotics. Various studies have shown that rifaximin is successful in eradicating SIBO with no or minimal side effects when compared with systemic antibiotics.[7, 15, 17–21] Of the predisposing conditions involved in SIBO pathogenesis, hypomotility seems to play a relevant role by impairing intestinal clearance and, as a consequence, the intestinal bacteria distribution.[21–24] Thus, we have hypothesized that adding a prebiotic such as partially hydrolysed guar gum (PHGG) to rifaximin can be of help in the decontamination of small bowel. In fact, it can have a beneficial effect on intestinal motility and therefore a synergic interaction between rifaximin and PHGG may lead to a higher eradication rate of SIBO. The primary end point of our study was to assess whether the combination of rifaximin with PHGG is more effective than rifaximin alone in eradicating SIBO, whereas the secondary end point was to evaluate whether the combined treatment obtains a greater symptomatic improvement than rifaximin alone.

MATERIALS AND METHODS

Patients

From May 2007 to March 2010, 500 consecutive patients were referred to our centre to perform GBT because of gastrointestinal symptoms, such as modification in stool frequency, abdominal pain, bloating, flatulence, tenesmus, nausea and vomiting. Patients who underwent previous treatment for SIBO and patients with basal H_2 sample >10 ppm were excluded from the study. Moreover, patients should not have taken either antibiotic or proton pump inhibitors (PPI), or pre- or probiotics for at least 10 days before the examination. Among these, we evaluated 390 patients who had both GBT performed on them and who answered our questionnaire based on gastrointestinal symptom. In this investigation, we included the 77 patients (male/female: 15/62; mean age 54; range 26–84 years) who had a positive GBT. In these subjects, the predisposing conditions for SIBO were impaired intestinal motility due to medications (i.e. antidepressant drugs) (n = 20), hypothyroidism (n = 5), diabetes mellitus (n = 4), scleroderma (n = 1) and Crohn's disease (n = 3); acquired anatomical conditions such as resection of the ileum-caecal valve (n = 3) or partial gastrectomy (n = 1), adhesions due to major abdominal surgery (n = 2). Also Rosacea (n = 5), non-alcoholic steatohepatitis (n = 4) and rheumatoid arthritis (n = 1) were considered disorders related to SIBO. These patients were randomized by a computer-generated random list, to receive rifaximin 1200 mg daily for 10 days or rifaximin 1200 mg daily plus PHGG 5 g/die for 10 days. All patients completed the questionnaire both in basal condition and 1 month after therapy. Adverse events were investigated during and 1 month after the end of treatment. Eradication of SIBO was assessed 1 month after the end of treatment by a further GBT. The study was evaluated and approved by our Institutional Review Board.

Glucose breath test

On the evening before GBT, patients followed a diet containing boiled rice, meat and water alone. Then, they fasted until the end of the test. Glucose was given in a dose of 50 g dissolved in 250 mL of water. Breath hydrogen concentration, in parts per million (ppm), was

measured by gas-chromatography (Quintron Microlyzer model DP plus, QuinTron Instrument Company, Milwaukee, WI, USA) on samples of end expiratory air collected every 15 min for 2 h. A basal sample was taken before glucose intake. Patients were asked to avoid smoking, food intake and physical exercise during the test. A single peak of hydrogen excretion higher than 12 ppm was the cut-off value for test positivity.

Questionnaire

All patients completed an interview questionnaire, according to previous studies performed by our group[7, 9, 21] and by other authors,[25–27] based on 10 variables (diarrhoea, upper and lower abdominal pain/discomfort, bloating, flatulence, abdominal tenderness, weight loss, nausea, constipation and tenesmus) scored from 0 (no symptoms) to 3 (severe), providing a global symptomatic score (GSS), calculated as the sum of all symptom scores, with a range from 0 to 30. A decrease of 50% in GSS after the end of therapy was arbitrarily considered a significant improvement of symptoms, in agreement with other studies carried out by our group on this topic.[7, 9, 21]

Statistical analysis

Data are shown as mean values, ranges and rates. Data were assessed on both per-protocol (PP) and intention-to-treat (ITT) analyses. Fisher's exact test was used to evaluate if the difference between the two groups was statistically significant in terms of both SIBO eradication rates and symptomatic relief. A P value <0.05 in a two-tailed test was considered significant. Statistical analysis was performed with GRAPHPAD Software, (QuickCalcs, San Diego, CA, USA) and with GNU Software (PSPP, Boston, MA, USA).

RESULTS

Table 1 shows the main demographic and clinical characteristics of the study population subdivided according to treatment received. There was no statistically significant difference between the two groups. Overall, eradication of SIBO was achieved in 57/77 patients (74.0%). In particular, SIBO eradication was obtained in 23/37 patients (62.1%; both PP and ITT analysis) treated with rifaximin alone, and in 34/39 (87.1%; PP) and 34/40 (85.0%; ITT) patients treated with rifaximin plus PHGG. SIBO eradication rates were significantly different between the two treatment arms on both PP (P = 0.017; OR = 0.241; 0.075, 0.781) and ITT (P = 0.036; OR 0.289; 0.095, 0.884) analyses.

Table 1 | Main demographic and clinical characteristics of the study population subdivided according to treatment received

	Rifaximin	Rifaximin + PHGG
Patients (*n*)	37	40
Gender (male/female)	8/29	7/33
Mean age (years)	55 [26–79]	52.5 [36–84]
BMI (kg/m^2)	24.3 [18–29]	24.5 [18–31]
Symptoms, *n* (%)		
Diarrhoea (d)	13 (35)	12 (30)
Constipation (c)	6 (16)	7 (17.5)
Alternating d/c	4 (11)	5 (12.5)
Abdominal pain	21 (57)	24 (60)
Bloating	25 (68.5)	28 (70)
Flatulence	14 (38)	17 (42.5)
Nausea	6 (16.2)	5 (12.5)
Tenesmus	4 (11)	3 (7.5)

n, number of patients; BMI, body mass index; M, male; F, female; PHGG, partially hydrolysed guar gum.

Figure 1 shows the flow of patients within the study, SIBO eradication rates and symptoms improvement. Among patients who obtained eradication, clinical improvement was observed in 86.9% and 91.1% of patients treated with rifaximin alone and rifaximin plus PHGG respectively (P = 0.677). On the other hand, among patients who did not obtain eradication, clinical improvement was observed in 7.1% (1/14) and 16.6% (1/6) respectively (P = 0.521). The overall symptomatic improvement in the two treatment arms was 56.7% and 80% in patients treated with rifaximin alone and rifaximin plus PHGG respectively (P = 0.1526).

Pretreatment mean symptomatic scores were 4.21 in the study population (77/77), 4.19 among patients included in the rifaximin arm (37/77) and 4.22 among patients included in the rifaximin plus PHGG arm (40/77). Post-treatment mean symptomatic scores of the group that received rifaximin decreased from 4.10 to 1.85 among eradicated patients with symptomatic improvement (20/37), from 4.60 to 4.00 among eradicated patients without symptomatic improvement (3/37) and from 4.43 to 4.14 among patients without SIBO eradication (13/37). Post-treatment mean symptomatic scores in the group that received rifaximin plus PHGG decreased from 4.23 to 1.81 among eradicated patients with symptomatic improvement (31/40), from 4.33 to 4.00 among eradicated patients without symptomatic

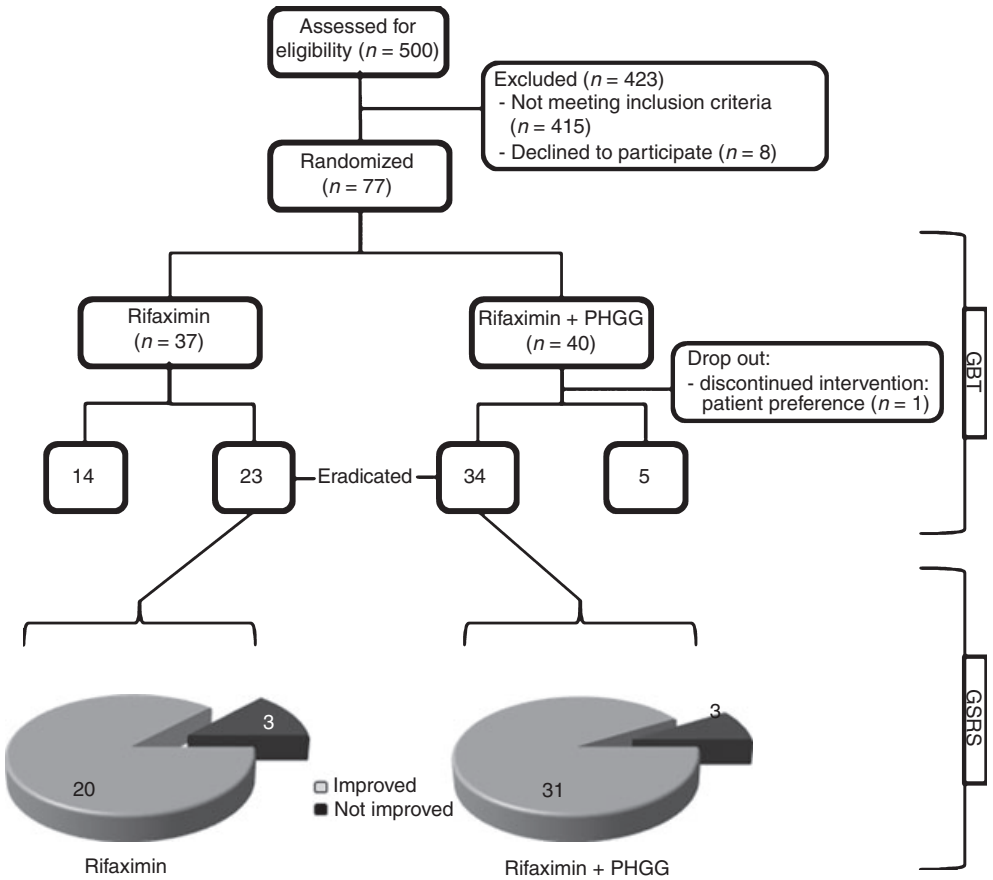

Figure 1 | Flow diagram of the progress through the phases of a randomized trial of two groups [patients within the study, small intestinal bacterial overgrowth (SIBO) eradication rates, symptom improvement]. GBT, glucose breath test; GSRS, gastrointestinal symptom rating scale.

improvement (3/40) and from 4.17 to 3.50 among patients without SIBO eradication (6/40). No serious adverse events were reported during treatment.

DISCUSSION

In patients diagnosed with SIBO, a broad-spectrum antibiotic therapy is recommended to obtain eradication of intestinal bacterial overgrowth. Rifaximin is a locally active non-absorbable antibiotic whose efficacy in eradicating SIBO has been demonstrated by several studies.[7, 15, 17–21] Its use is often preferred to other antibiotics such as levofloxacin and metronidazole because of its topical action and absence of adverse events.[28] In this study, we aimed at evaluating whether adding PHGG to rifaximin was able to increase SIBO eradication rate. Our hypothesis was based on the fact that antibiotics act only on intestinal bacteria, but do not solve the conditions predisposing to SIBO. On the other hand, impaired intestinal motility, by decreasing intestinal clearance, might promote the development of unfavourable habitat for physiological gut microflora and the invasion of small bowel lumen by colonic bacteria.

Our results show that the combination of PHGG and rifaximin was significantly more effective than rifaximin alone in the eradication of SIBO. Thus, this association reached an eradication rate of 87.1%, which was significantly higher than that of rifaximin alone (62.1%). This finding suggests that fibre supplementation positively interacts with rifaximin in SIBO treatment.

Several studies have shown a beneficial effect on intestinal motility by use of alimentary fibres.[29] In fact, alimentary fibres increase faecal mass and transit time, easing defecation. They could be generally distinguished into two categories. Unsoluble fibre is minimally modified in the intestinal lumen and it mechanically increases faecal mass by retaining water, thus decreasing transit time and improving defecation. Otherwise, soluble fibre is metabolized in the large bowel, thus producing short-chain fatty acids and leading to selective stimulation of

microbial growth, which influences bowel functions secondarily.[30] This is an important distinction because several studies conducted on IBS populations have shown that the global amelioration of IBS symptoms is mainly associated with the use of soluble fibres rather than with the use of insoluble ones. It was also found that insoluble fibre was no better than placebo in improving IBS and, rather surprisingly, that a large amount of insoluble fibre may worsen IBS-related symptoms.[31, 32]

In this study, we used PHGG, a vegetable, water-soluble, dietary fibre that is derived from guar gum with a lower molecular weight than the original guar gum, whose safety has been largely proved.[33–35] It is worth noting that PHGG increases faecal acetate content and the colonic concentration of Lactobacilli and Bifidobacteria, thus providing an important prebiotic action.[36–41] As PHGG is not used by these bacteria *in vitro*, it has been proposed that PHGG is degraded in the human colon providing substrates that favour the selective growth of Bifidobacteria and Lactobacilli.[41] This is an important mechanism because it is proved that loss of anaerobes is associated with a depletion in short chain fatty acids and an increase in stool pH, allowing overgrowth of other bacteria, which may contribute to altering intestinal function.[42] Moreover, acetate is one of the most important energy resources for colonocytes and is necessary to sustain colonic epithelial cell proliferation.[43] These factors are useful to preserve the mucosal integrity and to support its repairing process and, when altered, could lead to SIBO.

Glucose breath test and lactulose breath test (LBT) are the most commonly utilized tests for SIBO. Although there is no universal agreement about which test should be performed to diagnose SIBO, in our study, we used GBT because it is easier to interpret and more accurate in diagnosing SIBO than LBT.[14] This has been recently confirmed by the 1st Rome Consensus Conference that reported higher diagnostic accuracy for GBT with respect to LBT (71% vs. 55%).[16] In fact, glucose is highly absorbed in the proximal small bowel and rarely reaches the colon, showing a single 'early' H peak in case of SIBO. On the other hand, lactulose passes unabsorbed through the small bowel and reaches the large bowel where it is metabolized by colonic bacteria. Thus, lactulose reveals bacterial fermentation through the whole gut and can also be used as a measure of orocaecal transit. Nevertheless, being a non-absorbable carbohydrate, lactulose itself can accelerate small bowel transit that is a condition in which the 'early' peak can merge with the late 'colonic' peak, thus making it impossible to distinguish SIBO from colonic fermentation. Moreover, different portions of the given substrate might reach the colon at different times, thus causing two or more peaks in H_2 excretion that simulate SIBO.[44] GBT is associated with a lower incidence of false positive results when compared with LBT, and in healthy volunteers, GBT shows an optimal intra-individual reproducibility.[45]

Recently, studies on SIBO diagnosed by GBT and treated with rifaximin reported that the progressive increase in rifaximin dosage (from 600 mg/day up to 1600 mg/day for 7 days) may lead to an important gain in terms of SIBO eradication without enhancing the occurence of side effects.[18, 19] Similar results were also achieved by Lombardo *et al.* [46] by prolonging high-dose (1200 mg daily) rifaximin treatment to 14 days. These authors studied two specific groups and achieved an eradication rate as high as 87% in PPI users and 91% in IBS patients. Although the setting of our study was slightly different (i.e. we included patients with all the predisposing conditions to SIBO, given the frequent coexistence of different GI disorders in them), we obtained similar SIBO eradication rates by combining a shorter course of antibiotic treatment (1200 mg/day rifaximin for 10 days) with the supplementation of a soluble fibre such as PHGG.

Lastly, we observed that although symptom improvement was higher among patients who obtained SIBO eradication with the combined therapy, this tendency failed to achieve statistical significance. This could be due to the fact that both groups underwent an active treatment, rifaximin, whose efficacy has been already proved, and therefore clinical amelioration was very high in both groups.

In conclusion, the combination use of rifaximin with PHGG allows us to obtain a higher eradication of SIBO as compared with the use of rifaximin alone. Therefore, the prebiotic effect of PHGG is likely to provide a synergistic action with rifaximin inside the bowel lumen, by improving intestinal clearance and favouring the microflora balance.

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contributed to data acquisition; Dr Simona Marenco, Dr Edoardo Savarino, Dr Lorenzo Assandri, Dr Valentina Fazio, Dr Simona Inferrera and Dr Daria Bonfanti participated in patient management and data collection. All authors have seen and approved the final version of the manuscript. All authors declare that they have no conflict of interest and that the work is original. *Declaration of personal and funding interests*: None.

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