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Short Review

Small Intestinal Bacterial Overgrowth: Novel Insight in the Pathogenesis and Treatment of Irritable Bowel Syndrome

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SUMMARY

A total of 65-84% of patients with irritable bowel syndrome (IBS) presents with small intestinal bacterial overgrowth (SIBO). SIBO is defined as the presence of more than 10^5 cfu/ml of colonic type bacteria in the lumen of the small bowel. It is more common in patients with IBS and predominant bloating and diarrhea. Based on the implication of SIBO in the pathogenesis of IBS, six trials have been conducted and analyzed in this review aiming to define a role of rifaximin for the management of IBS. Rifaximin is an orally administered antimicrobial with limited systemic absorption and considerable potency against bacteria implicated in SIBO. In two trials patients with SIBO irrespective of the presence of IBS were enrolled. A positive effect of rifaximin was denoted in the eradication of SIBO in both. One double-blind, prospective randomized trial over placebo in patients with IBS denoted a substantial improvement of the global assessment of patients after treatment with rifaximin. Benefit remained for 10 weeks after stop of treatment. A major benefit was disclosed for bloating. Another three prospective randomized trials have been conducted in patients with both IBS and SIBO. Rifaximin significantly eradicated SIBO and improved bloating. These findings led the Task Force for IBS of the American College of Gastroenterology to appoint a grade of evidence of 1B for the administration of rifaximin in the management of IBS. The proposed oral regimen is 400 mg three times daily for 10 days. However, results of large Phase III trials are mandatory.

Key words: rifaximin, irritable bowel syndrome, intestinal bacterial overgrowth

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INTRODUCTION

Irritable bowel syndrome (IBS) is a common entity. Patients' everyday life is deteriorating and patients are continuously seeking medical attention where therapy is seldom satisfactory. In our country, a recent epidemiological survey attempted to estimate the prevalence of IBS in the general population. Answers to a total of 3112 questionnaires were collected seeking for symptoms diagnostic of IBS. In this prospective study, questionnaires were distributed through relatives of hospitalized patients and through brochures at hospitals. From them 715 were not analyzed due to the occurrence of organic disease. From the 2397 questionnaires that were finally analyzed, symptoms compatible with IBS were reported among 373 people revealing an overall disease prevalence of 15.1%[1].

Part of the explanation for the unsuccessful management of IBS relies on our poor understanding of its pathophysiology. There is growing evidence during the last years that overgrowth of bacteria in the small intestine may play a considerable role in the pathophysiology of IBS, so as to create a novel perspective for therapeutic management. The present review is aiming to provide an update of recent literature on the pathogenesis liaison between IBS and the syndrome of intestinal bacterial overgrowth and on the new available therapies.

NORMAL GUT FLORA AND SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

Under normal conditions the lumen of the digestive tract is colonized by bacteria. Both their number and their type differ from one part of the tract to the other. More precisely, stomach is sterile or contains bacteria up to 10^3 cfu/ml. Intake of agents increasing the intragastric pH like H_2-antagonists and proton pump inhibitors favors the colonization of the stomach[2]. Stomach flora consists mainly of *Streptococcus* spp and *Prevotella* spp. The number of bacteria in the proximal small intestine is 10^{3-4} cfu/ml being mainly *Streptococcus spp*, *Esherichia coli* and *Prevotella* spp. In the distal small intestine the number of bacteria increases into 10^{7-8} cfu/ml and in the large intestine into 10^{11} cfu/ml. Flora of the distal small intestine and of the large intestine is mainly *Bacteroides* spp and Entrobacteriaceae. In the latter case, anaerobes predominate over aerobes by a ratio of 1000:1[3].

SIBO is defined as any situation where the number of bacteria in the proximal small intestinal flora increases into more than 10^5 cfu/ml and they are of the large intestinal flora type[4]. Factors favoring the development of SIBO are lowering of intra-gastric pH, disorders affecting and lowering intestinal motility and disorders affecting local immunity. There is a high probability that SIBO create a variety of symptoms since overgrown bacteria produce gas.

Lactulose breath test (LBT) and glucose breath test (GBT) are the main diagnostic tools for SIBO. Their principle is based on the rapid fermentation of one orally administered substrate being either 15g of lactulose or 50g of glucose leading to an early production breath peak of hydrogen (H_2) or methane (CH_4). Gas production in breath is analyzed at serial time intervals after ingestion through a chromatographic apparatus and reported in a curve format. The curve is characterized by a peak and an area (area under the curve, AUC). The time of appearance of the curve is characteristic of the locus of bacterial overgrowth. A curve appearing at 90 minutes indicates bacterial overgrowth of the proximal small intestine whereas a curve appearing latter indicates bacterial overgrowth of the distal small intestine or of the large intestine. Diagnosis is done when the gas peak is greater than 20 ppm compared with the baseline[5].

The availability of LBT and GBT as a diagnostic tool lead to investigate a probable link between SIBO and IBS. Various studies have been published showing an incidence of SIBO ranging between 65% and 84% of the totally enrolled patients with IBS[6-8]. The predominant symptoms of those patients diagnosed with SIBO were bloating (87.9%) and diarrhea (73.1%).

In a recent publication, duodenal aspirates were collected for quantitative cultures from 162 patients with IBS and from 24 healthy controls. Results showed that 43% and 12% of patients (p: 0.02) had more than $5x10^3$ cfu/ml of bacteria in the duodenal lumen respectively. It was also found that 24% and 4% of patients respectively (p: 0.02) had more than 10^4 cfu/ml of bacteria in the lumen of the duodenum. When the detection threshold was increased up to 10^5 cfu/ml, no differences could be found between patients with IBS and controls. These findings probably indicate that the threshold of intestinal overgrowth may need to be decreased in the definition of SIBO[9].

COULD ANTIMICROBIALS PLAY ANY ROLE FOR THE MANAGEMENT OF IBS?

Based on the existing epidemiological and pathophysiological link between SIBO and IBS, it may be postulated that administration of antimicrobials could be beneficiary for the eradication of the patients' symptoms. However, antimicrobials used for that purpose should possess several major characteristics like those listed below[6]: a) activity against implicated pathogens; b) favorable pharmacokinetics in the gut lumen; c) lack of absorption in the systemic circulation; d) lack of toxicity; and e) lack of induction of antimicrobial resistance.

Available retrospective data have provided a comparison between rifaximin, neomycin and β-lactams for the management of patients with IBS and SIBO. Eighty-four patients were treated with rifaximin; 24 with neomycin and 61 with β-lactams. Results showed a significant superiority of rifaximin over the other administered regimens. More precisely, 69% of patients administered rifaximin reported clinical improvement compared with 38% of neomycin-treated and 44% of β-lactam-treated patients[10].

Despite the retrospective nature of these data, rifaximin seemed to be a candidate for the management of SIBO and IBS. Its antimicrobial spectrum comprises Enterobacteriaceae, *Streptococcus* spp and Gram-negative anaerobes whereas it presents favorable pharmacokinetics in the gut lumen reaching concentrations as high as 3500 μg/g of tissue. Systemic absorption is lower than 0.4% and it has not been implicated for the induction of *Clostridium difficile* colitis[11]. A recent in vitro comparison of rifaximin with other antimicrobials against 536 anaerobe isolates of the intestinal flora revealed a higher intrinsic activity of rifaximin over the comparators. Comparison of rifaximin with neomycin and amplicillin/sulbactam i.e. of antimi-

crobial agents that may be considered candidates for the management of SIBO, revealed that MIC_{50}s against isolates of *B.fragilis* were 0.25, >1024 and 1 μg/ml respectively. Respective values against *Bacteroides thetaiotaomicron* were 1, >1024 and 4 μg/ml and against *Prevotella* spp 0.25, 512 and 0.5 μg/ml[12].

In an attempt to define systemic absorption of rifaximin in the event of gut inflammation, diarrhea from *Shigella flexneri* 2a was induced in 13 healthy volunteers. Rifaximin was administered as a dose of 200 mg three times daily for 3 days and serum was sampled after the last dose. Cmax ranged between 0.68 and 2.26 μg/ml being compatible with minimal intestinal absorption[13].

These findings rendering rifaximin a promising candidate for the eradication of SIBO, led to two prospective studies in patients with SIBO of variable etiology. Inclusion criterion for these studies was the documentation of SIBO by GBT or LBT irrespective of the presence of IBS or not. These studies attempted to define which should be the applied dose for treatment and whether rifaximin was effective in the eradication of SIBO. In the first study[14], 90 patients were equally assigned to 10 days of oral rifaximin treatment either with 600 mg total daily dose (group 1), or with 800 mg total daily dose (group 2) or with 1200 mg total daily dose (group 3). Eradication of SIBO as documented by GBT was achieved in 16.7%, 26.77% and 60.0% of them respectively. These results indicated that a dose regimen of 400mg three times daily should be used for the management of SIBO.

In the next study[15], 400 mg of rifaximin were administered twice daily for 28 days in 20 patients with SIBO documented by LBT. LBT for H_2 had a mean peak of 52.2 ppm and a mean AUC of 3222 ppm/min before treatment; they were significantly reduced into 18.5 ppm and 1232 ppm/min at the end of treatment respectively showing a positive effect of rifaximin on SIBO. Four weeks after stop of rifaximin a more than 50% of clinical improvement was documented among 85.7% of patients with diarrhea and among 50% of patients with bloating[15].

SAFETY AND EFFICACY OF RIFAXIMIN FOR THE MANAGEMENT OF IBS

Based on the contribution of SIBO in the pathogenesis of IBS, particularly for patients with diarrhea and bloating, and on the pharmacology of rifaximin favoring an indication of local treatment, four prospective clinical trials have been conducted[16-19] to evaluate the safety and the efficacy of rifaximin for the management of IBS. The most important of these studies is the one by Pimentel and co-workers. This was a double-blind, randomized prospective trial aiming to evaluate the efficacy of rifaximin compared with placebo on the overall symptom improvement of IBS. Eighty-seven patients with IBS according to Rome I criteria were enrolled in the study and treated with either placebo or 400mg rifaximin three times daily for 10 days. A mathematical score to assess the global status of each patient was created taking into account self-scoring for each symptom and functional weeks for work. Self-scoring for each symptom was done by the Visual Analogue Scale (VAS). VAS is a Likert scale from 0 to 10 in cm where the patient is asked to score his symptom after being informed that 0 indicates absence of symptom and that 10 indicates the worst symptom intensity he has ever felt. Results revealed a significant improvement of the global status of rifaximin-treated patients compared with placebo-treated patients. The major benefit of rifaximin treatment was shown on bloating. The beneficiary effect of rifaximin was maintained regarding the global patient assessment for 10 weeks after stop of therapy. At that time, mean improvement was maintained among 21.0% of placebo-treated patients compared with 36.4% of rifaximin-treated patients (p: 0.020 between groups)[16].

Based on these results, a series of studies was conducted aiming to document the efficacy of rifaximin a) on the symptoms of patients with IBS and SIBO; and b) on the eradication of SIBO[17-19]. Patients enrolled in these trials were diagnosed with IBS according to the Rome II criteria[20]. They were administered oral treatment with rifaximin at a dose ranging between 400 mg twice daily to 400 four times daily for seven to 10 days. The cumulative results of these studies are given in Table 1. The common denominator of all three trials was a considerable efficacy of rifaximin in the eradication of SIBO connected with a relief of bloating. It should be underscored that in one of these trials[18] the change of H_2 excretion over treatment with rifaximin was positively correlated with the VAS self-scoring for bloating.

In all the above analyzed trials, rifaximin was well-tolerated and it was not implicated for any severe adverse events.

One ambiguity is what may be the chance for SIBO recurrence after end of treatment. To help resolve that question, eighty consecutive patients with SIBO were treated with rifaximin 400 mg three times daily for 10 days. The presence of SIBO was followed-up at months 3, 6 and 9 after end of treatment. Recurrence of SIBO was documented in 12.6% of patients at month 3; in 27.5% of patients at month 6; and in 43.7% of patients at month 9[21]. These re-

Table 1. Efficacy of rifaximin in patients with irritable bowel syndrome (IBS) and small intestinal bacterial overgrowth (SIBO): cumulative results of three trials.

Reference	**Dose regimen of rifaximin (no of patients)**	**Dose regimen of comparator (no of patients)**	**Effect on SIBO**	**Effect of symptoms**
17	400mg twice daily x 7 days (18)	Activated charcoal 400 mg bid x 7 days (16)	Decrease of AUC* for H_2	Decrease of flatus episodes
18	400 mg three times daily x 10 days (63)	Placebo (61)	Decrease of H_2 excretion correlating with bloating relief	• Global symptom relief (41.3% vs 22.9%, p: 0.03) • Decrease of bloating episodes
19	1600 mg/day x 7 days (40)	1200 mg/day x 7 days (40)	80% vs 58%	

**AUC: area under curve for H_2 excretion after breath test*

sults clearly raise the need for a second treatment course during patient's follow-up.

DOES TREATMENT OF SIBO WITH RIFAXIMIN INCREASE THE RISK OF COLONIZATION WITH RESISTANT BACTERIA?

Although not systemically absorbed, rifaximin remains an antimicrobial agent that may lead to the selection of resistant bacterial clones in the gut tract. These bacteria could be resistant not only to rifaximin but also to other antimicrobials. This is a risk existing for all available antimicrobials agents and few data are available to provide definite answers on the implication of rifaximin. Based on the assumption that the risk of acquisition of resistance is greater for isolates with elevated MICs of rifaximin, isolates of *E.coli* with MICs equal to 8 μg/ml were serially in vitro exposed to concentrations of rifaximin ranging between 8 and 128 μg/ml aiming to estimate the frequency of adaptation of mutants with MICs of rifaximin between 32 and 256 μg/ml[22]. Yielded frequency was very low and ranged between 9.3×10^{-8} and 1.2×10^{-6}. Taking into account that Cmax of rifaximin in the gut lumen reaches 3500 μg/ml[11] i.e. greater than the MIC for generated mutants, it may be postulated that the real danger of acquisition of isolates of *E.coli* resistant to rifaximin seems extremely limited.

Part of the hypothesis for the limited risk for acquisition of resistant *E.coli* isolates was verified in a prospective randomized study enrolling patients with traveler's diarrhea; 24 were treated with placebo for three days; 23 with rifaximin 200mg three times daily for three days; and 24 with rifaximin 400 mg three times daily for three days. Stool was collected at baseline and on days 3 and 5. None resistant *E.coli* was cultured from the stool of any patient either at baseline or during treatment follow-up. From the enrolled patients, 8 of the placebo group, 9 of the rifaximin 200 mg three times daily group and 10 of the rifaximin 400 mg three times daily group were carriers of *Enterococcus* spp in their stool at baseline. MIC_{90}s on day 0 of rifaximin for that species before treatment were 8, 2 and 16 μg/ml respectively; on day 3 at the end of treatment they were 8, 2 and 16 μg/ml respectively[23] so as to remain unaltered under the selection pressure of rifaximin. The latter clinical data clearly signify the limited risk for acquisition of resistant isolates after treatment with rifaximin. They should, however, be interpreted with caution since they derive from just one study.

IBS AND RIFAXIMIN: PRESENT AND FUTURE

There is accumulating evidence pointing towards benefit form short course treatment with rifaximin in the global improvement of patients with IBS. This evidence arises from all trials analyzed in the present review showing a major benefit for patients with IBS connected with SIBO. In all these trials, rifaximin substantially improved bloating. Based on that sense of reasoning and using the GRADE recommendation system, the Task Force for IBS of the American College for Gastroenterology appointed a grade of recommendation of 1B for the short course administration of rifaximin in one recently published evidence-based review for the management of IBS[24]. The proposed dose regimen is 400mg three times daily for 10 days. It should, however, be mentioned that all available evidence comes from Phase II trials and larger Phase III trials are mandatory to fully elucidate the role of rifaximin for the management of IBS. Another issue that remains to be clarified is whether repeated courses of therapy may be needed.

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