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EDITORIAL

Rifaximin in the treatment of inflammatory bowel disease

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Abstract

The gut microbiota plays a role in promoting and maintaining inflammation in inflammatory bowel diseases (IBD), hence the rationale for the use of antibiotics in the treatment of those disorders. Antibiotics, however, may induce untoward effects, especially during long-term therapy. Rifaximin α polymer is an antibacterial agent that is virtually unabsorbed after oral administration and is devoid of systemic side effects. Rifaximin has provided promising results in inducing remission of Crohn's disease (up to 69% in open studies and significantly higher rates than placebo in double blind trials) and ulcerative colitis (76% in open studies and significantly higher rates than placebo in controlled studies) and might also have a role in maintaining remission of ulcerative colitis and pouchitis. The potential therapeutic activity of rifaximin in IBD deserves to be further investigated and confirmed in larger, controlled studies. The optimal dosage still needs to be better defined.

Key words: Antibiotics; Gut microbiota; Inflammatory bowel disease; Rifaximin

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INTRODUCTION

The etiology of inflammatory bowel diseases (IBD) still remains obscure. Genetic, immunological, environmental, and psychological factors can all play a role in the pathophysiology of both ulcerative colitis and Crohn's disease.

The gut microbiota is now recognized as a further important factor involved in promoting and/or maintaining the inflammatory process typical for IBD[1-3].

The concentration of intestinal bacteria in IBD patients is higher than normal, gradually increasing with the severity of the disease[1]. A breakdown in the qualitative balance between protective and harmful bacteria (dysbiosis) has also been proposed as a potential mechanism[2].

Indeed, in Crohn's disease, an increased presence of *Campylobacter concisus*[4] and *E. Coli*[5], as well as a substantial decrease in the amount of the anti-inflammatory commensal *Faecalibacterium prausnitzii*[5,6], has been reported.

On the other hand, it has been suggested that *Fusobacterium varium* can promote the development of ulcerative colitis[7].

The above data constitute a good rationale for the use of antibiotics in IBD[8].

Various meta-analyses have demonstrated that antibiotics such as metronidazole, ciprofloxacin, clofazimine and antibiotic combinations can be successfully employed in the treatment of Crohn's disease[9-11], ulcerative colitis[12] and pouchitis[13].

However, prolonged administration of antibiotics is accompanied by systemic adverse effects.

Rifaximin α-polymer, a rifampicin derivative, is a

locally acting antibacterial agent that is virtually unabsorbed after oral administration, is mostly excreted as unchanged drug in the stools in the course of intestinal disorders, and is thus devoid of systemic side effects.

It exhibits a broad-spectrum activity against enteric bacteria and a lack of clinically relevant acquired resistance[14-16]. Currently approved in the United States for the treatment of travellers' diarrhea, rifaximin is being used in a variety of gastrointestinal disorders, such as small intestine bacterial overgrowth, colonic diverticular disease, *Clostridium difficile* infection, as well as in the treatment of portal systemic encephalopathy[16,17].

In particular, rifaximin has been shown to modulate the colonic microbiota of patients with Crohn's disease by increasing the concentration of *Bifidobacteria* and *Faecalibacterium prausnitzii*[18].

In addition, experimental studies have shown that the drug can reduce the development of trinitrobenzene sulfonic acid-induced colitis and accelerate healing by preventing bacterial translocation[19], as well as exerting anti-inflammatory activities by increasing the expression of pregnane-X-receptor and by antagonizing the effects of tumor necrosis factor -α on intestinal epithelial cells[20,21].

The possible therapeutic role of rifaximin in the treatment of IBD has been repeatedly investigated in recent years.

RIFAXIMIN AND CROHN'S DISEASE

Further to an open-label study where rifaximin 200 mg tid administered for 16 wk to 29 patients with active Crohn's disease reduced Crohn's disease activity index (CDAI) score by more than 40% and induced clinical remission in 59% of cases[22], and a recent retrospective analysis of the charts of 68 patients receiving adjunctive therapy with rifaximin (mean dose 600 mg/d for 16 wk) showing remission in up to 70% of cases[23], two controlled studies were carried out.

A multicenter, double-blind, placebo controlled trial including 83 patients with mild-to-moderate Crohn's disease[24] found that monotherapy with rifaximin 800 mg bid for 12 wk was superior to placebo in promoting clinical remission (CDAI < 150), which was observed in 52% of cases compared with 33% in the placebo group. The difference in remission rates, however, was statistically significant ($P = 0.032$) only between the subgroups of patients with baseline values of C reactive protein above the upper normal limit.

A recent, international, multicenter, randomised study enrolling 402 patients from 55 centers in Europe and Israel demonstrated that an extended intestinal release formulation of rifaximin 400 mg in daily doses of 400-1200 mg bid for 12 wk was significantly superior to placebo in inducing remission (as defined as a CDAI < 150).

The best results were observed at the dose of 800 mg bid (remission rate 62.2% *vs* 42.6% in the placebo group: $P = 0.005$) and the effects were maintained during a subsequent 12-wk follow-up without treatment[25].

RIFAXIMIN AND ULCERATIVE COLITIS

In an open-label study, 30 patients with a mild-to-moderate flare-up of ulcerative colitis during maintenance treatment with mesalazine, and in whom steroid treatment was not advisable because of a history of poor tolerability, rifaximin 400 mg bid was added for four weeks[26]. Clinical remission was obtained in 76.6% of cases.

On the other hand, a group of 28 patients refractory to steroid therapy received an adjunct therapy with either rifaximin 400 mg bid or placebo for 10 d, in a double blind fashion. In the rifaximin group clinical improvement was observed in 64.3% of patients, who showed a significant reduction in stool frequency ($P < 0.02$), rectal bleeding ($P < 0.05$) and sigmoidoscopic score ($P < 0.05$) compared with placebo[27].

A small pilot experience on six mesalazine-intolerant patients with ulcerative colitis, who were in remission after a course of oral steroids, employed a combination of rifaximin 400 mg + the probiotic agent *Saccharomyces boulardii* 500 mg as a maintenance treatment for three months. At the end of the treatment period, all patients were still in clinical remission, which suggests that this therapeutic combination can be useful in preventing early relapses of ulcerative colitis[28].

Rifaximin, in doses ranging from 200 to 1800 mg/d, was also assessed as a maintenance therapy in 51 patients who had undergone restorative proctocolectomy and ileal pouch-anal anastomosis for ulcerative colitis, affected by antibiotic-dependent pouchitis[29]. At 3 mo, remission was maintained in 65% of patients. 79% of these patients were still in remission at 6 mo, 58% at 12 mo and 6% at 24 mo.

A combination of rifaximin 1000 mg bid and ciprofloxacin 500 mg bid for 15 d had been previously found capable of promoting either improvement (55.5%) or remission (33.3%) in eighteen patients with chronic active pouchitis[30].

CONCLUSION

The role of the gut microbiota in the development and maintenance of inflammation in IBD provides the rationale for the use of antibiotics in the medical treatment of both Crohn's disease and ulcerative colitis. Systemic antibiotics, such as ciprofloxacin and/or metronidazole, are commonly employed with good results, but possible side effects limit their use, especially for prolonged periods.

On the other hand, rifaximin α polymer, thanks to its negligible intestinal absorption, represents a safer and more attractive alternative. Both in open and in controlled studies, rifaximin, either in monotherapy or as an adjunctive treatment, was found to provide satisfactory results when administered for up to 12 wk (Table 1).

In a preliminary experience in children with IBD, rifaximin induced encouraging results and proved to be well tolerated[31].

Additional controlled study are warranted to fur-

Table 1 Rifaximin in inflammatory bowel disease

Ref.	Year	Patient (*n*)	Study type	Dose (mg)	Duration (wk)	Concomitant medication	Outcome
Crohn's disease							
Shafran *et al*[22]	2005	29	Open	200 tid	16	Various	Remission up to 59%
Shafran *et al*[23]	2010	68	Open	200 tid	16	Steroids (46%)	Remission rate up to 65%
Prantera *et al*[24]	2006	83	Db RCT	800 bid	12	None	Remission rate > placebo
Prantera *et al*[25]	2010	402	Db RCT	400-1200 bid	12	Various (no steroids)	Remission rate > placebo (also at 12 wk follow-up)
Ulcerative colitis							
Guslandi *et al*[26]	2006	30	Open	400 bid	4	Mesalazine	Remission rate 76%
Gionchetti *et al*[27]	1999	28	Db	400 bid	10 d	Steroids	Clinical improvement > placebo
Guslandi *et al*[28]	2010	6	Open, pilot	400 od	12	*S.boulardii*	Remission maintained in 100%

Db: Double blind; RCT: Randomized controlled trial; >: Significantly higher.

ther confirm and expand the currently available data on the possible role of rifaximin in the treatment of IBD patients and to better define the optimal dosage of the drug in this clinical setting.

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