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.

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

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[3-8].

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[6] 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, etofloxine and antibiotic combinations can be successfully employed in the treatment of Crohn’s disease[9-13], ulcerative colitis[13] and pouchitis[14].

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\cite{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\cite{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*\cite{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\cite{19,20}, 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\cite{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\cite{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\cite{23}, two controlled studies were carried out.

A multicenter, double-blind, placebo controlled trial including 83 patients with mild-to-moderate Crohn’s disease\cite{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\cite{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\cite{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\cite{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\cite{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\cite{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\cite{29}.

**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\cite{30}.

Additional controlled study are warranted to fur-
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.

REFERENCES

1. Swidsinski A, Ladhoff A, Pernthaler A, Swidsinski S, Loe- ning-Baucke V, Ortner M, Weber J, Hoffmann U, Schreiber S, Dietel M, Lochs H. Mucosal flora in inflammatory bowel disease. *Gastroenterology* 2002; 122: 44-54

2. Tamboli CP, Neut C, Desreumaux P, Colombel JF. Dysbiosis in inflammatory bowel disease. *Gut* 2004; 53: 1-4

3. Macfarlane S, Steed H, Macfarlane GT. Intestinal bacteria and inflammatory bowel disease. *Cirt Rev Clin Lab Sci* 2009; 46: 25-54

4. Man SM, Zhang L, Day AS, Leach ST, Lemberg DA, Mitch- ell H. Campylobacter concisus and other Campylobacter species in children with newly diagnosed Crohn’s disease. *Inflamm Bowel Dis* 2010; 16: 1008-1016

5. Schwierz A, Jacobi M, Frick JS, Richter M, Rusch K, Köhler H. Microbiota in pediatric inflammatory bowel disease. *J Pe- diatr* 2010; 157: 240-244.e1

6. Sokol H, Pigneur B, Watterlot L, Lakhdari O, Bermúdez-Hu- marán LG, Gratadoux JJ, Blugeon S, Bridonneau C, Furet JP, Corthier G, Grangette C, Vasquez N, Pochart P, Trugnan G, Thomas G, Blottière HM, Doré J, Marteau P, Seksik P, Lan marán LG, Gratadoux JJ, Blugeon S, Bridonneau C, Furet JP, Corthier G, Grangette C, Vasquez N, Pochart P, Trugnan G, Thomas G, Blottière HM, Doré J, Marteau P, Seksik P, Langel- gella P. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proc Natl Acad Sci USA* 2008; 105: 16731-16736

7. Ohkusa T, Okayasu I, Oghara T, Morita K, Ogawa M, Sato N. Induction of experimental ulcerative colitis by Fusobacte- rium varium isolated from colonic mucosa of patients with ulcerative colitis. *Gut* 2003; 52: 79-83

8. Guslandi M. Antibiotics for inflammatory bowel disease: do they work? *Eur J Gastroenterol Hepatol* 2005; 17: 145-147

9. Feller M, Huwiler K, Schroepfer A, Shang A, Furrer H, Eg- ger M. Long-term antibiotic treatment for Crohn’s disease: systematic review and meta-analysis of placebo-controlled trials. *Clin Infect Dis* 2010; 50: 473-480

10. Rahimi R, Nikfar S, Rezaie A, Abdollahi M. A meta-analysis of broad-spectrum antibiotic therapy in patients with active Crohn’s disease. *Clin Ther* 2006; 28: 1953-1988

11. Nikfar S, Mirfazaelian H, Abdollahi M. Efficacy and toler- ability of immunoregulators and antibiotics in fistulizing Crohn’s disease: a systematic review and meta-analysis of placebo-controlled trials. *Curr Pharm Des* 2010; 16: 3684-3698

12. Rahimi R, Nikfar S, Rezaie A, Abdollahi M. A meta-analysis of antibiotic therapy for active ulcerative colitis. *Dig Dis Sci* 2007; 52: 2920-2925

13. Elahi B, Nikfar S, Derakhhani S, Vafaie M, Abdollahi M. Benefit of antibiotic therapy on pouchitis after ileal pouch anal anastomosis: a systematic review and meta-analysis of clinical trials. *Cent Eur J Med* 2009; 4: 164-170

14. Scarpignato C, Polosini I, Rifaxim in, a poorly absorbed an- antibiotic: pharmacology and clinical potential. *Chemotherapy* 2005; 51 Suppl 1: 36-66

15. Jhang ZD, DuPont HL. Rifaximin: in vitro and in vivo anti- bacterial activity--a review. *Chemotherapy* 2005; 51 Suppl 1: 67-72

16. Ojetti V, Lauritano EC, Barbaro F, Mirigoccio A, Ainora ME, Fontana L, Gabrielli M, Gasbarrini A. Rifaximin pharmacol- ogy and clinical implications. *Expert Opin Drug Metab Toxicol* 2009; 5: 675-682

17. Koo HL, DuPont HL. Rifaximin: a unique gastrointestinal-selective antibiotic for enteric diseases. *Curr Opin Gastroen- terol* 2010; 26: 17-25

18. Maccaferri S, Vitali B, Klinger A, Kolda S, Ndagijimana M, Laghi L, Calamini F, Brigidi P, Gibson GR, Costabile A. Rifaximin modulates the colonic microbiota of patients with Crohn’s disease: an in vitro approach using a continuous culture colonic model system. *J Antimicrob Chemother* 2010; 65: 2556-2565

19. Fiorucci S, Distretti E, Mencarelli A, Barbanti M, Palazzini E, Morelli A. Inhibition of intestinal bacterial translocation with rifaximin modulates lamina propria monocytic cells reactivity and protects against inflammation in a rodent model of colitis. *Digestion 2002; 66: 246-256

20. Mencarelli A, Migliorati M, Barbanti M, Cipriani S, Palla- dino G, Distretti E, Renga B, Fiorucci S. Pregnane-X-receptor mediates the anti-inflammatory activities of rifaximin on detoxification pathways in intestinal epithelial cells. *Biochem Pharmacol* 2010; 80: 1700-1707

21. Cheng J, Shah YM, Ma X, Pang X, Tanaka T, Kodama T, Krausz KW, Gonzalez FJ. Therapeutic role of rifaximin in inflammatory bowel disease: clinical implication of human pregnane X receptor activation. *J Pharmacol Exp Ther* 2010; 335: 32-41

22. Shafar I, Johnson LK. An open-label evaluation of rafixi- min in the treatment of active Crohn’s disease. *Curr Med Res Opin* 2005; 21: 1165-1169

23. Shafar I, Burgunder P. Adjunctive antibiotic therapy with rifaximin may help reduce Crohn’s disease activity. *Dig Dis Sci* 2010; 55: 1079-1084

24. Branca C, Locchi H, Campieri M, Scibiano ML, Stariniolo GC, Casteiglione F, Cottone M. Antibiotic treatment of Crohn’ s disease: results of a multicentre, double blind, randomized, placebo-controlled trial with rifaximin. *Aliment Pharmacol Ther* 2006; 23: 1117-1125

25. Prantera C, Locchi H, Gionchetti P, Campieri M, Danese S, Fogli M, Scibiano M, Grimoldi M. Rifaximin-ELIR (extended intestinal release) 400 mg tablets in the treatment of moder-ately active Crohn’s disease: results of the international multicentre, double-blind, placebo-controlled trial. *Cot 2010;*
Guslandi M. Rifaximin for IBD

26 Guslandi M, Petrone MC, Testoni PA. Rifaximin for active ulcerative colitis. *Inflamm Bowel Dis* 2006; 12: 335

27 Gionchetti P, Rizzello F, Ferrieri A, Venturi A, Brignola C, Ferretti M, Peruzzo S, Miglioli M, Campieri M. Rifaximin in patients with moderate or severe ulcerative colitis refractory to steroid-treatment: a double-blind, placebo-controlled trial. *Dig Dis Sci* 1999; 44: 1220-1221

28 Guslandi M. Saccharomyces boulardii plus rifaximin in mesalamine-intolerant ulcerative colitis. *J Clin Gastroenterol* 2010; 44: 385

29 Shen B, Remzi FH, Lopez AR, Queener E. Rifaximin for maintenance therapy in antibiotic-dependent pouchitis. *BMC Gastroenterol* 2008; 8: 26

30 Gionchetti P, Rizzello F, Venturi A, Ugolini F, Rossi M, Brigidi P, Johansson R, Ferrieri A, Poggioli G, Campieri M. Antibiotic combination therapy in patients with chronic, treatment-resistant pouchitis. *Aliment Pharmacol Ther* 1999; 13: 713-718

31 Muniyappa P, Gulati R, Mohr F, Hupertz V. Use and safety of rifaximin in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2009; 49: 400-404

S-Editor Sun H L-Editor Stewart GJ E-Editor Zhang DN