# Review – Antibiotic treatment in inflammatory bowel disease: rifaximin, a new possible approach

P. GIONCHETTI, F. RIZZELLO, A. VENTURI, F. UGOLINI*, M. ROSSI**,
P. BRIGIDI**, R. JOHANSSON, A. FERRIERI***, G. POGGIOLI*, M. CAMPIERI

Clinica Medica I, Nuove Patologie, Bologna University (Italy)
*Istituto di Clinica Chirurgica II, Bologna University (Italy)
**Dipartimento di Scienze Farmaceutiche, Bologna University (Italy)
***Direzione Medica Alfa Wassermann, Bologna (Italy)

**Abstract.** – The etiology of inflammatory disease is still unknown, but a body of evidence from clinical and experimental observation indicates a role for intestinal microflora in the pathogenesis of this disease. Reduction of microflora using antibiotics, bowel rest and fecal diversion decreases activity in Crohn's disease and in ulcerative colitis. Several trials have been carried out on the use of antibiotic treatment in patients with active ulcerative colitis with contrasting results. A number of trials have been carried out using Rifaximin, a non-absorbable broad-spectrum antibiotic, confirming the absence of systemic bioavalaibility of the drug even when administered at very high doses and for prolonged periods. It may therefore be useful in treatment of ulcerative colitis and pouchitis, since its absorption through inflamed mucosa is negligible, it maintains a topical action without systemic effects and the lack of resistant bacterial strains may allow prolonged and repeated treatments.

Key Words:

Rifaximin, Antibiotic, IBD, Ulcerative colitis.

## Introduction

The ethiology of inflammatory bowel disease (IBD) remains unknown, but a body of evidence from clinical and experimental observations indicates a pathogenetic role among others for intestinal microflora[1]. The distal ileum and the colon are the areas with the highest intraluminal bacterial concentration, and represent the sites of primary inflammation in IBD. Recent studies have reported the presence of a breakdown of tolerance to the normal commensal intestinal flora in active IBD[2-3]. Reduction of microflora by antibiotics, bowel rest and fecal diversion decreases inflammatory activity in Crohn's disease and to a lesser extent in ulcerative colitis (UC). The pathogenetic role of intestinal microflora is further suggested by the observation that experimental colitis, in germ-free or antibiotic treated animals, is less severe compared to that inducible in normal animals or at times is not inducible at all. Moreover, bacterial products, such as N-formil-methionyl-leucyil-phenylalanine (FMLP), lipopolysaccharidase (LPS) and peptidoglycan-polysaccharidase (LPS), can induce and perpetuate experimental colitis[4-8].

Pouchitis, a non-specific inflammation of the ileal reservoir (pouch) mucosa, is the major long-term complication encountered after proctocolectomy and ileo-anal anastomosis for UC. The etiology and pathophysiology of pouchitis are not well understood, and a variety of hypotheses have been proposed to explain this inflammatory condition. Among this, a major role has been attributed to fecal stasis and bacterial overgrowth, recurrent UC, misdiagnosed Crohn's disease and mucosal ischemia of the pouch[9]. However, pouchitis most likely seems to be the result of a complex interaction between a genetical or immunological susceptibility of the patient and the morphological and functional modifications of the ileal-pouch, due to the fecal stasis and consequent bacterial overgrowth[10-11].

Several trials have been carried-out on the use of antibiotic treatment in patients with ac-

tive UC, with contrasting results. Intravenous metronidazole was not found to be superior to placebo when used in association with corticosteroids in severe UC[12], while oral vancomicyn showed a certain efficacy, that however did not reach statistical significance[13].

Favorable results have been obtained with tobramicyn, an aminoglycoside active against Gram negative bacteria, administered together with standard steroid treatment; 74% of patients achieved a complete symptomatic remission compared with only 43% in the placebo treated group[14]. However, a more recent trial with cyprofloxacin has not been able to demonstrate a favourable effect of antibiotic treatment when compared to placebo[15].

Treatment of pouchitis remains empirical, and antibiotics are the mainstay of therapeutic regimens; metronidazole is the most common administered first-line antibiotic, and most patients show remission of clinical symptons within a few days. One double-blind, placebo-controlled study utilizing metronidazole showed a significant reduction of bowel motions however without improvement of endoscopic appearance of the inflammed intestinal tract or of the histological inflammatory activity[16]. Other antibacterial agents that have shown some positive results are ciprofloxacin, the association of amoxicyllin+clavulanic acid, tetracycline and erythromycin.

No attempt has been made to compare metronidazole with other therapeutic regimens. About 15% of patients with pouchitis present a chronic inflammatory condition. In same cases, this inflammation is treatment-responsive and requires maintainance metronidazole therapy with a high incidence of side effects (dysgeusic nausea and peripheral neuropathy). In other cases pouchitis shows no response to antibiotic-treatment and is defined as treatment-resistant.

Rifaximin is a non-absorbable antibiotic. Its mechanism of action is based on the inhibition of prokaryotic RNA-polymerase. The inhibition of this enzyme suppresses initiation of chain formation during RNA synthesis. The drug has bactericidal rather than bacteriostatic property having a low ratio between bactericidal and inhibitory activity (1:1 to 4:1 in susceptible strains)[17]. It shares the same antibacterial spectrum with other rifamycins, covering all the main Gram positive and neg-

ative, aerobic and anaerobic species associated with gastro-intestinal infection[17-18].

Resistance to rifaximin has been demonstrated to occur either in vitro and in vivo in residual intestinal flora; drug resistance however decreases rapidly after the end of the treatment, and disappeares completely after 1 to 2 weeks for anaerobic cocci, enterococci and *Enterobacteriacee*, and after 8 to 16 weeks for *Clostridium* and *Bacteroides* species. Therefore it appears that rifaximin resistant strains are unable to permanently colonize the gastro-intestinal tract[19].

Several experimental and clinical observations have shown that rifaximin is virtually not absorbed. Recent experiments with ^{14}C-rifaximin performed in rat and dog models showed that, after intravenous administration, plasma levels were detectable for 4 and 12 hours respectively, whereas after oral administration, serum radiolabelled product levels were very low and detectable only for 1 and 6 hours, respectively. Following oral administration in rats, after 48 hours the excretion of radioactivity in urine was about 0.7% of the dose, whereas in faeces the radiolabelled product was found in quantities that reached 90% or more of the oral dose; similar results were observed in dogs. Following intravenous administration in dogs, within 24/48 hours most of the radioactivity was excreted in faeces (83% dose), whereas urinary excretion was about 6% of the administered dose; 168 hours after administration, radioactivity was totally excreted in faeces, possibly as a consequence of enterohepatic circulation of ^{14}C-rifaximin or its metabolites[20].

Blood levels in healthy volunteers, after single oral administration of a dose of 400 mL, were undetectable in 50% of volunteers and below 5 ng/mL in the other 50%, using techniques with detection limit of 2 ng/mL. After 48 hours, urinary recovery of the drug did not exceed 0.025% of the administered dose (unpublished observation).

More recently, in one study which investigated the systemic absorption of rifaximin after single oral administration of 400 mg, in patients with mild to moderate ulcerative colitis, urinary excretion was found to be negligible, and plasma concentration was undetectable in almost all patients[21].

Largely variable amounts of rifaximin have been recovered in faeces, depending on mass

of the faeces and transit time. In some cases up to 76% of the administered dose could be recovered in faeces in 24 hours. Therefore, independently from its poor absorption, rifaximin is not distributed at a systemic level but undergoes a first pass removal by the liver and its behaviour is like rifamycin SV, which does not show any systemic absorption, remaining in the enterohepatic circulation, and being subsequently almost totally excreted in faeces.

Rifaximin has been used successfully in the treatment of hepatic encephalopathy, acute infectious diarrheal disease, preparation for colonic and biliary surgery and diverticulitis[22-25].

Because of its broad spectrum and its mainly topical activity, we recently conducted a pilot placebo-controlled study in a group of patients with severe UC refractory to steroid treatment using rifaximin as an adjunct to standard steroid treatment.

Fourteen patients received rifaximin (800 mg/day) and 14 received an identical placebo. Overall nine patients (64.3%) receiving rifaximin and five (41.7%) (p NS) receiving placebo showed a positive response to the treatment, as defined by an improvement of the disease's clinical activity from baseline to the 10th day, and tapered steroids gradually. Moreover rifaximin determined a significant reduction in stool frequency ($p<0.02$), rectal bleeding ($p<0.05$) and sigmoidoscopic score ($p<0.01$) compared with placebo. Twelve hours after the last dose of rifaximin, it was not possible to identify the drug in any of the plasma samples (2 ng/mL was the detection limit of the analytical method). The total amount of rifaximin excretion in 24-hrs urine after 10 days was $64,617.14 \pm 20,976.57$ ng/mL (mean±SEM)[26]. These findings suggest that rifaximin may be useful in patients with steroid refractory UC. More recently we utilized rifaximin (1 g b.d.) in association with ciprofloxacin (500 mg b.d.), given for 15 days, in patients with chronic, antibiotic-resistant pouchitis. Eighteen patients, who failed to respond to metronidazole as well as to other commonly used treatments for pouchitis, entered the study. Sixteen of 18 treated patients (88.8%) either improved (n=10) or went into remission (n=6), with a decrease of the median Pouchitis Disease Activity Index (PDAI) score from 12 (range 8-17) to 4 (range 0-16). Pharmacokinetic study of rifaximin showed

the absence of the drug in any at the plasma samples 12 hrs after from the last dose, and the presence of negligible levels of the unchanged active principle in 24 hrs urine samples. These data further confirm the absence of systemic bioavailability of the drug even when administered at very high dosage (2 g/day) and for a prolonged period[27].

It is possible to conclude that rifaximin may be useful in treatment of ulcerative colitis and pouchitis; its absorption through inflamed mucosa is negligible as in normal mucosa. The drug maintains a topical action without systemic effects. The absence of resistant bacterial strains, able to permanently colonize the gastro-intestinal tract, may allow prolonged and repeated treatment cycles.

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