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Use of antibiotics in the treatment of Crohn's disease

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Abstract

Many data coming from animal models and clinical observations support an involvement of intestinal microbiota in the pathogenesis of Crohn's disease (CD). It is hypothesized in fact, that the development of chronic intestinal inflammation is caused by an abnormal immune response to normal flora in genetically susceptible hosts. The involvement of bacteria in CD inflammation has provided the rationale for including antibiotics in the therapeutic armamentarium. However, randomized controlled trials have failed to demonstrate an efficacy of these drugs in patients with active uncomplicated CD, even if a subgroup of patients with colonic location seems to get benefit from antibiotics. Nitroimidazole compounds have been shown to be efficacious in decreasing CD recurrence rates in operated patients, and the use of metronidazole and ciprofloxacin is recommended in perianal disease. However, the appearance of systemic side effects limits antibiotic long-term employment necessary for treating a chronic relapsing disease. Rifaximin, characterized by an excellent safety profile, has provided promising results in inducing remission of CD.

Key words: Antibiotics; Crohn's disease; Gut microbiota; Mycobacteria

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ROLE OF GUT MICROBIOTA IN CROHN'S DISEASE

Crohn's disease (CD) is a chronic inflammatory bowel disease characterized by an altered composition of the intestinal commensal bacteria (dysbiosis)[1,2]. Dysbiosis is considered to have a preeminent role in CD pathogenesis by inducing an abnormal immune response in genetically susceptible individuals[3-7].

Intestinal sites commonly affected by CD lesion, in fact, are those with the highest bacterial concentration, such as colon, terminal ileum, especially after the loss of the ileocecal valve, and upstream from strictures. The luminal content is necessary for causing intestinal inflammation, and CD lesions do not appear when it is diverted from the gut, whereas restoration of bowel continuity or infusion of faecal material into the bypassed intestine rapidly results in recurrence of the disease[8-10]. In genetically engineered rodent models susceptible to spontaneous colitis, inflammation does not occur when the animals are raised in germ-free conditions[11]. Patients with CD have an altered composition of gut microbiota with increased concentrations of invasive bacteria, especially *Escherichia coli* (*E. coli*) and a decreased number of protective bifidobacteria, lactobacilli and the more recently studied *Faecalibacterium prausnitzii,* that has been shown to have anti-inflammatory properties[12-15]. Genetic susceptibly in a subgroup of patients with CD is related to polymorphisms in the *NOD2/CARD15* gene, suggesting that individuals with mutations in *NOD2* present defective intestinal immune responses to gut microbiota[16-20]. About 20% of CD patients are homozygous for *NOD2* variants and they may have an increased susceptibility to CD localized at the ileum[21].

Moreover, a loss of immunologic tolerance to the

commensal flora has been observed in patients with active IBD[22].

Experimental studies in animal models have shown that broad-spectrum antibiotics are efficacious in almost all models of acute and chronic colitis and ileitis[23]. However, they have only a transient benefit in HLA-B27 transgenic rats[24]. Broad-spectrum antibiotics can both prevent and treat experimental colitis of rodent models, while metronidazole and ciprofloxacin can only prevent the onset of colitis, but not reverse the established disease[25,26].

ANTIBIOTIC TREATMENT IN CROHN'S DISEASE

These and other data, confirming the role of the gut microbiota in the pathogenesis of CD, provide the rationale for a therapeutic manipulation of the intestinal flora through the use of antibiotics and probiotics[27-30].

Some of the suggested mechanisms of action for antibiotics in CD are the ability to reduce luminal and mucosa adherent bacteria concentrations, to eliminate in a selective way aggressive bacterial species, to decrease bacterial tissue invasion and translocation. Additionally, some antibiotics also exert a potential immunosuppressive action.

The role of antibiotics as primary or adjunctive treatment of active, uncomplicated CD has not been clearly demonstrated and their use is controversial. A recent meta-analysis suggests that antibiotics may be effective as primary therapy of CD[31], but guidelines do not recommend their use except for the treatment of septic complications of CD, symptoms attributable to bacterial overgrowth, or perianal disease[32].

ANTIBIOTICS FOR INDUCTION AND MAINTENANCE OF DISEASE REMISSION

The similarity of CD to tuberculous enteritis and Johne's disease of ruminants, caused by *Mycobacterium Avium* subspecies *Paratuberculosis* (MAP), and the isolation of atypical Mycobacteria from blood and tissue of CD subjects, have lead to evaluate the efficacy of anti-mycobacterial drugs in these patients[33-37]. However, the results of the randomized controlled trials performed with antibiotics active against atypical Mycobacteria for obtaining and maintaining CD remission have been conflicting.

A meta-analysis that considered eight trials employing different associations of anti-mycobacterial drugs showed that these drugs seem to be ineffective for inducing remission without a course of steroid therapy[38].

In the largest study 213 Australian patients were randomized to receive a combination of clarithromycin plus rifabutin and clofazimine, antibiotics active against MAP, or placebo for up 2 years, in addition to a 16-week course of corticosteroids[39]. The results showed a significant benefit only at 16 wk, when the antibiotic combination was added to steroids, confirming the data founded by the meta-analysis, and suggesting that the short-term advantage could be related to a generic antibacterial effect. Therefore, this study does not support a significant role for MAP in CD pathogenesis, although several objections to this conclusion have been raised[40-44]. At the present time the mycobacterial hypothesis cannot be completely ruled out, and it continues to be plausible that an infectious agent could start the inflammatory process[45].

Pathogenic adherent and invasive *E. coli* have been detected in Crohn's ileal and colonic tissue[46-49]. This bacterium can invade and replicate within macrophages, inducing the secretion of large quantities of tumor necrosis factor[50]. Clarithromycin is a broad spectrum macrolide antibiotic that can penetrate into macrophages, and may therefore be effective in eradicating the bacteria. However, a study comparing clarithromycin 1 gr to placebo for 3 mo in patients with active CD, was stopped because of poor efficacy[51].

Metronidazole, which is active against anaerobic bacteria and some parasites, and ciprofloxacin, particularly active against *E. coli* and *Enterobacteriacee*, are the most frequent studied and used antibiotics. Several randomized clinical trials have been performed employing metronidazole and/or ciprofloxacin for induction of CD remission.

The results of the trials have indicated that metronidazole is efficacious in active Crohn's colitis and ileo-colitis, but not in small bowel location[52-55]. Five randomized controlled studies evaluating the efficacy of ciprofloxacin, alone or in association with metronidazole, in patients with active CD, have shown uncertain results[56-60].

Patients with colonic involvement get more benefit from antibiotics, probably because of the high concentration of bacteria in the colon.

The efficacy of antibiotics in CD seems to be related to a prolonged therapy, that is frequently burdened by an elevated number of systemic adverse events (AEs). In particular, there is concern about the *Clostridium difficile* infection caused by antibiotics, especially fluoroquinolones such as ciprofloxacin[61]. *Clostridium difficile* infection can induce CD relapse and gastroenterologists in charge of CD patients must be aware of this serious complication. In 2007 two retrospective studies demonstrated a dramatically increased incidence of *Clostridium difficile* infection in patients with IBD, who appeared to be more susceptible to this infection than non IBD-patients[61,62].

The minimally absorbed antibiotic rifaximin, which is active against gram-positive and gram-negative bacteria, has been shown to be effective in active CD patients. In an exploratory study, a gastro resistant formulation of rifaximin [extended intestinal release (EIR)] (rifaximin-EIR) at a dose of 800 mg twice daily for 12 wk reported significantly higher rates of remission and response compared to placebo, in a subgroup of patients with mild to moderate CD and an elevated value of C-reactive protein[63].

In a recent, larger study 402 patients with moderately active CD were randomized to receive rifaximin-EIR 400, 800, 1200 mg or placebo twice daily for 12 wk[64]. The

results showed that rifaximin-EIR 800 mg twice daily was significantly superior to placebo in inducing remission, defined as a Crohn's Disease Activity Index (CDAI) score < 150, after 12 wk of therapy (62 % *vs* 43%). The effect was maintained throughout a subsequent 12-wk follow-up period in 65% of patients. Remission rates in patients treated with 400 and 1200 mg twice daily (54 % and 47 %, respectively) showed a trend towards but without reaching the statistical significance in comparison with placebo. The lack of a dose-response relationship was probably caused by the higher percentage of subjects who discontinued the treatment due to AEs in the 1200 mg twice daily group. Median CRP values over time showed no statistically significant differences between treatment groups. The most frequent AEs were of gastrointestinal origin, either determined by an underlying disease, with consequent CDAI score increase and treatment failure, or to rifaximin related side effects. Also in this study colonic location appeared to be associated with a higher response to the antibiotic therapy. Overall, the safety profile of rifaximin-EIR was good, indicating that rifaximin could be administered for a long period of time. However, *Clostridium difficile* infection was reported in a single patient with rifaximin 800 mg twice daily 20 d after the end of the treatment period. Rifaximin has been successfully employed for the treatment of CDI in metronidazole resistant patients[65], however it is probable that rare clones of rifaximin-unresponsive *Clostridium* can develop[66].

ANTIBIOTICS FOR PREVENTION OF POSTOPERATIVE RECURRENCE

Prevention of recurrence after intestinal resection is one of the major aims in the treatment of CD, and antibiotics have been used in this setting in 3 randomized placebo-controlled studies. The rationale for the employment of antibiotics is that bacteria are strongly suspected to be the main reason for the recurrence of lesions. In the first trial, metronidazole, at a dosage of 20 mg/kg per day for a 3-mo period, significantly decreased the incidence of early severe endoscopic recurrence, and also seemed to delay the symptomatic recurrence at 1 year, but it was associated with a high percentage of side effects[67]. The same authors have later performed a 12 mo placebo-controlled trial employing ornidazole, which has the same bacterial spectrum with a better safety profile. Ornidazole at a dose of 1 g/d proved significantly to reduce the clinical recurrence rate at 1 year, but more than 30% of patients in the antibiotic group discontinued the therapy because of side effects[68]. More recently, D' Haens *et al*[69]compared metronidazole (250 mg 3 times per day) given for 3 mo plus azathioprine for 12 mo to metronidazole alone in 81 operated CD patients at high risk of recurrence. This drug combination uses metronidazole as bridge therapy, given the slowness of azathioprine activity. At 3 mo after surgery severe endoscopic recurrence occurred in 34.3% of patients in the metronidazole/azathioprine group and in 52.6% of patients in the metronidazole/placebo group (P = 0.11). At month 12, severe endoscopic recurrence was observed in 43.7% of patients in the metronidazole/azathioprine group and in 69.0% of patients in the metronidazole/placebo group (P = 0.048). The study treatment was well tolerated and only 3 patients discontinued the therapy in the first 3 mo because of side effects, probably ascribable to metronidazole. The authors concluded that the combined treatment seems to be recommendable to CD patients with an elevated risk for postoperative recurrence. Recurrence prevention requires a long-term treatment, and this is burdened by a high number of AEs. Given its high safety profile, rifaximin, provided that its efficacy is completely demonstrated, should be employed for long term recurrence prevention.

ANTIBIOTICS FOR TREATMENT OF PERIANAL DISEASE

Antibiotics are widely employed for treatment of perianal CD, alone or as adjuvant therapy, and, despite the lack of controlled trials, European Crohn's and Colitis Organisation consensus statements recommend them in simple and complex fistulising perianal disease[70].

Most of the studies of perianal disease treated with antibiotics are, in fact, uncontrolled with a small sample size. In these studies, metronidazole and ciprofloxacin used alone or in combination have proved to induce a decrease of fistula drainage, but rarely induce closure. Moreover, symptoms tend to recur after suspending the treatment[71-73]. AEs resulting from prolonged use of antibiotics may, however, limit their use.

Recently, a randomized, placebo-controlled pilot study evaluating ciprofloxacin or metronidazole for the treatment of perianal fistulas in 25 CD patients failed to demonstrate a significant benefit of either antibiotic treatment over placebo in the cessation of drainage[74]. However the study was probably too small to permit detecting differences between treatment arms.

In conclusion, the different antibiotic regimens evaluated in the randomized controlled studies, the limited number of patient enrolled, the heterogeneity between the trials, and the uncertain results have led to the conclusion that antibiotics cannot be recommended for treatment of active CD, except for septic complications, symptoms attributable to bacterial overgrowth, or perianal disease. In addition, their efficacy could be limited by the prolonged therapy usually required for treating CD. However, there seems to be a subgroup of patients with colonic disease who can respond to these medications, likely due to the differences in gut microbiota between ileal and colonic location. Nitroimidazole antibiotics seem to be effective in decreasing both endoscopic and clinical recurrence rates after surgery, but their long-term use is complicated by an elevated number of AEs.

Treatment of patients with mild and moderate CD with rifaximin seems promising, but further larger studies are needed.

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