Probiotics and IBD

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Abstract

The pathophysiology of inflammatory bowel disease is still incompletely understood. While the development of the immune system and the establishment of the microflora take place during infancy young patients often have a more severe and extensive disease. The differences in composition and concentration of intestinal microbiota and aberrant immune responses towards the luminal bacteria prompted the concept of an 'ecological' approach to control the disease course. Probiotics, living, non pathogenic micro organisms with a beneficial effect on the host, and prebiotics, oligosaccharides promoting the growth of the beneficial microflora, have been studied to this effect. Results have so far been disappointing for Crohn's disease but encouraging for ulcerative colitis. An overview of studies using probiotics in adults or children and a perspective on specific pediatric issues is provided in this review. (Acta gastroenterol. belg., **2013**, 76, **15-19**).

Key words : Crohn's disease, inflammatory bowel disease, paediatrics, probiotics, ulcerative colitis.

Abbreviations

breastfeeding (BF)
Crohn's disease (CD)
inflammatory bowel disease (IBD)
Pediatric Crohn Activity Index (PCDAI)
ulcerative colitis (UC)

Introduction

The treatment of inflammatory bowel disease (IBD) is a subject of ongoing research. Biologicals have become part of daily practice in therapy resistant Crohn's disease (CD) and ulcerative colitis (UC) patients. Despite the excellent results obtained in clinical studies (1-4) and the new perspectives in IBD treatment that were obtained, unmet therapeutic needs remain a concern due to primary non response, loss of response or disease recurrence and complications. Advents for alternatives and/or adjuvant therapy are being investigated.

Our understanding of the pathophysiology of IBD is incomplete. A combination of environmental factors and an inadequate immune response towards intestinal flora in genetically predisposed people play an important role (5,6). We know that composition and concentration of intestinal flora differs in pediatric IBD patients (7,8). Subtypes such as bacteroides species are less prevalent compared to the healthy children (9). Intestinal biopsies obtained from IBD patients are covered by a dense concentration of bacteria with less biodiversity (7,8,10).

The installation of the microbiota is a dynamic process in infants. Genetic predisposition and early intestinal colonization during childbirth, lifestyle factors such as type of feeding and exposure to antibiotics influence this process. The interaction with the intestinal flora is crucial for priming the adaptive immune system. As a consequence, factors influencing the intestinal flora also impact on immune development.

Definition of a probiotic

Probiotics are live, non pathogenic microorganisms that have a positive influence on health or physiology (11). Their mechanism of action involves competitive action with commensal and pathogenic bacteria and influence epithelial function and immune response (12). They influence luminal composition, pH, metabolic products and biodiversity of the microbiota. Space occupation, competitive exclusion for bacterial substrates and increased mucosal IgA are the main mechanisms described to explain these modifications (13,14). Some probiotics reinforce the integrity of the mucosal barrier by normalizing intestinal permeability (15,16). All these factors make them interesting candidates for the treatment of intestinal inflammation.

Probiotics are generally safe but sepsis and even death has been reported in immunocompromised patients. A foreign body, such as a central cathether is a contra-indication for their use. The effect of a specific probiotic cannot be extrapolated to other probiotic strains, doses or conditions. It is crucial to study and use a particular strain, in well defined dosages and conditions as in other types of efficacy studies.

Microbiota and the immune system in infancy

The intestinal microflora is an eco-system that is mostly stable in a single individual but varies between different individuals. The adaptive immune system is primed as it distinguishes between self and non-self antigens in

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the intestinal lumen and between the pathogenic and non-pathogenic bacteria. The intestine of an unborn child is sterile and becomes colonised by the maternal vaginal flora during delivery (17). During the first year of life, the intestinal microbiota evolve to an extremely dense population consisting of 10^{13} cfu/g with diverse composition (18).

The establishment of the intestinal flora is influenced by genetics, as proven by the similarity in microflora of identical twins compared to their siblings (19). Furthermore, the mode of delivery, sanitary environment, feeding mode and maternal flora profoundly impact on the development of the intestinal flora and hence on the immune system as both seem to be linked (20,21).

The influence of breastfeeding (BF) on the intestinal microflora is well known as it favours a more bifidogenic intestinal population. BF contains several immunological factors such as prebiotics, probiotics and maternal Ig A that impact on the composition of the intestinal flora and immune system development.

In infants born by C-section colonisation by Bificobacteria and Bacteroides fragilis is delayed while C difficile is more prevalent and the total population is less dense (21-23). In preterm infants, the microbiota, determined by the clean environment and early antibiotic use, consist predominantly of Staphilococci (24).

The link between intestinal flora and development of immunity is suggested by the multiple epidemiological studies on allergy, demonstrating that C-section predisposes for atopy (22,25). A recent study on the influence of delivery mode on the development of IBD, suggests a mild increase in patients born by C-section (26).

The intestinal flora and IBD

Genome-wide association studies published in 2007 identified genes associated with the occurrence of IBD (27). Study of gene function led to a novel perspective on pathophysiology based on aberrant innate and adaptive immunity in IBD patients. Thus, commensal flora potentially triggers immune reactions that lead to chronic intestinal inflammation (28,29).

This hypothesis is further supported by data from animal studies : in mice with sterile guts, bacterial inoculation is a condition for the experimental IBD model (30). Several probiotics were shown to reduce colitis in mice and rats (31). Moreover, in humans, anti-bacterial agents are efficacious as therapeutics for IBD and surgical deviation of the faecal stream heals bowel inflammation in excluded segments (32,33).

The composition and concentration of microbiota of IBD patients differ from the normal population (7,34). UC patients harbour a higher bacterial concentration, especially in faecalibacteria Prauznitzi but a decreased concentration of bacteroides compared to CD patients (35). Interestingly, siblings and family members of IBD patients have an altered microflora even though they do not have the disease (36).

Altering the microbiota of IBD patients

1. *The role of enteral nutrition*

Enteral nutrition (EN) or enteral therapy is a monotonous diet consisting exclusively of a polymeric formula during at least 4 to 6 weeks. It s use is limited to pediatric CD patients. It can be consumed by mouth or be administered through a nasogastric tube. This therapeutic intervention is at least as efficient as steroids for induction of remission, lacks severe side effects and holds a beneficial influence on growth and weight gain (37,38). EN can induce remission and mucosal healing, one of the important factors in determining the rate and time to relapse. Borelli randomized 37 active pediatric CD patients to a polymeric formula or to steroids and showed a significantly higher remission rate (79% vs 67%) and obtained mucosal healing in 74% vs 33% in the group receiving EN (39). This therapeutic method is used in several pediatric centers worldwide (40,41). The mechanism of action however remains unclear. A decreased antigenic load and a benefical effect of the microbioia are suspected. Lionetti et al compared pediatric CD patients on EN to healthy controls by sampling stools throughout treatment. Microbiota were studied using 16s RNA PCR and TGGE for profiling. While healthy controls maintained a stable and host specific profile, CD patients underwent significant modifications of their flora after complete or even partial EN (42).

2. *Treating with probiotics : data in CD and UC*

a) CD

So far, results have been disappointing in adult CD (43-46). Evidence is lacking for any efficacy in induction of remission, prevention of relapse or postoperative prophylaxis. Malchov treated 28 patients with active CD with steroids + *E Coli Nissle* or placebo and did not show any difference in remission rate (75% *E Coli Nissle* vs 92% placebo), nor in the time until remission was obtained (21 vs 23 days). It is of note that time to relapse was longer, although not significant, in the probiotic group (47). Schulz, using *Lactobacillus GG* or placebo, for 6 months after induction therapy with steroids and antibiotics in a small placebo controlled study with 11 adults with active disease, failed to show a difference in the time until relapse and relapse rate itself (45). Maintenance of remission, studied by the same group, was not influenced by the administration of LGG (48). Even though a small pilot study in 4 children with *Lactobacillus GG* showed an increase in intestinal permeability and a decrease of clinical symptoms (49). *Saccharomyces Boulardii*, a yeast, which showed its efficacy in infectious diarrhoea and antibiotic associated diarrhoea (44,50), is also considered a probiotic. Guslandi studied 32 CD patients in remission during 6 months and treated them with 5-ASA or 5-ASA+*S Boulardii*. In the group treated with probiotics, there was significantly less relapse (p=0.04) (44), unfortunately no further large

studies have been performed to confirm these findings. *VSL#3*, a probiotic mix of 8 different typse of *Lactobacillus, Bifidobacterium* and *Streptococcus*, was succesfully used in a small adult study (51).

The use of probiotics as postoperative prophylaxis has been studied separately, without any advantage of the studied probiotics (*Lactobacillus GG en Lactobacillus johnsonii LA1)* on duration of clinical and endoscopic remission (46,52,53).

The number of studies using probiotics in pediatric CD is currently limited. One open label study in 4 pediatric patients with active disease, with ¾ children receiving Lactobacillus Rhamnosus GG reports a decrease in Pediatric Crohn Activity Index and intestinal permeability (49). In another study in 75 pediatric CD patients in remission, the addition of Lactobacillus Rhamnosus to maintenance therapy tended towards a reduced time until relapse, but could not reach significance (48).

The design of studies performed in CD is often unsatisfactory and therefore no final conclusion can be reached. Only a few probiotic strains have been tried and doses varied widely. It is possible that only a subgroup of CD patients respond to the treatment, depending on the underlying defect or the stage of disease. Probiotics remains an interesting therapeutic option, but there is an urgent need for large, well designed studies in children and adults.

b) UC and pouchitis

Results in Ulcerative Colitis (UC) are more optimistic. In mild to moderate disease, the combination therapy of VSL#3 with 5-ASA is superior to 5-ASA alone for inducing remission and the time to remission is decreased (54). An open label trial in active UC, unresponsive to conventional therapy, showed remission in 77% of patients with VSL#3 (55).

Studies on duration of remission did not show an additional effect in 187 UC patients on a combination therapy with *Lactobacillus GG* and 5-ASA compared to 5-ASA monotherapy (56). Maintenance of remission in UC with *E Coli Nissle* was looked at in 3 studies, two of them from the same research group. They show that probiotic treatment has similar results as 5-ASA, on clinical, endoscopic and histologic disease outcomes (57,58). A third study with E *Coli Nissle* confirms the results in a group of active UC patients who obtained remission with conventional therapy with or without probiotics (59). Probiotics could have a role in maintenance of remission in UC patients and would be as efficiënt as 5-ASA.

Pouchitis is present in 15-53% of UC patients after total colectomy and ileo-anal pouch anastomosis (60-62). Here, the use of probiotics, has been shown to be most effective. They were studied for the prevention, the induction of remission and the maintenance of remission.

VSL#3 and *L GG* were tested as pouchitis prophylaxis. In a 12 month randomized controlled study with VSL#3 and placebo in 40 postoperative patients, only 2/20 patients on *VSL#3* and 8/20 patients on placebo developed acute pouchitis ($p < 0.01$) ; stool frequency in the probiotic group was reduced compared to the placebo group after 8 weeks of treatment (5 vs 8×/d) (63). The incidence of acute pouchitis and recurrence or chronic pouchitis was lower in a Dutch group of patients on *L GG* compared to placebo (64).

Data on remission induction in acute pouchitis is limited. There is one small study looking at the treatment of acute pouchitis with *L GG* in 20 patients for 3 months. No difference in symptoms or histologic inflammation was noted in both groups (65).

The best results for the use of probiotics in IBD are described in chronic and recurrent pouchitis. Gionchetti randomized 40 patients in remission on antibiotics. They received *VSL#3* (6 g, 1.8×10^{12} bacteria/d) or placebo for 9 months. All patients on placebo relapsed, while 17/20 patients on *VSL#3* maintained remission (66,67). These results could be confirmed in a 12 month follow up study (66).

Conclusions

Given our current knowledge, the recommendations regarding infant nutrition made by pediatricians to mothers who cannot breastfeed are of great importance and may determine the risk for later disease.

It is unclear which 'ecological' interventions may be favorable at the stage that disease has developed. Today, most of the evidence regarding the use of probiotics in CD or UC is found in the adult literature. For CD none of the agents studied showed any efficacy. In UC however there is substantial evidence for the use of VSL#3. The effects of the studied probiotics cannot be extrapolated to other indications, other doses or other strains. In children, the success of enteral therapy may be in part the consequence of altered intestinal microbiota.

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