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CLINICAL USEFULNESS OF PROBIOTICS IN INFLAMMATORY BOWEL DISEASES

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Probiotics are live nonpathogenic bacteria or bacterial components that may be helpful in the prevention and treatment of acute diarrhoea in adults and children and have some effects on the course of inflammatory bowel diseases (IBD). Many experimental and clinical studies suggest that intestinal bacterial flora plays an important role in the pathogenesis of IBD, and manipulation of the luminal contents with antibiotics or probiotics represents a potentially effective therapeutic option. The beneficial effect of probiotics was demonstrated mainly in the prevention and treatment of pouchitis and in maintaining remission of mild to moderate ulcerative colitis. Probiotics seems to be less effective in patients with Crohn's disease. Randomized clinical trials are still required to further define the role of probiotics as preventive and therapeutic agents. This review summarizes the current data about probiotics in IBD.

Key words: *inflammatory bowel disease, ulcerative colitis, Crohn's disease, pouchitis, probiotics*

INTRODUCTION

Inflammatory bowel diseases (IBD) consist mainly of two forms: ulcerative colitis (UC) and Crohn's disease (CD). Both diseases are chronic with the characteristic relapses and remissions. The diagnosis of UC and CD together with accurate differentiation between them and other inflammatory diseases of the colon relies on a combination of clinical, radiological, endoscopic and histological features (1).

The pathogenesis of IBD is complex and not completely elucidated. It involves at least three interacting elements: genetic susceptibility factors, enteric microflora, and immune-mediated tissue injury. These factors govern the life-long crosstalk between host and intestinal flora.

A popular theory regarding the pathogenesis of IBD contends that the initiation and perpetuation of the intestine inflammation are the results of an abnormal host response to the endogenous microflora. Thus, it seems to be rational to modify host bacteria in the hope that this would downregulate the pathological immune response. Moreover, it was shown that *Lactobacillus* and bifidobacteria counts are significantly reduced in faeces of patients with IBD compared to controls, suggesting that normalization of gut flora is a logical means of treatment (2, 3). Experiments in rodents have demonstrated the potential of this approach, and preliminary studies in humans have been reported (1).

The theory of endogenous microflora in IBD can be supported by the long clinical observations that the two most important medications used for treatment of IBD, sulfasalazine and its derivative 5-aminosalicylate (mesalasine, 5-ASA), have some antibacterial activity. Therefore it was postulated that the flare of UC and CD might have some linkage with intestinal bacteria (4).

Sulfasalazine is used for more than 50 years and is highly effective for UC. On the contrary, the randomized trials showed that sulfasalazine was only marginally superior to a placebo for the induction of remission in active CD (1, 4). An ideal treatment for active CD should rapidly and reliably induce remission of symptoms, and chronic maintaining therapy is recommended to prevent relapses of the disease. The current treatment for active CD as well as UC is based on the use of five classes of drugs: non-specific anti-inflammatory drugs such as the 5-ASA, glucocorticoids, antimetabolites (e.g. azathioprine or 6-mercaptopurine), monoclonal antibodies (e.g. infliximab) and antibiotics (1).

The chronic inflammation in the gastrointestinal wall of the patient with IBD seems to be the result of an abnormal host response to the endogenous microflora (5). Thus, modification of host bacteria with antibiotics or probiotics could have some beneficial effect on the course of IBD. Intestinal microflora has been well described. The human intestinal lumen houses a complex bacterial microflora constituted of over 400 cultivable species. The microbiota established after birth is considered to be essential in priming the immune system during ontogeny, to limit dysfunctional responses. Recent evidence clearly demonstrated that commensal bacteria regulate intestinal development and function, and interruption of these interactions results in pathological features (5). Different factors have been reported to contribute to the protective function of gut microflora such as maintaining a physical barrier against colonization or invasion by pathogen, facilitating nutrient digestion and assimilation, and providing immunological surveillance signals at the gut mucosa-lumen interface. Lactic acid bacteria are normal inhabitants of the human gastrointestinal tract and are major components of the dominant flora in the

small bowel. They are considered beneficial to the host and as such are being developed for probiotic applications (5).

The distal ileum and the colon are the areas with the highest bacterial concentrations and represent the most frequent localization of the intestinal inflammation in IBD (6). However, there is still lack of data whether a specific pathogen is responsible for onsets or relapses of CD and UC. The most compelling evidence that intestinal bacteria play a role in IBD is derived from animal models. Although there is a great diversity in genetic defects and immunopathology, a consistent feature of transgenic and knockout mutant murine models of colitis is that the presence of normal enteric flora is required for full expression of inflammation (6). There is evidence that immunological tolerance to commensal bacteria is lost in patients with IBD. These findings have led to the proposal that manipulation of intestinal microflora either with antibiotics or probiotics may be therapeutic in IBD (4, 6).

Enteric microflora profiles vary considerably between active IBD and healthy conditions. In IBD patients the bacterial flora becomes aberrant with normal microflora such as *Lactobacillus* and bifidobacterium decreased and pathogenic or potentially harmful bacteria increased. Supplements with probiotics may balance the indigenous microflora in IBD patients (2, 7). There is a growing body of evidence from experimental studies and clinical trials that probiotics have therapeutic effects in UC, CD and pouchitis (6). Introduction of probiotics can changes the enteric microflora in IBD patients, and reinforce the various lines of intestinal defence by inhibiting microbial pathogens growth, increasing intestinal epithelial tight junction and permeability, modulating immune response of intestinal epithelia and mucosal immune cells, secreting antimicrobial products, decomposing luminal pathogenic antigens. Suggested mechanisms of probiotics in IBD are summarized in *Table 1* (2, 3, 6, 8).

Probiotics are defined as living microorganisms that, on ingestion, act with benefit on the host by altering the microbiological balance in the bowel. Recent study has unexpectedly demonstrated that beneficial effects were achieved not only by live bacteria but also by heat-inactivated or gamma-irradiated nonviable bacteria, isolated bacterial DNA or even probiotic-cultured media (8). Probiotics preparations are mainly based on a variety of lactic acid bacteria (lactobacilli, bifidobacteria and streptococci), which are normal and important components of the human gastrointestinal microflora where they exist as harmless commensals (4). Probiotic mixture often contains some non-pathogenic bacteria such as *Escherichia coli* (*E. coli*) or enterococci (e.g. *Enterococcus faecies*) or yeast *Saccharomyces boulardii*. Probiotic strains should be of human origin, and other required properties include: resistant to acid and bile, able to survive and be metabolically active within the intestinal lumen, where they should not persist for long term (4). Probiotics must also be antagonistic against pathogenic bacteria via many mechanisms including production of antimicrobial substances, competitive

Table 1. Suggested mechanisms of action of probiotics in IBD (2, 3, 6, 8)

Inhibition of pathogenic enteric bacteria growth by: • Interference with bacterial adherence to the epithelium • Decreasing luminal pH (Lactobacilli produce acetic and lactic acid) • Secretion of bacterial proteins (bacteriocins) that act as local antibiotics • Resisting colonization
Improvement in epithelial and mucosa barrier function by: • Production of short-chain fatty-acids • Enhancing mucus production • Increasing barrier integrity
Alteration of immunoregulation by: • Increasing IL-10 and TGFβ, and decreasing in the secretion of pro-inflammatory cytokines: IFNγ, TNFα, IL-12 • Increasing IgA production
Downregulation of proinflammatory cytokines secretion: • Inhibition of NF-κB activation • Modulation of PepT1 activity • Reduction of the number of CD4 intraepithelial lymphocytes • Regulation of anti-inflammatory effect via TLR9 signalling pathway • Modulation of apoptosis and proliferation of immune cell by TLR2 signalling • Modulation of peroxisome proliferator activated receptor (PPAR)γ pathway

exclusion or promoting a reduction of luminal colonic pH, moreover they must be safe and tested for human use (3, 4, 6).

Many clinical trials have documented that probiotics can achieve and maintain remission in patients with UC, prevent post surgical recurrence of CD, prevent and maintain remission in pouchitis, but probiotics have only established their role in UC and pouchitis (3).

Ulcerative colitis

Treatment of active UC with probiotics has been extensively investigated in clinical trials (9 - 12) and results are presented in *Table 2*. All the studies showed that probiotics are effective at least on one of the following: clinical and endoscopic improvement or decrease of the proinflammatory cytokine expression (3).

Several controlled studies showed that probiotics can be used in the maintenance treatment of UC (13-17) (*Table 2*). Patients in the clinical remission of UC were given oral 5-ASA or a non-pathogenic strain of *E. coli* Nissle 1917 as maintenance therapy and no significant difference in relapse rate was observed between the two methods. In the other study probiotic preparation VSL#3 administered at a very high dose (3600 billion bacteria/day) for 6 weeks induced remission in 77% of 32 patients with active mild to moderate UC (18). In addition, Guslandi *et al.* have found in an open uncontrolled study that a 4-week

Table 2. Results of clinical trials with probiotics in patients with UC

Author	Number of patients	Probiotic	Duration of therapy	Final effect	Effect
Rembacken 1997 (16)	116	*E. coli* Nissle 1917	1 year	Induction of remission; prevention of relapses	Similar to 5-ASA (68% vs 75%) Similar to 5-ASA (67% vs 73%)
Kruis 1999 (13)	120	*E. coli* Nissle 1917	12 weeks	Maintaining the remission	Similar to 5-ASA; relapse rate: 16% vs 11.3% on 5-ASA
Venturi 1999 (20)	20	VSL#3	1 year	Maintaining the remission	75% in remission (open study)
Kruis 2001 (14)	327	*E. coli* Nissle 1917	1 year	Induction of remission	5-ASA better than probiotic
Ishikawa 2003 (19)	21	Milk with bifidobacteria	1 year	Maintaining the remission	Exacerbation on 27% vs 9% control
Guslandi 2003 (9)	25	*Saccharomyces boulardii*	4 weeks	Induction of remission, on treatment with 5-ASA	71% in remission (open trial)
Bibiloni 2005 (18)	32	VSL#3	6 weeks	Induction of remission	77% in remission (open trial)

Table 3. Results of clinical trials with probiotics in patients with CD

Author	Number of patients	Probiotic	Duration of therapy	Final effect	Effect
Malchow 1997 (26)	24	*E. coli* Nissle 1917	3 months	Maintaining the remission	Relapse rate decreased vs placebo
Guslandi 2000 (28)	32	*Saccharomyces boulardii*	6 months	Postsurgical prevention of CD recurrence	Relapse rate decreased in probiotic + 5-ASA vs 5-ASA alone (6.25% vs 37.5%)
Prantera 2002 (22)	45	*Lactobacillus* GG	1 year	Postsurgical prevention of CD recurrence	No effect vs 5-ASA
Marteau (GETAID French group) 2006 (25)	98	*Lactobacillus johnsonii*	6 months	Postsurgical prevention of CD recurrence	Recurrence rate decreased vs placebo

treatment of 25 patients with mild to moderate UC with the probiotic yeast *Saccharomyces boulardii* could induce remission in 71% of patients (9).

In several recent trials involving *E. coli* Nissle 1917, similar efficacy has been observed to that of 5-ASA in the maintenance treatment of patients with UC. Kruis *et al*. randomly assigned 120 patients with UC in remission to receive either 1.5 g/day of 5-ASA or identically appearing tablets that contained *E. coli* Nissle 1917 (13). At the end of this 12-weeks study 11.3% of patients treated with 5-ASA relapsed as compared with 16% treated with the probiotic. However, this study can be criticized because of the very low relapse rate observed in the control group despite the rather modest dose of 5-ASA that was used (1).

In another study, Rembacken *et al.* randomized 116 patients with active UC to receive 5-ASA or the *E. coli* Nissle 1917 for one year (16). At the end of the trial 73% of the patients who had entered remission with conventional therapy relapsed as compared with 67% of those assigned to the probiotic. The authors concluded that the two strategies were of equivalent efficacy (1).

The other controlled trial of *E. coli* Nissle 1917, 327 patients with remission of UC were randomized to 0.2g daily of the probiotic or 1.5g daily of 5-ASA for one year of treatment (14). The rate of relapse was 45% in patients treated with *E. coli* Nissle 1917 compared with 36% in favour of 5-ASA. These results from relatively large studies suggest that the use of probiotics to maintain remission of UC can be effective but deserves further investigation (1). In a randomized trial performed on a small group of 21 patients with UC, Ishikawa *et al.* showed that the bifidobacteria-fermented milk supplemented as a dietary adjunct was successful in maintaining remission and had possible preventive effect on the relapse of UC (19). In an open uncontrolled study Venturi *et al*. treated 20 patients with the probiotic preparation VSL#3 containing 5×10^{11} bacteria/g in doses of 6g per day for one year (20). They have shown that faecal concentration of probiotic bacteria has increased and 75% of patients remained in remission during the study. They concluded that probiotic preparation is able to colonize the intestine and may be useful in maintaining remission of UC (20).

In the recent controlled trial Zocco *et al.* compared in 187 patients the efficacy of *Lactobacillus* GG in a dose of $18x10^9$ bacteria/day with 5-ASA (2.4 g/day) or 5-ASA plus *Lactobacillus* GG (21). They showed no difference in relapse rate at 6 and 12 months among the three treated groups and concluded that *Lactobacillus* GG seems to be effective and safe for maintaining remission in patients with UC (21). The other authors (Tursi *et al.*) compared the efficacy of low-dose balsalazide (2.25g/day) plus probiotic VLS#3 (3g/day) with medium dose balsalazide or 5-ASA in the 8 weeks treatment of 90 patients with mild to moderate active UC (12). They observed that balsalazide with probiotic was superior to balsalazide alone or 5-ASA in obtaining clinical, endoscopic and histological remission (85.71% versus 80.77% and 72.73%, respectively) (12).

Crohn's disease

Clinical trials with probiotics have been conducted in patients with CD, and the results are shown in *Table 3* (22, 23). Campieri *et al.* compared probiotic preparation VSL#3 (6g/day) with 5-ASA (4 g/day) in 40 patients and found that endoscopic recurrence was significantly reduced to 10% in probiotic-treated patients as compared to 40% in patients treated with 5-ASA, but *Lactobacillus* GG and *Lactobacillus johnsonii* effect cannot prevent post surgical recurrence of CD (23). In two other clinical studies, the probiotic agent *Lactobacillus* GG was similar to placebo in the prevention of post-operative endoscopic relapse at one year in 45 adults with CD and a complete resection of the intestine (22), and in treating clinical relapse at six months in 11 patients with moderate to active CD (24). All these studies were performed on a limited number of patients and the efficacy of the probiotics must be evaluated with caution. Similar results have been recently reported by the GETAID French group (25). In a randomized controlled trial 98 patients who had undergone surgical resection for CD were treated either with lyophilised *Lactobacillus johnsonii* strain LA1 (bacterial doses 2×10^9 cfu) or placebo for six months. Endoscopic recurrence of CD was observed in 49% of probiotic treated patients and in 64% of the placebo group. The probiotic was not superior to placebo in preventing endoscopic recurrence of CD (6).

In the other trial in patients with active CD probiotic has been assessed (26, 27), but no definite conclusion could be reached partially because of the methodological drawbacks (3). In this pilot study small number of patients with remission of colonic CD was treated for 3 months with either *E. coli* Nissle 1917 or placebo, and the relapse rate was 33% in the probiotic group and 63% in the placebo group (26). According to Guslandi *et al.*, in 32 patients with CD of the ileum or colon, in remission for over three months, six month maintenance therapy with 5-ASA (1g/day) plus *Saccharomyces boulardii* was significantly more effective in preventing a relapse than 5-ASA (1.5 g/day) alone in a small open trial (28).

Pouchitis

Total proctocolectomy with ileal pouch-anal anastomosis is the preferred surgical procedure in patients with refractory UC or UC complications. The most common long-term complication is pouchitis. It is a relatively new but frequent disease, which is a non-specific chronic inflammation within an ileal reservoir. Pouchitis is recognized as an important third form of IBD. The aetiology of pouchitis is still unknown, but it seems that a history of UC and bacterial overgrowth with reduced counts of lactobacilli and bifidobacteria and dysbiosis are main factors (29). The diagnosis is based on clinical symptoms and should be confirmed by typical findings at endoscopy and mucosal biopsy of the pouch (29). The medical therapies of pouchitis include: antibiotics, probiotic bacteria, 5-ASA, corticosteroids, immune modifier agents (e.g. azathioprine, 6-mercaptopurine),

Table 4. Results of clinical trials with probiotics in patients with pouchitis

Author	Number of patients	Probiotic	Duration of therapy	Final effect	Effect
Gionchetti 2000 (29)	40	VSL#3	9 months	Maintaining the remission, prevention of relapses	Better than placebo (15% vs 100%)
Ulisse 2001 (33)	40	VSL#3	1 year	Postsurgical prevention of pouchitis	Better than placebo (10% vs 40%)
Kuisma 2003 (32)	20	*Lactobacillus rhamnosus* GG	3 months	Postsurgical prevention of pouchitis; effect on microflora	Ineffective therapy (similar to placebo); changed the pouch bacterial flora
Mimura 2004 (31)	36	VSL#3	1 year	Maintaining the remission	Better than placebo (15% vs 94%)

nutritional agents (e.g. short chain fatty acids, dietary fibre), oxygen radical inhibitors (e.g. allopurinol), antidiarrhoeals (e.g. bismuth carbomer foam enemas) (30). Most patients with pouchitis who are empirically treated with antibiotics experience clinical improvement. Metronidazole or ciprofloxacin have become the standard medical therapy for acute attacks of pouchitis and for those patients with recurrent or chronic refractory pouchitis (30). Another approach to altering pouch bacterial contents is to administer probiotic bacteria.

Therapy with probiotics has been proved to be highly effective in three controlled trials (*Table 4*). Gionchetti *et al.* had evaluated in 40 patients the efficacy of 9 months therapy with probiotic preparation VSL#3 (6g/day) in maintenance of chronic pouchitis remission compared with placebo (29). VSL#3 contained 300 billion viable lyophilized bacteria per gram of 4 highly bile and acid resistant strains of *Lactobacillus* (*L. casei*, *L. plantarum*, *L. acidophilus* and *L. delbrueckii* subsp. *bulgaricus*), 3 strains of *Bifidobacterium* (*B. longum*, *B. breve* and *B. infantis*) and 1 strain of *Streptococcus salivarius* subsp. *thermophilus*. The patients were evaluated symptomatically, endoscopically and histologically. The therapy was very effective, and the relapse rate in the VSL#3 group was 15% as compared with 100% in the placebo group (29).

In a second controlled trial (31), 36 patients with refractory or recurrent pouchitis were treated with antibiotics and then randomized to maintenance therapy with probiotic VSL# in a high dose of 3.6 g (1800 billion bacteria/day) or placebo for one year. The patients were evaluated symptomatically, endoscopically and histologically. The relapse rates were 15% in the VSL#3 group and 94% in the placebo group. In the other study, patients undergoing colectomy and pouch surgery were randomized to prophylactic therapy with VSL#3 or placebo

for one year. During the first year 10% treated with VSL#3 developed pouchitis and 40% in the placebo group. In contrast to these trials, the other probiotic *Lactobacillus* GG has been ineffective in preventing relapses in patients with chronic pouchitis (32).

Ulisse *et al*. carried out the other controlled trial to evaluate the efficacy of the preventive role of probiotics in 40 patients following ileal-anal anastomosis for refractory UC (33). The patients were treated with VSL#3 (900 billion bacteria/day) or placebo. The results indicate that 10% of patients treated with VSL#3 experience acute pouchitis compared with 40% of treated with placebo during the first year after the surgery.

Possible mechanisms of action of probiotics in IBD

Significant decrease in the number of anaerobic bacteria, anaerobic Gram negatives and lactobacilli was shown in patients with active UC, whereas no changes were seen in the number of aerobic bacteria and enterobacteriaceae. However, no significant difference in colonic mucosa associated microflora could be shown in patients with inactive UC and healthy conditions (2, 3, 20, 34). The luminal microflora in IBD patients lost the anti-inflammatory function that exists in normal conditions, with a reduction in the number of anaerobic bacteria and *Lactobacillus*. Probiotics administration can help restore microbial homoeostasis in the gut, down-regulate intestinal inflammation and ameliorate the diseases. Many clinical trials presented in this review have shown that probiotics may have beneficial effect on IBD patients, and suggested mechanisms of their action were recently described in details (2).

In conclusion, the rationale for employing a probiotic in the treatment of IBD relies upon the proposed pathogenic role of intestinal microflora in these diseases. The mechanisms of action of probiotics may explain the beneficial effects observed in several studies in patients with IBD. Probiotics can achieve and maintain remission of UC, prevent and maintain remission of pouchitis, but seem to be ineffective in CD (3). Preliminary data for their therapeutic use in selective patients with mild to moderate IBD are encouraging, but controlled clinical trials are still required to investigate the unresolved issues related to efficacy, dose, duration of use, single or multistrain formulation and the concomitant use of probiotics, synbiotics or antibiotics (35).

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