Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

doi: 10.5455/2319-2003.ijbcp20130803

Review Article

The emerging therapy with probiotics in the management of inflammatory bowel disease: current status

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Received: 27 May 2013
Accepted: 14 June 2013

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ABSTRACT

Inflammatory Bowel Disease (IBD) comprises Ulcerative Colitis (UC) and Crohn's Disease (CD) with unknown aetiology. Most of the drugs used to treat IBD as standard treatment produce adverse effects during long term therapy. Evidence has suggested a role of intestinal microbiota in IBD. The use of probiotics and prebiotics is the natural approach to treat IBD. The objective of this article was to review the studies on probiotics that cover the therapeutic status in Inflammatory Bowel Disease. Appraisal of published articles from peer reviewed journals, search from PubMed and Wiley Blackwell website for English language publications using defined key words according to disease type. Studies have shown that probiotic agents play an important role in IBD and these are VSL#3, Bifido-ferminted milk, *Escherichia coli* Nissle 1917, *Saccharomyces boulardi* and "BIO-THREE for inducing remission in patients with active UC, for preventing relapses in inactive UC patients and also in UC patients with ileo-anal pouch anastomosis. *Lactobacillllus rhamnosus* GG and *Lactobacillllus johnsonii* LA1 can prevent endoscopic recurrences in patients with inactive CD. Probiotic intervention study designs in IBD patients searched were RCT vs Placebo / RCT vs standard treatment . Studies - with uncontrolled design, - with prebiotics intervention and with helminths were also searched. There is a promising role of probiotics and prebiotics in chronic mucosal inflammation that occurs in Inflammatory Bowel Disease. Sufficient evidence to support the role of probiotics in CD are not available. Well designed RCT studies based on intention -to- treat analyses are required.

Keywords: Probiotics, Inflammatory Bowel Disease, Ulcerative Colitis, Crohn's Disease

INTRODUCTION

Inflammatory Bowel Disease (IBD) - chronic relapsing inflammatory disorder of GIT, Comprises – ulcerative colitis (UC) and crohn's disease (CD) with heterogenic clinical presentation, aetiology is not clear. Ulcerative colitis (UC) involve rectum and extend proximally in to colon and may involve small intestine, UC is characterized by continuous superficial mucosal inflammation limited to colon. Crohn's disease (CD) involve segment of both small and large intestine with transmular involvement leading to stricture and bowel obstruction, and is frequent in ileum and colon, but can affect any portion of gut, associated with intestinal granuloma and complicated by stricture and fistula.[1,2] Complex interplay of genetic, immunological, microbiological, environmental factor, and psychic factor are known to play a role. An antigen initiate the inflammatory process leading to cascade of proinflammatory events and proinflammatory mediator are cytokines like TNF - α and free radicals. The aim of the treatment is to provide clinical remission and endoscopic remission is the secondary goal. Standard medical therapy includes corticosteroids in the acute phase, mesalazine and immunomodulators to maintain remission and biological agent for refractory and for severe cases. Most of the drugs used to treat IBD as standard treatment produce adverse effects during long term therapy, such as leukopenia, liver function abnormalities because of non specific suppression of immune system can develop opportunistic infections except mesalazine.[1-3)] Increase risk of lymphoma with thiopurine, TNF - α blocking agents.[4,5] Body of evidence suggested a role of enteric microbial flora (intestinal microbiota) in inducing and maintaining

intestinal inflammation with gut immune system in patients with Inflammatory Bowel Disease.[6,7]

A safer therapeutic alternative is offered by probiotics with or without addition of prebiotics a natural approach to IBD treatment. The yeast saccharomyces boulardii with mesalazine has been shown to maintain remission of inactive crohn's disease more effectively than mesalazine alone.[8] VSL#3 a probiotic mixture i.e. consisting of four strains of Lactobacillus (L Casei, L Plantarum, L acidophilus and L delbrueckii subsp. Bulgaricus), three strains of Biofidobacterium (B llongum, B brave and B infants) and one strain of Streptococcus (S salivarius subsp. Thermophilus) has been shown to prevent recurrence of pouchitis in several clinical trial, but has provided disappointing results in experimental model.[9]

Hence the observation carried out in experimental models does not necessarily predict same in clinical trials. There is the potential role of probiotics with or without addition of prebiotics in IBD.[9,10]

Studies were reviewed on probiotics that cover the therapeutic status in Inflammatory Bowel Disease. Search Strategies was the appraisal of published articles from peer reviewed journals, search from PubMed and Wiley Blackwell website for English language publications using defined key words according to disease type.

NORMAL INTESTINAL MICROBIOTA

Sterile GIT at birth rapidly colonized by successive waves of microorganism, comprising.[13-14] bacteria and stabilizes at the time of weaning.[11,12] Human intestinal microbial composition present in three clusters or Enterotypes and are Bacteroides, Prevotella, and Ruminococcus.[13] The denisity and diversity increases from stomach to colon, high interindividual diversity and microbiota is dominated by the phyla Firmicutes and Bacteroidetes.[12,14,15]

Production of short chain fatty acid (SCFAs) i.e. acetate propionate and butyrate by saccharolytic bacterial fermentation of nondigestable carbohydrate. SCFAs-are– energy source for intestinal epithelial cell - affect cell proliferation, differentiation, mucus secretion and barrier function, and provide antiinflammatory and anti-oxidant function.[7,13,16]

Inflammatory Bowel Disease and Changes that occur in intestinal microbiota

Studies have suggested that intestinal microbiota changes, mucosal bacterial counts are higher in IBD patients.[17,18] Antibiotic showed a significant benefit over placebo for inducing remission in CD and UC.[19] Fewer fremicutes was found and low bacterial count for Faecalibacterium *Prausnitzll*[20-23] and bifidobacteria,[24,25] SCFAs production reduced. Faecal microbiota less diverse.[26,27] Diversity of bacteroidetes phylum also reduced.[15] Increase of enterobacteriaceae, and E. coli[22,25,28], decrease faecal concentration of butyrate in UC,[12,29] and significant decreases of the transcriptional activity of the mucosa associated microbiota –IBD.[21] Molecular approaches like FISH, PCR and pyrosequencing have identified a microbial disbiosis in IBD patients.[26,27] CARDIS -1st CD gene identified.[30,31]

Other changes that occur in IBD

Loss of oral tolerance to commensal bacteria in IBD, increase response to commensal bacteria – contributing the intestinal inflammation. Increase mucosal infiltration of CD4 - lymphocytes, dysfunctional dendrite cells, dysregulated macrophage induced immune response and abnormalities in regulatory pathway have been reported,[32,33] and in CD increase production of the per (Th)-l cytokines and the Th17 cytokine interleukin (IL)-17 have been observed.[7,33,34] In UC, preferential expression of Th-2 cytokines, IL-4, IL-5 and increase in IL-17 have been observed.[32,33,35] In both UC and CD - reduced number of regulatory T cell have been observed.[7,32]

Reduced number of regulatory T cell, and genetic susceptibility observed in IBD will contribute to the loss of oral tolerance.[36]

PROBIOTICS

Probiotics are "live microorganisms, which when administered in adequate amount confer a health benefit to the host".[37,38] At the start of the 20th century, Russian Nobel prize winner Elie Metchnikoff,[39] a scientist at the Pasteur Institute, was the first to conceptualize "Probiotics" , and the term coined in 1965 by Lilly and Stillwell. [(40)] Criteria: They should be of human origin, must be safe, genetically stable and able to survive passage through the GIT (* low pH, bile and digestive enzymes), different bacterial strain can have different effects, they may act complimentarily or even synergistically.[5] Probiotics are bacteria, these are- lactic acid bacteria, Lactobacillus acidophilus, L. casei, L. lactis, L. helviticus, L. salivarius, L. plantrum, L. bulgaricus, L. rhamnosus, L. johnsonii, L. reuteri, L. fermentum, L. delbrueckii, Streptococcus thermophilus, Enterococcus faecium, E. faecalis, Bifidobacterium bifidum, B. breve, B. longum and Saccharomyces boulardii are commonly used probiotics.[41]

The probiotics when attached to the wall of intestine increase the number of beneficial bacteria and fight against harmful bacteria thus maintaining a balance between the beneficial and harmful bacteria by following mechanisms: Production of inhibitory substances, Blocking of adhesion sites by competitive inhibition, Competition for nutrients otherwise consumed by pathogenic microorganisms, Stimulation of immunity.[45,46]

Prebiotics are indigestible carbohydrates, which stimulate the growth of particular species of the microflora of the host, resulting in an ameliorated enteric function. These nondigestible food constituents act primarily by increasing the population of certain bacteria and thus quantitatively altering the microflora.[41] When reaching the colon, they are fermented by anaerobic bacteria, producing short-chain fatty acid (SCFA) and gas (CO_2 and H_2). As a result, intraluminal pH drops,[42] favouring the increase of Bifidobacteria, Lactobacilli and nonpathogenic E. coli and decreasing Bacterodaceae. These are Lactulose, Germinated barley foodstuff, Fructo-oligosaccharides, and Goat's milk oligosaccharides.[41]

Synbiotics are substances containing both probiotics and prebiotics,[41] synbiotics introduced as "pharmabiotics" by Shanahan.[43]

PROBIOTIC INTERVENTION STUDIES RETRIEVED IN INFLAMMATORY BOWEL DISEASE WERE:

A- Probiotic intervention studies retrieved in *adult ulcerative colitis patients with active disease (Table 1).*[56-66]

B- Probiotic intervention studies retrieved in *adult patients with ulcerative colitis in remission (Table 2).*[67-73]

C- Probiotic intervention studies retrieved in adult ulcerative colitis patients with an ileo-anal pouch anastomosis (Table 3).[74-77]

D- Probiotic intervention studies retrieved in *adult patients with Crohn's disease (Table 4).*[78-81]

Table 1: Probiotic intervention studies retrieved in adult ulcerative colitis patients with active disease.

Intervention (daily dose*)	Disease activity	Design	Clinical outcome
Saccharomyces boulardii (750mg) + mesalazine (3g)	Mild to moderate active	Uncontrolled 4wk (N=25)	68% in remission, decreased clinical activity-significant [56]
Bifido-fermented milk [Bifidobacterium breve, Bifidobacterium bifidum and Lactobacillus acidophilus] ($10x10^9$) Vs PL	Mild to moderately active	RCT Vs no additive tx, 12mo (N=21)	Significant relapse rate, & no differences in colonoscopic findings[57,58]
VSL # 3 ($9x10^{11}$) + balsalazide (2.25g) Vs balsalazide (4.5g) Vs Mesalazine (2.4g)	Moderately active	RCT Vs standard tx, 8wk (N=90)	Significant remission rate, & faster remission induction[59]
VSL # 3 (3.6×10^{12})	Moderately active	Uncontrolled, 6wk (N=34)	53% entered remission, 77% decreased >3 points in clinical activity index[60]
BIO-THREE (Streptococcus faecalis 18mg, Clostridium butyricum 90mg. Bacillus mesentericus 90mg) [n=10; also 100g dietary fibre daily]	Mild to moderately refractory active	Uncontrolled, 4wk (N=20)	45% in remission.[61]
VSL#3 ($1.8x10^{12}$)	UC pts (active+inactive)	Uncontrolled, 5wk (N=15)	Decrease in clinical disease activity.[62]
Bifidobacterium longum Bb536 ($2\text{-}3x10^{11}$)	Active	Uncontrolled, 24wk (N=14)	67% reached remission.[63]
VSL#3 ($3.6x10^{12}$) vs PL	Mild to moderately active	RCT vs PL, 12wk (N=147)	>50% improved disease activity at wk 6, remission at wk 12-significant [64]
Escherichia coli Nissle 1917 enema ($4x10^9$) Vs ($2x10^9$) Vs (10^9) Vs PL.	Mild to moderately active	RCT Vs PL, 8wk (N=90)	Significant remission rates as per analysis[65]
5-ASA (2.4g) Vs 5-ASA + Lactobacillus casei (1.6×10^9) orally Vs 5-ASA + L. casei (1.6×10^9) rectally.	Mild active	RCT Vs standard tx, 8wk (N=26)	Improved clinical activity in 5-ASA group. Improved histology in both L. casei groups.[66]

Daily dose* in CFU=colony-forming units; pts=patients; PL=placebo; tx=treatment; mo=months; N=number of patients; RCT=randomized controlled trial; UC= ulcerative colitis; 5-ASA=5- aminosalicylic acid

Table 2: Probiotic intervention studies retrieved in adult patients with ulcerative colitis in remission.

Intervention (daily dose*)	Disease activity	Design	Clinical outcome
Escherichia coli Nissle 1917 enema ($50x10^9$) Vs mesalazine (3x500mg).	Inactive	RCT Vs standard tx, 12wk (N=103)	Similar relapse rate, NS.[67]
E.Coli Nissle 1917 ($50x10^9$) Vs mesalazine (3 x 400mg)	Inactive (after remission induction)	RCT Vs standard tx, 12mo (N=83)	Similar relapse rate, NS.[68]
VSL # 3 ($3x10^{12}$)	Inactive (intolerant / allergic to 5-ASA)	Uncontrolled 12mo (N=20)	75% maintained remission.[69]
Bifid triple viable capsule (1.26g) vs PL	Inactive after inducing remission	RCT vs PL, 8wk (N=30)	Significant relapse rate.[70]
Lactobacillus rhamnosus GG ($18x10^9$) vs mesalazine (2400mg) vs L.GG ($18x10^9$) + mesalazine (2400mg)	Inactive	RCT vs standard tx, 12mo (N=187)	Similar relapse rate, NS. No difference in clinical, endoscopic and histological scores.[71]
Saccharomyces boulardii (500mg) + rifaximin (400mg)	Inactive (mesalamine intolerant)	Uncontrolled, 3mo (N=6)	Maintained remission based on clinical activity.[72]
Lactobacillus acidophilus (La-5) + Bifidobacterium animalis lactis [Bb-12] $91.5x10^{11}$) vs Pl	Inactive	RCT vs PL, 52wk (N=32)	Maintenance remission.[73]

Daily dose* in CFU=colony-forming units; PL=placebo; tx=treatment; mo=months; N=number of patients; NS=not significant; RCT=randomized controlled trial; 5-ASA=5- aminosalicylic acid.

Table 3: Probiotic intervention studies retrieved in adult ulcerative colitis patients with an ileo-anal pouch anastomosis.

Intervention (daily dose*)	Disease activity	Design	Clinical outcome
Escherichia coli Nissle 1917 ($2.5\text{-}5 \times 10^{10}$)	Active pouchitis	Uncontrolled, 315/56d (N=2)	Both in remission from day 50 and 5, respectively.[74]
VSL # 3 (36×10^{11})	Mild to active pouchitis	Uncontrolled 4wk (N=23)	69% in remission, Decreased PDAI.[75]
VSL # 3 (18×10^{11}) vs PL	After induction remission by antibiotics	RCT vs PL, 9mo (N=40)	Significant relapse rate.[76]
Lactobacillus rhamnosus GG ($2\text{-}4 \times 10^{10}$) vs PL	With history of pouchitis (subgroup had pouchitis)	RCT vs PL, 3mo (N=20)	No change in PDAI scores between groups.[77]

Daily dose* in CFU=colony-forming units; PL=placebo; mo=months; N=number of patients; RCT=randomized controlled trial; PDAI=Pouch Disease Activity Index.

Table 4: Probiotic intervention studies retrieved in adult patients with Crohn's disease.

Intervention (daily dose*)	Disease activity	Design	Clinical outcome
Prednislon + Escherichia coli Nissle 1917 ($5x10^{10}$) vs prednisolon + PL	Active, all colon	RCT vs PL, 12mo (N=23)	Entered in remission, & relapse rate NS.[78]
Lactobacillus acidophilus, Bifidobacterium, Lactobacillus casei + Streptococcus salivarius subsp. Thermophilus ($8x10^{9}$)	Active, disease locations unknown	Uncontrolled (case reports), 7-12mo (N=3)	Maintained remission but 1 wk abdominal pain (after 7 and 8mo) in 2 of 3 pts.[79]
Saccharomyces boulardii (1g) + mesalazine (2g) vs mesalazine (3g)	33-Inactive, (9 ileum, 1 colon, 23 ileum + colon)	RCT vs standard therapy, 6mo (N=33)	Significant relapse rate.[80]
Lactobacillus rhamnosus GG (12×10^{9}) vs PL	45-Inactive (10 d after curative resection, 35 ileum, 3 colon, 7 ileum + colon)	RCT vs PL, 12mo (N=45)	Clinical relapse & had endoscopic recurrence of those in remission.[81]

Daily dose* in CFU=colony-forming units; PL=placebo; mo=months; N=number of patients; RCT=randomized controlled trial;

Role of Helminths in Inflammatory Bowel Disease:

There is evidence from studies that Inflammatory Bowel Disease (IBD) is much less common in countries with poor sanitation and low hygiene levels, where helminth infections are common, in comparison with Western countries.[54] It has thus been assumed that helminths may lead to the prevention of IBD by some unknown mechanism. Studies have revealed, the use of helminths such as Trichuris *suis* for the treatment of IBD patients,[55] and helminths are in clinical trial.

DISCUSSION AND CONCLUSIONS

Studies have revealed that probiotics affect the composition of the microbial ecosystem by competition of nutrients and adhesion sites, by the production of antimicrobial substances and / or via cell-cell communication.[44,45] Probiotics affect host immune system by interaction of bacterial products, cell wall components or DNA with epithelial and gut-associated immune cell.[46] There is evidence from studies that probiotics causes changes in cytokine production, modulation in dendritic cell function, and increase of natural killer cell activity, and induction of regulatory T cell and defensins.[44,46,47]

Probiotics contribute to SCFAs, butyrate / or affect barrier function by induction of mucin secretion, by enhancement of tight junction expression and functioning,[48,49] also probiotics decreases epithelial cell apoptosis.

There is evidence from studies that intestinal microbiota play a role not only in the chronic mucosal inflammation in IBD but also in Irritable Bowel Syndromes (IBS), Obesity, and the Metabolic Syndrome.[2,50-53]

The main rationale for probiotics interventional studies is the manipulation of the indigenous intestinal microbiota composition and activity, the immune system and host barrier function.[44,46,47] Studies have shown that probiotic agents play an important role in IBD, These are VSL#3, Bifido- ferminted milk, Escherichia coli Nissle 1917, Saccharomyces boulardii and "BIO-THREE for inducing remission in patients with active UC , for preventing relapses in inactive UC patients and also in UC patients with ileo-anal pouch anastomosis. Lactobacillllus rhamnosus GG and Lactobacillllus johnsonii LA1 can prevent endos -copic recurrences in patients with inactive CD. Probiotic intervention study designs in IBD patients searched were RCT vs Placebo / RCT vs standard treatment.

Studies with uncontrolled design, with prebiotics intervention and with helminths were also searched. There is a promising role of probiotics and prebiotics in chronic mucosal inflammation that occurs in Inflammatory Bowel Disease. Sufficient evidence to support the role of probiotics in CD are not available. Well designed RCT studies based on intention -to- treat analyses are required.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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doi:10.5455/2319-2003.ijbcp20130803
Cite this article as: Kumar R, Singh J. The emerging therapy with probiotics in the management of inflammatory bowel disease: current status. Int J Basic Clin Pharmacol 2013;2:360-7.