CLINICAL VIGNETTE

The Role of Probiotics in Inflammatory Bowel Disease

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Case Report

A 36-year-old male with history of severe Crohn's disease presents for a routine physical. He was diagnosed with Crohn's disease at the age of 25, and his course of disease was complicated by mouth to anus involvement, multiple fistulas, and small intestinal strictures. Refractory to medical treatment, he required distal small bowel resection and fistulectomy at the age of 32. After surgery, he had significant improvement in symptoms but still suffered from persistent mouth ulcerations and diarrhea. Multiple medications were tried including 6-mercaptopurine, mesalamine, and adalimumab, which resulted in intolerable side effects. Frustrated by the situation, he sought out alternative treatments to control the disease. Eventually with daily VSL#3 probiotics (two capsules once daily) and diet changes including the elimination of processed foods, he has been in remission for three years. Colonoscopy one year after probiotic treatment showed minimal inflammation and no ulcerations. Currently, on daily probiotics and diet free of processed foods, he is symptom-free and feeling great. Inspired by his story, I sought to research the role of probiotics in inflammatory bowel disease.

Background

Crohn's disease (CD) and ulcerative colitis (UC) are the two major forms of inflammatory bowel disease (IBD), and both diseases lead to high morbidity and health care costs. Complex interactions between the immune system, enteric commensal bacteria, and host genotype are thought to underlie the development of IBD, although the precise etiology is still unknown. As it is understood that intestinal bacteria play a key role in inflammatory bowel disease, there is emerging interest on the part of the general public and scientific communities in the use of probiotics in the treatment of IBD. Many studies have been conducted with the purpose of identifying differences in microbial diversity between healthy individuals and IBD patients. Overall, these studies have found evidence for a decline in bacterial diversity in IBD patients, although disease-specific bacteria have not been identified. Commensal bacteria have been shown to facilitate diverse functions including but not limited to: 1. digestion, absorption, and storage of nutrients; 2. protection against pathogen colonization through competition for nutrients and secretion of antimicrobial substances; 3. promoting angiogenesis and development of the intestinal epithelial lining; and 4. playing a key role in the development and function of the immune system.[1] Probiotics including VSL#3 have been shown in animal models to induce changes in gut microbial species composition and diversity, increase mucosal barrier function, and modulate local immune responses within the gut.[2] Given all of these potential theoretical benefits, I reviewed studies that examine the role of probiotics as therapy for inflammatory bowel disease in humans.

Results of Clinical Trials

Below is a summary of the most commonly referred to clinical trials exploring the role of probiotics in IBD:

Kruis et al[3] reported in a randomized, double-blind clinical trial with 120 UC patients that oral administration of *E. coli* strain Nissle 1917 as a maintenance treatment of remission showed no difference in relapse rates compared with patients on mesalazine. Relapse rates were 11.3% for the mesalazine-treated group and 16.0% for the *E. coli* group. Life table analysis showed a relapse free time of 103 ± 4 d for mesalazine and 106 ± 5 d for *E. coli*. From the results of this preliminary study, probiotic treatment appears to offer another option for maintenance therapy of UC.[3] These results were confirmed by Rembacken et al.[4] A total of 116 patients with active UC were recruited into this study, and 75% and 68% of the mesalamine and *E. coli* groups achieved remission, respectively. The relapse rate in both groups was markedly higher than the investigators anticipated: 73% for the mesalamine group and 67% for the *E. coli* group. The time to relapse was not significantly different between the groups. In a larger (327 patients) multicenter, randomized, double-blind, remission maintenance study, *E. coli* was shown to be as effective as mesalazine in maintaining remission and therefore offers an alternative to mesalazine in maintenance of remission in UC patients.[5]

VSL#3, a mixture of 4 lactobacilli strains (*Lactobacillus plantarum, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus delbrueckii* ssp. *bulgaricus*), 3 bifidobacteria

strains (*Bifidobacterium infantis, Bifidobacterium breve, Bifidobacterium longum*), and 1 strain of *Streptococcus salivarius* ssp. *thermophilus*, has been examined in UC, CD, and pouchitis patients. Gionchetti et al[6] demonstrated the efficacy of this probiotic mix in maintenance of remission in patients with chronic pouchitis. In a randomized, double-blind, placebo-controlled trial, 40 patients in clinical and endoscopic remission received VSL#3 or placebo for 9 mo. All patients received 1 mo. of antibiotic treatment before the trial. At the end of the study, 3 patients (15%) had relapsed in the VSL#3 group compared with 20 (100%) in the placebo group. In another double-blind, randomized study the efficacy of VSL#3 combined with antibiotic treatment on the postoperative recurrence of CD was compared with treatment with mesalamine alone. Forty patients were randomized to receive rifaximin for 3 months followed by VSL#3 for 9 months or mesalamine for 12 months. At the end of the trial, 20% of the patients had recurrent CD in the probiotic/antibiotic group, whereas 40% of patients in the mesalamine group relapsed.[7]

Limitations of Current Evidence

Although the trials summarized above are promising, the current consensus is that a number of larger controlled trials are necessary before the use of probiotics as a routine medical treatment is warranted. Few studies have included enough subjects, leading to inconclusive findings or results researchers cannot generalize. In addition, the number of potential beneficial bacteria and the challenge of determining how they benefit the human host make it more difficult to reach a consensus on recommendations for specific strains and dosing. Research also has been done at different phases of disease activity, which makes comparing results more difficult. Some bacteria have shown a positive impact in maintaining remission but not in controlling symptoms during active disease. Other obstacles to providing probiotic therapy include selection of appropriate strains, poorly regulated probiotic quality standardization, and processing and human biologic factors which impair probiotic viability.[8] One positive is that the research has indicated that a very low risk of adverse effects is associated with the use of probiotics in IBD patients.

Conclusion

Although theoretical and animal studies on the role of probiotics in IBD are promising, clinical evidence suggests they are likely to offer only small benefits. For that reason, probiotics are not a replacement for conventional medication but may be a useful adjunct to prescriptions medications for maintenance of remission and in the treatment of mild to moderate disease. Although the safety of co-administering immunomodulators commonly used in IBD with probiotics has not been established, it is likely safe based on current evidence. Probiotics should be used with caution in severe disease or in severely immunocompromised patients. Future considerations for better understanding the role of probiotics in the treatment of IBD include large controlled trials, individualization of treatment based on the type and stage of disease, and individualization of treatment based on the patient's unique microbiome.

Application to Clinical Practice

Based on current evidence on the role of probiotics in IBD, I feel comfortable prescribing high-dose multi-strain refrigerated probiotics such as VSL#3 or *E. coli* strain Nissle 1917 as an adjunctive agent for the maintenance of remission and in the treatment of mild to moderate IBD. To ensure they are worth the expense, consider starting a food and symptom diary before initiating probiotics. Keep track of symptoms before and after starting treatment. After several weeks, try going off the product and observe for any increase in symptoms. If clinical improvement is sustained, then continue use of probiotics.

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