BACKGROUND

The human intestine contains 300–500 different bacterial species. Concentrations of living bacteria in the large intestine may reach $10^{11}$–$10^{12}$ cells per gram of luminal contents (1). Some of these bacteria are protective, some neutral, and others pathogenic (2). This dynamic community of intestinal micro flora plays a critical role in maintaining intestinal health serving both metabolic, digestive, trophic and protective functions (1). Probiotics are viable microorganisms with beneficial physiologic and therapeutic properties that when ingested in specific numbers, exert health benefits beyond those of basic nutrition (2-4). Examples of bacteria demonstrated to have beneficial effects include lactic acid bacilli, lactobacillus, Bifidobacterium, E. coli Nissle 1917, clostridium butyricum, streptococcus salivarius thermophilus and a non-pathogenic yeast, Saccharomyces boulardii (2, 4). Properties of an ideal probiotic should include total host safety, resistance to gastric acidity and pancreatic secretions, adherence to epithelial cells, antimicrobial activity, inhibition of pathogenic bacteria, resistance to antibiotics, tolerance to food additives and stability in food matrix (4).

ROLE OF BACTERIA IN THE PATHOGENESIS OF IBD

Inflammatory Bowel Disease (IBD) is a chronic inflammatory disorder of the intestine. Subtypes of IBD include Crohn’s disease, ulcerative colitis, microscopic colitis and celiac disease. One of the postulated pathophysiologic mechanisms in the development of Crohn’s disease and ulcerative colitis relates to the loss of tolerance to commensal bacteria resulting in a hyperactive immune response in genetically susceptible hosts (2,5–7). Levels of commensal bacteria appear to be altered in IBD patients with increased numbers of bacteroides, adherent/invasive Escherichia coli, enterococci and decreased Bifidobacterium and Lactobacillus species (8–10). Experiments have demonstrated the therapeutic effect of diversion of the fecal stream and subsequent recurrence of the inflammatory response when fecal stream is restored (11). In 1998, D’Haens, et al demonstrated earlier, more severe recurrences of inflammatory bowel disease after 8 days of bolus infusions of ileal effluent into the excluded ileal limbs of 3 patients with diverting loop ileostomies (12). In all patients, the excluded limb was histologically normal before the infusion of ileal contents. The implication of this experiment was that the pathogenic agent responsible for triggering the inflammatory response resided within the fecal stream. In clinical trials, the finding that nitro-imidazoles decrease the frequency and sever-
ity of endoscopic recurrence following ileal resection in patients with Crohn’s disease also lends support to the hypothesis that bacterial antigens initiate an inflammatory host response (13). Host susceptibility genes also play an important role in the regulation of mucosal immune response, barrier function and microbial defenses. For example, genetic polymorphisms in the NOD 2/CARD 15 gene (a cytoplasmic receptor for muramyl dipeptide and a specific peptidoglycan in bacterial cell walls) lead to impaired activation of nuclear factor kappa B (NFκB) which results in impaired clearance of invasive bacteria (2). Clinically, NOD 2/CARD 15 mutations are associated with a Crohn’s disease phenotype characterized by younger age at diagnosis, ileal involvement, ileocecal resections, and a high risk of postoperative disease recurrence requiring re-operation (14). These scientific observations lend support to a rationale of selective therapeutic manipulation of enteric bacterial populations with probiotics.

**CLINICAL TRIALS OF PROBIOTICS IN IBD**

**Crohn’s Disease**

To date there has been a limited number of controlled clinical trials examining the role of probiotic therapy in IBD. In particular, very little data exists to support the use of probiotics in the management of Crohn’s disease. The only published controlled clinical trial to date studied the effectiveness of lactobacillus species GG in the postoperative prevention of recurrent Crohn’s disease following ileocolonic resection. This was a randomized, placebo-controlled trial with a one-year follow-up period comparing lactobacillus to placebo that failed to demonstrate efficacy with clinical recurrence rates in the Lactobacillus group and the placebo-treated group of 16.6% and 10.5%, respectively. Nine of 15 subjects in clinical remission and 6/17 subjects receiving placebo had endoscopic evidence of recurrence (15). Two other small clinical trials examining *E. coli Nissle* 1917 (EcN) and *S. boulardii* for maintenance of clinical remission in Crohn’s disease have been performed. The first study of *E. coli Nissle* in maintenance of remission in Crohn’s disease was a randomized, double-blind, placebo-controlled study of patients with active Crohn’s disease following a corticosteroid-induced remission(16). At the end of the one-year follow-up period, there was no significant difference in the remission rate between the probiotic group when compared to the placebo group. Another randomized study of maintenance of remission in Crohn’s disease compared Saccharomyces boulardii plus mesalamine 3 g per day to mesalamine alone over a six-month period (17). Although the rate of clinical relapse (defined as a CDAI >150) was higher in the mesalamine monotherapy group (37.5% versus 6.25%, p < 0.004), the small number of patients enrolled in this study severely limits its statistical power. Also, measurement indices were not reported in detail.

**Ulcerative Colitis**

Some data does exist for probiotic use for maintenance therapy in ulcerative colitis. Venturi, et al showed that a special probiotic preparation, VSL#3, significantly increased fecal concentrations of the probiotic bacteria as long as patients were taking the probiotic (18). VSL#3 contains $5 \times 10^{11}$ of viable lyophilized bacteria consisting of three strains of bifidobacteria (*B. infantis*, *B. longum*, and *B. breve*), 4 strains of lactobacilli (*L. acidophilus*, *L. delbrueckii subsp. Bulgaricus*, *L. plantarum*, and *L. casei*) and 1 strain of streptococcus salivarius subsp. *thermophilus*. A 1999 randomized controlled trial demonstrated equivalence of nonpathogenic *E. coli* to mesalamine for maintenance of remission in UC (19). Fifty-nine patients were randomized to the mesalamine group (Asacol 800 mg t.i.d.) and 57 to the *E. coli* group (2 capsules b.i.d., each capsule containing $2.5 \times 10^{10}$ viable bacteria per capsule). After a mean follow-up of 12 months, the remission rates (75% for mesalamine and 68% for *E. coli*) and relapse rates (73% for mesalamine versus 67% for *E. coli*) were shown to be similar between the two groups. In 2001, *E. coli Nissle* 1917 was shown in a multi-center, double-blind, mesalamine-controlled trial to be equivalent to mesalamine for maintenance of remission in CUC (20). In this study, 327 patients with UC in remission were followed over a 12-month period. Both clinical and endoscopic estimates of disease severity were performed using the Crohn’s activity index (CAI) and the endoscopic activity index (EI) according to Rachmle-
Witz’s criteria. Relapse rates were 45.1% for the EcN group and 36.4% for the mesalamine group by intention to treat analysis. In 2003, Fedorak and colleagues studied 30 patients with mild to moderately active CUC in a small, open-label trial of VSL#3 for efficacy of induction of remission or response. Clinical symptoms and sigmoidoscopic ratings were performed at baseline and at week 6 using the UCCS and the modified Baron score (21,22). Nineteen of 30 (63%) patients achieved remission, 7/19 (37%) achieved a response, and 4/19 (13%) had no response (23). An uncontrolled trial of S. boulardii by Guslandi in 2003 was suggestive of benefit in maintaining clinical remission (using Rachmilewitz’s activity index) in patients with mild to moderate CUC in combination with a stable dose of mesalamine 1 g daily. Seventeen of 24 patients achieved clinical and endoscopic remission (24).

**Pouchitis**

The largest body of evidence demonstrating efficacy of probiotics in IBD exists for pouchitis. Gionchetti, et al published a randomized, placebo-controlled trial in 2000 which demonstrated a significant benefit of VSL#3 over placebo for maintenance of remission in patients suffering from chronic, relapsing pouchitis (25). The dose of VSL#3 employed in this study was much higher than doses used in other trials of VSL#3. The relapse rate in the VSL#3 treated group was 15% compared to the placebo-treated group with a relapse rate of 100%. Additionally, the investigators observed a 100% clinical and histological relapse rate within 4 months of VSL#3 discontinuation. Another group published equally impressive results of VSL#3 for maintenance of remission following an antibiotic-induced remission in patients with chronic pouchitis (26). Two of 36 patients (10%) in the VSL#3 group versus 15/36 patients (94%) in the placebo group experienced relapses as defined by an increase in the Pouch Disease Activity Index Score (PDAI) of greater than 2 (27). Inflammatory bowel disease questionnaire (IBDQ) scores were significantly better in the VSL#3 group compared to those of the placebo group. Gionchetti’s group published another study in 2003 evaluating the efficacy of VSL#3 for primary prevention of pouchitis in CUC patients following ileostomy closure in patients having recently undergone an IPAA (28). Forty patients were randomized to either one packet (3 grams per packet) of VSL#3 or placebo immediately following ileostomy closure for the period of one year. Patients were assessed clinically, endoscopically and histologically at months 1, 3, 6, 9, and 12 according to the PDAI. Health-related quality of life was also assessed using the IBDQ. Ten percent of patients (2/20) in the VSL#3 group versus 40% of patients (8/20) in the placebo group developed acute pouchitis after one year of follow-up. IBDQ scores improved significantly in the VSL#3 group but not in the placebo group.

A recent open-label study of VSL#3 in antibiotic-dependent pouchitis from the Cleveland Clinic failed to demonstrate significant benefit (29). Thirty-one subjects having had an antibiotic-induced remission were maintained on VSL #3, 6 g per day, for a mean duration of 14.5 months. PDAI scores were evaluated at baseline, week 2 (when VSL#3 was initiated) and at 8 months. Twenty-five patients (81%) discontinued the probiotics due either to lack of response or the development of adverse effects including bloating, constipation or hematochezia. In fact, only 6/31 patients (19%) were still on the probiotic cocktail after 8 months of follow-up. Although the 6 responders were virtually asymptomatic with a mean PDAI symptom score of 0.33 ± 0.52, the mean PDAI endoscopy score of 1.83 ± 0.72 was not significantly better than at baseline. The discrepancies between the results of these clinical trials are likely, in part, due to lack of uniform diagnostic criteria for chronic pouchitis and inconsistent dose administration of probiotic preparations. The two most commonly used pouchitis scoring systems in clinical trials today include the Heidelberg Pouch Activity Score (PAS) and the Pouch Disease Activity Index (PDAI) which attempt to provide more objective means of diagnosing and grading the severity of pouchitis (27,30). This is critically important given the lack of correlation between endoscopic, clinical and histologic sub scores in pouchitis (31).

**REGULATORY AND SAFETY CONCERNS**

There have been no reports of severe adverse events with the use of probiotics in humans in the context of...
clinical trials. A series of adverse events, in most instances occurring in critically ill and/or immunosuppressed individuals, has been reported in the form of case reports in the literature (32–39). Probiotics in food and food supplements have been poorly regulated. Studies have shown a large discrepancy between claimed and actual viability of some commercial probiotic products (40,41). Consequently, quality and bacterial viability are unpredictable unless microbiological analyses are performed on individual commercial products thus limiting the physicians’ ability to prescribe and monitor probiotics in clinical practice. Also, no consensus exists concerning dosage or selection of a particular probiotic. More recently, scientists are studying the administration of genetically engineered strains of specific probiotic species which deliver anti-inflammatory cytokines directly to intestinal epithelial cells (42).

CONCLUSION

At this point in time, very little evidence exists to justify the use of probiotics for the treatment of Crohn’s disease. Although some data exists to suggest that certain probiotics may be useful in the management of select cases of ulcerative colitis, the evidence is weak due to heterogeneity of study design, lack of placebo-controlled trials, and the use of soft endpoints. Although the strongest evidence supporting the use of probiotics exists for the prevention and/or treatment of pouchitis, larger randomized-controlled trials using uniform doses of probiotic preparations and standardized objective measurements of pouch disease activity are necessary. This will better define the most effective type, dose, and duration of probiotic therapy, as well as who is most likely to benefit. The administration of genetically modified strains of bacteria that will deliver anti-inflammatory cytokines directly to the intestine have great potential. Much research is required before such bacteria can be administered to humans.

References


