Short Communication

Is Lactobacillus GG Helpful in Children With Crohn’s Disease? Results of a Preliminary, Open-Label Study

Puneet Gupta, Haikaeli Andrew, Barbara S. Kirschner, and Stefano Guandalini

Section of Pediatric Gastroenterology, Hepatology and Nutrition, The University of Chicago Children’s Hospital, Chicago, Illinois, U.S.A.

ABSTRACT

Background: Lactobacillus GG is a safe probiotic bacterium known to transiently colonize the human intestine. It has been found to be useful in treatment of several gastrointestinal conditions characterized by increased gut permeability. In the current study, the efficacy of Lactobacillus GG was investigated in children with Crohn’s disease.

Methods: In this open-label pilot evaluation viewed as a necessary preliminary step for a possible subsequent randomized placebo-controlled trial, four children with mildly to moderately active Crohn’s disease were given Lactobacillus GG (10^10 colony-forming units [CFU]) in enterocoated tablets twice a day for 6 months. Changes in intestinal permeability were measured by a double sugar permeability test. Clinical activity was determined by measuring the pediatric Crohn’s disease activity index.

Results: There was a significant improvement in clinical activity 1 week after starting Lactobacillus GG, which was sustained throughout the study period. Median pediatric Crohn’s disease activity index scores at 4 weeks were 73% lower than baseline. Intestinal permeability improved in an almost parallel fashion.

Conclusions: Findings in this pilot study show that Lactobacillus GG may improve gut barrier function and clinical status in children with mildly to moderately active, stable Crohn’s disease. Randomized, double-blind, placebo-controlled trials are warranted for a final assessment of the efficacy of Lactobacillus GG in Crohn’s disease.


There is increasing experimental evidence to support a role for intestinal bacteria in the pathogenesis of Crohn’s disease. Spontaneous colitis develops in mice deficient in interleukin (IL)-2 (1), IL-10 (2), and T-cell receptors only in the presence of luminal bacteria and not in mice raised in germ-free conditions. The intestinal mucus layer from patients with inflammatory bowel disease has a high number of bacteria compared with that of control subjects (3). Antibiotics such as metronidazole and ciprofloxacin are useful in treatment of Crohn’s disease.

Recently, probiotic organisms have been used to treat gastrointestinal disorders with altered gut microflora. Lactobacillus GG (LGG; American Type Culture no. 53103) is the most widely studied probiotic bacterium that has been shown to survive gastric and bile secretions, adhere to intestinal epithelial cells, and colonize the intestine (4). It has been used in treatment of small bowel bacterial overgrowth in children with short gut, antibiotic-associated diarrhea (5), and Clostridium difficile colitis (6). Lactobacillus species have been shown to prevent colitis in IL-10–deficient mice (7). Preliminary data show that probiotics may be useful in maintaining remission in patients with ulcerative colitis (8). Lactobacillus GG has been shown to promote gut immunoglobulin (Ig)A response and thereby improve gut immunologic barrier in patients with Crohn’s disease(9). We thus conducted an open-label pilot trial to assess the effect of LGG supplementation on intestinal permeability and clinical parameters in children with Crohn’s disease.

METHODS

Patient Selection

Children in whom Crohn’s disease was diagnosed by established clinical, radiographic, and endoscopic criteria were included in the study. Patients with mildly to moderately active disease, despite concomitant therapy with prednisone and immunomodulatory drugs, such as 6-mercaptopurine (6-MP), aza-
thioprine (AZA), or methotrexate were included in the study. A Pediatric Crohn’s Disease Activity Index (PCDAI) of 10 or higher was used to define the active disease (10,11). The PCDAI is a multi-item index including subjective reporting of abdominal pain, general well-being, and diarrhea and physical findings, including linear growth and laboratory parameters (hematocrit, serum albumin, and erythrocyte sedimentation rate). All patients had to be receiving stable doses of immunomodulatory drugs for at least 3 months before screening and stable doses of prednisone for at least 4 weeks before the screening visit. Patients were allowed to decrease the steroid dose during the study period as clinically indicated. Patients with intestinal strictures that are likely to necessitate surgery, patients receiving antibiotics other than metronidazole, and those with concurrent intestinal or systemic infection were excluded from the study.

Protocol Design

The study was a 6-month open-label pilot evaluation of the efficacy of LGG at a dose of 10^8 colony-forming units (CFU) in enterocoated tablets twice a day. The dosage was based on previous studies that demonstrated adequate, albeit transient, colonization at this dose. The LGG was provided by Valio (Helsinki, Finland). The trial was conducted at the University of Chicago Children’s Hospital. The University of Chicago’s institutional review board approved the protocol, and all patients or their guardians gave informed written consent before the patients were enrolled in the trial.

Subjects were screened 1 week before the initiation of LGG therapy. Clinical features and disease activity were assessed at baseline and at 1, 4, 12, and 24 weeks of LGG therapy. The PCDAI was calculated at each visit. Stools were cultured at each follow-up visit to assess colonization by LGG.

Intestinal permeability was assessed by a cellobiose-mannitol sugar permeability test at each visit. After an overnight fast, patients drank a sugar test solution containing 2 g mannitol and 5 g cellobiose made up to 100 mL with tap water to give an osmolality of approximately 270 mOsm, and their urine was collected for the next 5 hours. The ratio of concentrations of cellobiose and mannitol in urine was determined according to published methods. Ratios higher than 0.022 were considered abnormal (12).

Statistical Analysis

Quantitative variables are described as medians with ranges in parentheses. The significance of changes was evaluated using analysis of variance (ANOVA) for parametric variables and the Mann–Whitney test for nonparametric variables.

RESULTS

Four patients were enrolled. All were male with a median age of 14.5 years (range, 10–18). Two patients had ileocolonic disease and two others had gastrocolonic disease. None had a fistula. Median duration of Crohn’s disease was 3 years (range, 1–5). All patients were taking prednisone at entry, with a median dose of 22.5 mg (range, 15–50 mg). All patients had also been taking immunomodulator drugs (6-MP or azathioprine) at a dose of 1 to 2 mg/kg, for an average of 10 months (range, 4.5–18). Two patients were also receiving metronidazole. All patients had mildly to moderately active disease at the beginning of the study. The median PCDAI score at entry was 19 (range, 12–35). The cellobiose-mannitol ratio was also high at baseline, reflecting altered intestinal permeability (median, 0.12; range, 0.023–0.17). Patients’ characteristics are shown in Table 1.

There was effective transient intestinal colonization with LGG in all patients. The LGG was in fact recovered in stool samples of all the patients at each follow-up visit. Fecal concentrations ranged from 10^7 to 10^9 CFU/g stool. Treatment of Crohn’s disease with metronidazole did not inhibit intestinal colonization with LGG (Fig. 1).

The patients showed significant improvement in Crohn’s disease activity, when measured by PCDAI scores (P = 0.02) 1 week after beginning LGG, and this improvement was sustained throughout the study period. Median PCDAI score at 4 weeks was 5 (range, 0–12.5), 73% lower than baseline and three patients (75%) had a PCDAI score of less than 10 indicative of inactive disease (Fig. 2). In three patients, it was possible to taper the dose of steroids while they were receiving LGG. Average reduction in steroid dose in these patients was 50% at 12 weeks.

The intestinal permeability, measured by a double sugar permeability test, improved significantly (P < 0.05) at 12-week follow-up (median 0.021; range, 0.009–0.046). This improvement was largely because of a decrease in cellobiose levels in urine, which suggests that LGG improves the intestinal paracellular permeability. However, this improvement was not sustained at 24-

### TABLE 1. Baseline features of individual study patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Disease location</th>
<th>Duration of CD (yr)</th>
<th>Medications at initiation of LGG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>Ileal, colonic</td>
<td>5</td>
<td>Prednisone, azathioprine</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>Ileal, colonic</td>
<td>1</td>
<td>Asacol, prednisone, azathioprine</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>Gastric, colonic</td>
<td>3</td>
<td>Azulfidine, metronidazole, prednisone, 6-mercaptopurine</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>Gastric, colonic</td>
<td>2</td>
<td>Pentasa, metronidazole, prednisone, azathioprine</td>
</tr>
</tbody>
</table>

CD, Crohn’s disease; LGG, Lactobacillus GG.
week follow-up (Fig. 3). No patient reported any adverse effects during the study period.

**Follow-up**

Three patients had relapse of Crohn’s disease within 4 to 12 weeks of discontinuation of LGG. One patient subsequently needed colectomy and one patient had ileocecal resection.

**DISCUSSION**

Although the cause of Crohn’s disease is unknown, there is increasing evidence that suggests that endogenous bacterial flora plays an important role in the initiation and perpetuation of the disease (13,14). It has been hypothesized that the intestinal inflammatory response is the result of an exaggerated intestinal host immune response to commensal enteric bacteria or their components in genetically predisposed individuals. A defect in mucosal barrier function could allow luminal bacterial antigens to initiate a chronic relapsing inflammation. Several studies have shown an increased intestinal permeability for various sugar molecules in patients with Crohn’s disease and their healthy relatives, which supports the role of mucosal barrier defect in initiation of Crohn’s disease (15).

The normal intestinal microflora may offer resistance to colonization by pathogens and thus functions as an important constituent of the gut defense barrier. Recently, probiotic micro-organisms have been shown to be effective in treatment of altered intestinal microflora (8,16). The most frequently studied probiotic is LGG. It is stable in acid and bile, adheres to human epithelial cells, and transiently colonizes the human intestine (17). It inhibits attachment of pathogens to intestinal mucus (18). Recently, LGG has been shown to enhance the expression of mRNA for two predominant mucins MUC2 and MUC3. These glycoproteins are known to inhibit adherence of pathogenic bacteria such as enteropathogenic *Escherichia coli* (19). *Lactobacillus GG* has also been shown to secrete inhibitory products that have antimicrobial properties against potential pathogens (20).

In clinical studies, LGG has been shown to be effective in prevention and treatment of antibiotic associated diarrhea (5), *C. difficile* colitis, traveler’s diarrhea, and acute childhood diarrhea, particularly when caused by rotavirus enteritis (21). *Lactobacillus GG* also acts by modulating host immune response. Several studies have shown that LGG enhances immune response during rotavirus diarrhea, including nonspecific humoral immune response and rotavirus-specific antibodies and shortens the duration of diarrhea (22). *Lactobacillus GG* has also been shown to stabilize the gut mucosal barrier. It reverses the increased intestinal permeability induced by cow’s milk in young rats (23) and promotes intestinal barrier function in children with food allergy (24). These studies show that LGG may be effective in treatment of Crohn’s disease by several potential mechanisms such as altering the intestinal mucins, promoting local immune response, and stabilizing the gut mucosal barrier.

*Lactobacillus GG* also has an impressive record of safety. Indeed, although a liver abscess due to a *Lactobacillus rhamnosus* strain indistinguishable from LGG
has been recently reported (25), lactic acid bacteria (LAB) in foods have a long history of safe use and have been given generally recognized as safe (GRAS) status (26). In a study from Finland, lactobacilli were identified in only 8 of 3317 blood culture isolates (0.2%), and none of the isolates was similar to LGG, in spite of its widespread use in that country (27).

Based on the observations made in this open-label pilot study Lactobacillus GG appears to be effective in ameliorating the disease activity in children with mildly to moderately active, stable Crohn’s disease. A dose of $10^{10}$ CFU twice a day resulted in intestinal colonization in all the patients, including those taking metronidazole. All patients in this study had active Crohn’s disease, despite use of steroids and immunomodulatory drugs. Their PCDAI scores improved significantly during LGG therapy, and this improvement was sustained throughout the study period. Median PCDAI score at 4 weeks was 73% lower than baseline. Three patients were also able to achieve a 50% reduction in steroid dose. No patient reported any adverse effects on LGG. In our patients, the cellobiose-mannitol ratio was elevated at baseline, mainly as a result of increased cellobiose absorption, reflecting increased intestinal paracellular permeability. This parameter improved significantly on treatment with LGG, mainly as a result of a decrease in cellobiose levels, again suggesting a reduction in paracellular permeability. After 24 weeks of treatment, the intestinal permeability showed a trend toward increase, although it remained at levels below baseline.

Overall, the improvement in clinical activity appeared to be accompanied by a reduction in paracellular intestinal permeability. In two patients, however, the clinical improvement documented by a lower PCDAI preceded the effect on intestinal permeability. Thus, it is unclear whether LGG acted by stabilizing gut mucosal barrier or by other mechanisms. It clearly was well beyond the scope of this preliminary investigation to address the question of underlying mechanisms of action of this probiotic in Crohn’s disease.

In conclusion, and fully acknowledging the limitations of an open-label study in only four patients, we believe that this study provides preliminary evidence that LGG is safe and may be effective in improving gut barrier function and clinical response in pediatric patients with mildly to moderately active Crohn’s disease. It is obviously that only in randomized double-blind placebo-controlled trials in large numbers of patients that significant, solid evidence of efficacy can be reached. Until then, use of this and any probiotic in inflammatory bowel diseases does not appear warranted. Also, it is our opinion that future research in this area should be designed to verify whether continuous or cyclic administration of LGG is preferable in achieving a more prolonged maintenance of remission in patients with pediatric Crohn’s disease.

REFERENCES

A 9-year-old boy with diagnoses of hepatitis and cholecystitis was transferred to Mount Sinai Medical Center for further management. He developed intermittent right upper quadrant abdominal pain 5 months before admission. He traveled with his family to Ecuador 2 months before admission and stayed for 1 month. His abdominal pain increased 5 days before admission, and he developed nausea, vomiting, and jaundice 3 days later. He denied fever and pruritus. An abdominal sonogram showed marked thickening of the walls of the gallbladder. He was started on intravenous antibiotics (for a possible gangrenous gallbladder) and transferred. Laboratory data included the following: hemoglobin 13.6 g/dL; white blood cell count 7000/mm³ (46% polymorphonucleotides, 39% lymphocytes, 7% monocytes, 5% eosinophils); platelets 351,000/mm³; alanine aminotransferase level 1725 U/L; aspartate aminotransferase level 1185 U/L; alkaline phosphatase 353 U/L; gamma-glutamyl transpeptidase 199 U/L, total bilirubin 5.6 mg/dL, direct bilirubin 3.4 mg/dL; PT 15.9 seconds; and albumin 38 g/L. Repeat fasting hepatobiliary ultrasound showed a shrunken, edematous gallbladder whose wall thickness was 14.1 mm, a normal sized liver, no evidence of intrahepatic biliary dilation, and common bile duct diameter of 3 mm (Fig. 1). The carbamoyl-methyl iminodiacetic acid (HIDA) scan revealed delayed hepatic uptake with filling of the gallbladder and intestinal excretion of the radionuclide (Fig. 2).

What is the most likely diagnosis?

A. Acalculous cholecystitis  
B. Hepatitis A  
C. Ascaris lumbricoides  
D. Gangrenous gallbladder  
E. Salmonella typhi

**FIG. 1.**  
**FIG. 2.**  

**ANSWER:** See page 463.