Multicenter Randomized-controlled Clinical Trial of Probiotics (*Lactobacillus johnsonii,* LA1) on Early Endoscopic Recurrence of Crohn's Disease after Ileo-caecal Resection

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Background: Seventy percent of Crohn's disease (CD) patients exhibit anastomotic recurrence within 1 year after ileo-caecal surgery. Recent clinical trials suggest the beneficial use of probiotics in the control of intestinal inflammation in pouchitis and ulcerative colitis. This study is a multicenter clinical trial evaluating the efficacy of an oral administration of the probiotic LA1 on early postoperative endoscopic recurrence of CD.

Methods: Seventy patients with CD were enrolled prior to elective ileo-caecal resection and randomly assigned after surgery to daily treatment with either *Lactobacillus johnsonii,* LA1, Nestlé (10^{10} colony-forming units, CFU) (group A, $n = 34$) or placebo (group B, $n = 36$) for 12 weeks. The primary objective was to assess the effect of LA1 on the endoscopic recurrence rate at 12 weeks. Stratification was performed according to smoking status at randomization.

Results: Seven and 14 patients were excluded in the LA1 and placebo groups, respectively. In intention-to-treat analysis, the mean endoscopic score was not significantly different between the two treatment groups at 3 months (LA1 versus placebo: 1.50 ± 1.32 versus 1.22 ± 1.37, treatment effect: $P = 0.48$, smoke effect: $P = 0.72$). The percentage of patients with severe recurrence (i3 + i4) was 21% and 15% in the LA1 and placebo groups, respectively ($P = 0.33$). Using a per-protocol (PP) analysis, the mean endoscopic score was not significantly different between the two treatment groups (LA1 versus placebo groups: 1.44 ± 1.31 versus 1.05 ± 1.21, $P = 0.32$). The percentage of patients with severe recurrence (i3 + i4) was 19% and 9% in the LA1 and placebo groups, respectively ($P = 0.054$). Clinical relapse rate (CDAI [CD activity index] > 150, with an increase of CDAI > 70 points or greater from baseline) in the LA1 and placebo groups was 15% (4/27) and 13.5% (3/22), respectively (PP analysis: chi-square test, $P = 0.91$ and log-rank test: $P = 0.79$).

Conclusion: Oral administration of the probiotic LA1 in patients with CD failed to prevent early endoscopic recurrence at 12 weeks after ileo-caecal resection.

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Key Words: Crohn's disease, endoscopic recurrence, probiotics

Upon scrutiny of the natural history of Crohn's disease (CD), a great majority of patients will eventually require surgery.[1,2] Seventy percent of these patients will then develop mucosal recurrence at 1 year after surgery that may translate into clinical relapse, potential complications, and repeat the need for surgery.[3–6] Therefore, the ultimate therapeutic goal in these patients is to prevent mucosal disease recurrence.[7] Regrettably, attempts to prevent endoscopic or clinical recurrence with current medications were met with poor success. The weak therapeutic gain of mesalamine discourages its further use in this indication.[8,9] On the other hand, a recent randomized placebo-controlled trial evaluating azathioprine in CD patients after ileo-caecal resection offers great promise,[10] despite its potential side effects, but awaits further confirmation.[11,12]

Preliminary clinical studies and the identification of pattern recognition receptor signaling pathways as disease susceptibility genes in CD revealed that a major trigger of mucosal inflammation and disease recurrence is the luminal microbial flora.[13–15] Fecal diversion from diseased small bowel loops induces mucosal healing, with resolution of intestinal inflammation, while infusion of intestinal contents in excluded ileum cause early mucosal ulcerations.[16,17] In fact, the therapeutic efficacy of metronidazol and ornidazol in preventing anastomotic recurrence after ileal resection suggests that targeting the microbial flora may indeed prevent mucosal disease recurrence.[18,19] Although administration of antibiotics is effective, their clinical use is hampered by the

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relatively high rate of side effects, thus leading to poor adherence.[18,19] Thus, targeting the altered microbial flora in CD appears to be more valuable than treating the resulting intestinal inflammation.

Probiotics are live and safe microbes that beneficially restore the intestinal microbial flora.[14] Several animal studies have shown the clear advantage of probiotics, and in particular *Lactobacillus* species, in the prevention and treatment of experimental colitis.[20–25] In addition, their modes of action are now better characterized and give more insight into their protective and immune-mediated effects.[26–28] Strong clinical evidence supports the therapeutic efficacy of probiotics in preventing the development and maintaining remission of chronic pouchitis.[29–31] Furthermore, recent randomized clinical trials suggest that probiotics could be as effective as mesalamine for maintaining remission in ulcerative colitis.[32–35] However, the fervor and enthusiasm for the use of probiotics is much less substantiated in CD, where clinical study is still in its infancy.[36–40]

Lactobacillus johnsonii (LA1, Nestec, Nestle, Verschez-les blancs, Lausanne, Switzerland), formerly known as *Lactobacillus acidophilus,* isolated several years ago, is a unique strain of bacteria with enhanced adherence properties to the intestinal epithelial monolayer, preventing colonization of potentially pathogenic bacteria. This LA1 strain dampens lipopolysaccharide (LPS) responsiveness of human intestinal epithelial cells, possibly through its lipoteichoic acid (LTA) and competitive binding, preventing LPS from binding to the TLR4/MD2/CD14 complex.[41] Its potential regulatory action on the mucosal immune system is demonstrated by the ability of LA1 to sensitize human intestinal epithelial cells to express TGFβ, which may in turn control mucosal T-cell homeostasis.[42] The aim of this study was to assess the safety and efficacy of *L. johnsonii* (LA1, Nestec) supplementation in the prevention of endoscopic recurrence after ileo-caecal resection in patients with CD.

PATIENTS AND METHODS

Study Design

This study was a multicenter prospective randomized double-blind placebo-controlled trial comparing LA1 (*Lactobacillus johnsonii,* Nestec) with placebo in a parallel design over a 12-week postoperative period. This study was conducted in six university hospitals and three large community teaching hospitals starting in February 2001 and was completed by January 2004.

Patient Population

Patients were eligible for the study if they were between 18 and 65 years of age and scheduled for curative ileo-caecal resection for CD. Inclusion criteria were a diagnosis of CD for at least 6 months, ability to start oral nutrition within 7 days of operation, need for curative ileo-caecal resection, and resection margins free of inflammation. Exclusion criteria were active perianal disease or any active disease in other segments of the intestine, anti-TNFα, and/or investigational treatment within 4 months prior to surgery; current treatment with 5-ASA, azathioprine/6MP, or methotrexate; bowel surgery performed less than 3 months previously; history of colostomy or ileostomy; infections, neoplasia, or uncontrolled diseases; or anticipation of noncompliance with protocols. Subjects who were receiving steroids preoperatively were tapered and weaned according to a strict schedule.

Study Drugs

The treatment consisted of the probiotic *L. johnsonii,* (LA1, Nestec) in freeze-dried form and blended with maltodextrin at 10^{10} colony-forming unites (CFU)/day. The placebo was maltodextrin only. The LA1 powder was supplied in foil sachets (weight 2 g) containing 10^{10} CFU of probiotics. The placebo was a powder of the same appearance and weight, also in individual foil packets. Both probiotics and placebo were administered in combination with an enteral formula at 120 mL/day (ACD004, Nunspeet, Holland, Konolfingen, Switzerland). The identity of the treatment sachet was blind to patients, support staff, and investigators (numerical codes). Treatment codes were broken only by the statistician after completion of the trial.

Procedure and Randomization

Patients with CD were randomly assigned after surgery to daily treatment with either LA1 (group A) or placebo (group B). Randomization between the two groups was centralized and performed on current smoking status at the time of surgery as balancing the factor using the Nestle Trial Balance program. The treatments were given for 12 weeks. No other medication (including antidiarrheal agents) was allowed during the study period. No other fermented products or yogurts were allowed during the 12 weeks of treatment. Patients were enrolled prior to elective ileo-caecal resection. All subjects enrolled in the study received 3 days of antibiotics (Amoxicilline/Clavulanic Ac. 500 mg PO TID) prior to surgery (intestinal decontamination). In case of emergency ileo-caecal resection, antibiotics may be administered beginning on the day after surgery for a total of 3 days. At the day of surgery, examination of the margins of the resection specimen confirmed the absence of residual CD. Oral feeding was generally initiated 3–7 days postoperatively. On days 6–12 following surgical intervention, patients were randomly assigned to one of the two groups (visit 0). The protocols were approved by Institutional Review Board / Independent Ethics Committee at each site and all patients provided written informed consent.

Objectives

The primary outcome was to assess the effect of oral administration of LA1 on the endoscopic recurrence (neoterminal ileum) in CD patients at 12 weeks after surgery or on relapse. The secondary outcomes were 1) the histological score (neoterminal ileum) at 12 weeks or on relapse; 2) the clinical relapse rate (CD activity index (CDAI) >150 with an increase of 70 points or higher from baseline) at 12 weeks; 3) serum C-reactive protein levels at 12 weeks or on relapse; and 4) safety and tolerance at 12 weeks.

Patient Monitoring and Outcome Measurements

The endoscopic relapse rate was assessed according to the Rutgeerts scoring system (Table 1A). The histological score was assessed by the Geboes scoring system (Table 1B). Biopsy samples of the neoterminal ileum were taken and assessed blindly by two pathologists. Relapse rate was defined by a CDAI > 150 with an increase of 70 points or higher from baseline. Follow-up visits were scheduled at 4, 8, and 12 weeks and included CDAI calculations, registration of medication and smoking status, and measurement of hematocrit and C-reactive protein (CRP) measurements. Compliance and tolerance were checked by the research nurse with a daily intake and tolerance monitoring agenda.

Data Analysis

All data were analyzed according to both an intention-to-treat (ITT) and a per-protocol (PP) approach. Determination of sample size: the distribution of the 5-point endoscopic scale was assumed to be approximately uniform. Detection of a difference of 1 endoscopic score (5 scores: i0 to i4) between the two groups at $\alpha = 0.05$ and $\beta = 80\%$ requires a sample size of 31 patients per group (Pass 6.0 program). To compensate for potential missing data, 20% additional patients were recruited (37 patients per group). For primary outcome (endoscopic score), all available data from randomized patients were considered in an ITT model. Data of patients, which are incomplete due to one of the reasons described below, were evaluated using the worst-case model.

Statistical Analyses

All statistical analyses were done with SAS software (v. 8.2, Cary, NC). The rejection level in tests was equal to 5%. Statistical evaluation was performed at Nestle Research Center (Vers-chez-les blancs, Lausanne, Switzerland). The endoscopic scores after 12 weeks of study treatment were compared using the *t*-test. The secondary outcomes were analyzed using the *t*-test, mostly after log transformation. The clinical relapse-free periods were compared by the log-rank test for differences between both groups. For primary outcome, the linear mixed model was used to compare the two treatment groups with visit and treatment as fixed effects, patient as random effects, the initial value (visit 0) and smoking as covariates. The covariate smoking is the status at the time of surgery. The comparison of the percentages of endoscopic levels between the two treatment groups was calculated by logistic regression with treatment as fixed effect and the i0 and smoking as covariates. For secondary outcomes at 3 months, the linear mixed model was used to compare the two treatment groups, with treatment as fixed effect, patient as random effect, and smoking as covariate. Tolerance parameters were calculated for treatment period, using the logistic regression with repeated measurements and visit as covariates.

TABLE 1. Endoscopic (Rutgeerts) and Histological (Geboes) Scoring System

A.Rutgeerts Scoring System of Endoscopic Recurrence

I0:No lesions.

I1: ≤5 aphtous lesions.

I2: >5 aphtous lesions with normal mucosa between the lesions or skip areas of larger lesions or lesions confined to ileocolonic anastomosis.

I3: Diffuse aphtous ileitis with diffusely inflamed mucosa.

I4: Diffuse inflammation with already larger ulcers, nodules, and/or narrowing.

B. Geboes Scoring System of Histologic Recurrence

Histology	Score
Epithelial damage	Normal
	Focal pathology
	Extensive pathology
Architectural changes	Normal
	Moderately disturbed
	Severely disturbed
Infiltration of MNC in the lamina propria	Normal
	Moderate increase
	Severe increase
Infiltration of polymorph cells In the lamina propria	Normal
	Moderate increase
	Severe increase
Polymorphonuclear cells in epithelium	Normal
	Moderate increase
	Severe increase
Presence of erosions and/or ulcers	No
	Yes
Presence of granuloma	No
	Yes

TABLE 2. Demographics of the Study Population

	All Patients	Probiotics Group [A]	Placebo Group [B]
Patients randomized	70	34	36
Mean age	37 ± 13	38.7 ± 14.5	35 ± 11.7
Gender F	33	15 (44%)	18 (50%)
Smokers	25	13 (38%)	12 (33%)
Age at onset	26 ± 9	27.9 ± 10.6	25.4 ± 8.3
Disease location			
Ileum only	6	2	4
Colon only	3	1	2
Ileo-colonic	61	31	30
Disease type			
Fibrostenosing (%)	87	88	86
Perforating (%)	23	22	24
Inflammatory (%)	0	0	0
First resection (%)	74	79	69
Length of resected ileum (cms)	24 ± 16	27 ± 17	22 ± 14

RESULTS

Patients

The baseline clinical demographics of patients in both treatment groups, LA1 and placebo, are listed on Table 2. Of the 77 enrolled patients, 70 patients were randomized. In ITT analysis, a total of 34 patients were assigned to the LA1 group and 36 to the placebo group. There were 4 and 3 protocol violations, and 3 and 11 dropouts in the LA1 and placebo groups, respectively (Fig. 1A). Protocol violations included the following: no ileo-caecal resection ($n = 3$), maintenance of 5-ASA ($n = 1$) and antibiotics ($n = 1$), infliximab within 2 months before enrolment ($n = 1$), and consent withdrawal after randomization ($n = 1$). Dropouts included the following: adverse events ($n = 9$), consent withdrawal ($n = 1$), antibiotics use ($n = 2$), and loss of follow-up ($n = 2$). The PP population consisted of 27 and 22 patients in the LA1 and placebo group, respectively (Fig. 1A).

In ITT analysis, the endoscopy was not performed in all the recruited patients because of dropouts and violations. In all, 28 endoscopic scores were available in the LA1 group (28/34) and 27 in the placebo group (27/36) (Fig. 1B, upper panel). Because the study was slightly underpowered (28 versus 27 instead of 31 versus 31), a few patients were reentered using the worst-case model. The worst-case model (severe recurrence or i4) was applied for the following reasons: symptomatic relapse requiring additional medical (including antibiotics) or surgical therapy, clinical recurrence with symptoms interpreted by the investigator as active disease, delayed surgical complication, feeding intolerance related to treatment, suspected complication related to treatment, unable to withdraw steroid treatment within 4 weeks

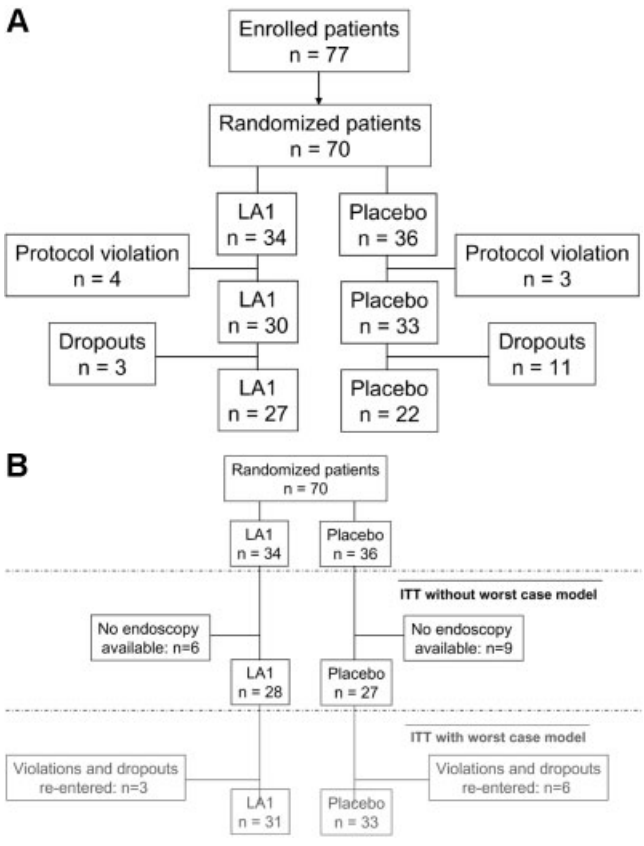
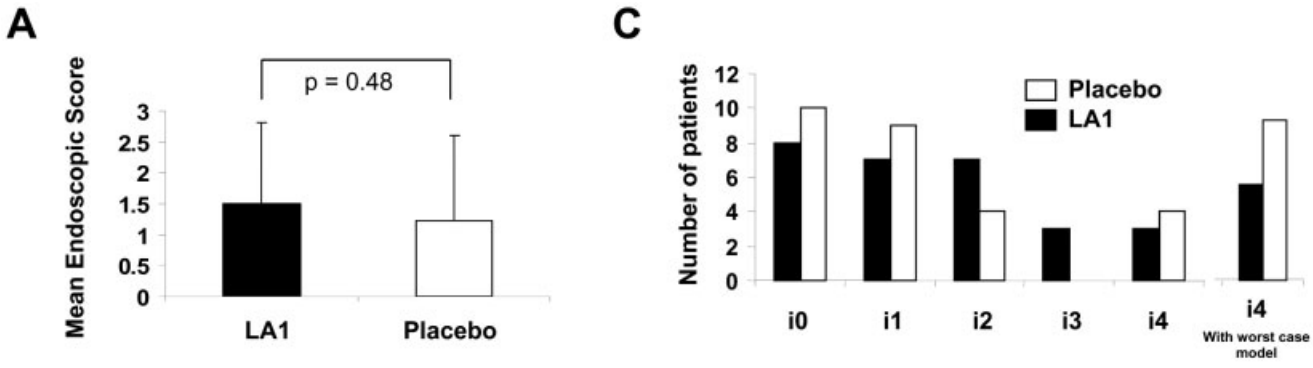


FIGURE 1. A: Flow chart of protocol violations and dropouts in both treatment groups. B: Flow chart of endoscopic scores for ITT analysis without (upper panel) and with (lower panel) worst-case model in both treatment groups.



GROUP		i0	i1	i2	i3	i4
LA1	Smoking (n: 11)	27.3% (n: 3)	27.3% (n: 3)	27.3% (n: 3)	9.1% (n: 1)	9.1% (n: 1)
(n: 28)	No smoking (n: 17)	29.4% (n: 5)	23.5% (n: 4)	23.5% (n: 4)	11.8% (n: 2)	11.8% (n: 2)
Placebo	Smoking (n: 8)	37.5% (n: 3)	25.0% (n: 2)	12.5% (n: 1)	0.0% (n: 0)	25.0% (n: 2)
(n: 27)	No smoking (n: 19)	36.8% (n: 7)	36.8% (n: 7)	15.8% (n: 3)	0.0% (n: 0)	10.5% (n: 2)

FIGURE 2. A: Mean endoscopic (Rutgeerts) scores in both treatment groups (ITT analysis without worst-case model). B: Stratification of patients in each treatment group according to endoscopic recurrence severity (ITT analysis without worst-case model). C: Stratification of patients in each treatment group per endoscopic score (ITT analysis with or without worst-case model) and according to smoking status (ITT analysis without worst-case model).

postoperatively, and withdrawal at physician recommendation. Of the 15 patients for whom the endoscopy was not available, nine patients were considered as severe recurrence or i4 using the worst-case model: three and six patients in the LA1 and placebo group, respectively.

Thus, the ITT population without the worst-case model is 28 and 27 patients in the LA1 and placebo group, respectively (Fig. 1B, upper panel). The ITT population with the worst-case model consisted of 31 (28 + 3 worst cases) and 33 (27 + 6 worst cases) patients in the LA1 and placebo group, respectively (Fig. 1B, lower panel). The PP population consisted of 27 and 22 patients in the LA1 and placebo group, respectively (Fig. 1A).

Clinical relapse rate (CDAI > 150, with an increase of CDAI > 70 points or greater from baseline) in the LA1 and placebo groups was 15% (4/27) and 13.5% (3/22), respectively (PP analysis: chi-square test, $P = 0.91$ and log-rank test: $P = 0.79$). In patients with clinical relapse, two and one patients had no endoscopic recurrence in the LA1 and placebo group, respectively.

Primary Outcome: Endoscopic Score

ITT Analysis.

After 3 months of treatment, the mean endoscopic score was not significantly different between the two treatments (LA1 versus placebo [$n = 28$ versus $n = 27$]: 1.50 ± 1.32 versus 1.22 ± 1.37, treatment effect: $P = 0.48$, smoke effect: $P = 0.72$) (Fig. 2A). The percentage of patients with mild to moderate recurrence (i1 + i2) was 50% (14/28) and 48% (13/27) in the LA1 and placebo groups, respectively. The percentage of patients with severe recurrence (i3 + i4) was 21% (6/28) and 15% (4/27) in the LA1 and placebo groups, respectively (chi-square comparing all groups: $P = 0.33$) (Fig. 2B). The stratification of patients in each treatment group per endoscopic score (upper panel) according smoking status (lower panel) is shown on Figure 2C. Using the worst-case model, the mean endoscopic score was not significantly different between the two treatments (LA1 versus placebo [$n = 31$ versus $n = 33$]: 1.74 ± 1.46 versus 1.73 ± 1.64, treatment effect: $P = 0.97$, smoke effect: $P = 0.94$). Using the worst-case model, the percentage of patients for either mild to moderate or severe recurrence was not significantly different (chi-square comparing all groups: $P = 0.68$) (data not shown).

PP Analysis.

After 3 months of treatment, the mean endoscopic score was not significantly different between the two treatments (LA1 versus placebo: 1.44 ± 1.31 versus 1.05 ± 1.21, treatment effect $P = 0.32$-mixed model). The percentage of

patients with mild to moderate recurrence (i1 + i2) was 52% (14/27) and 50% (11/22) in the LA1 and placebo groups, respectively. The percentage of patients with severe recurrence (i3 + i4) was 19% (5/27) and 9% (2/22) in the LA1 and placebo groups, respectively (chi-square comparing all groups: $P = 0.054$).

Secondary Outcomes

After 3 months of treatment the mean histological score was not significantly different between the two treatments (LA1 versus placebo: 4.58 ± 2.82 versus 3.73 ± 2.19, treatment effect $P = 0.83$, mixed model after log-transformation). After 4, 8, and 12 weeks of treatment, there was no significant modification of CDAI between both treatments (treatment effect: $P = 0.67$, visit effect $P = 0.004$; treatment and visit interaction: $P = 0.10$, mixed model). The differential CRP serum levels (serum level at 3 months – serum level at surgery) between both treatment groups were not significantly different ($P = 0.13$). In the LA1 group, 65% of patients had at least one minor adverse event (2% "probably" in relation to treatment) and 21% at least one severe adverse event ("none" related to treatment). In the placebo group, 72% of patients had at least one minor adverse event (8% "probably" in relation to treatment) and 22% at least one severe adverse event ("probably" in relation to treatment in one patient).

DISCUSSION

In this randomized, prospective, controlled, double-blind trial, oral administration of the probiotic LA1 failed to exert any protective effect on early endoscopic recurrence in patients with CD who underwent an ileo-caecal resection. Moreover, the histological score, the serum inflammatory parameters, and the clinical relapse rate were similar in both treatment groups. In the present study, LA1 was chosen because of its beneficial in vitro immune properties.[41,42] We chose the Rutgeerts score, a well-recognized score to measure CD recurrence for ileal disease, to measure endoscopic recurrence rate.[16,18,19] The patient population enrolled was quite homogeneous in its presentation, with many patients suffering from an ileal fibrostenosing CD, who had to be off medications during the study period. Patients were enrolled according to their smoking habit, as smoking is a major deleterious factor for intestinal inflammation. The early assessment at 12 weeks was preferred to better discriminate the effect of LA1 on early mucosal events preceding endoscopic recurrence. The percentage of endoscopic recurrence at week 12 was indeed similar to that reported in previous series at 6 months.[16,18,19] In addition, all patients received preoperative gut decontamination, and recommendations were made to avoid the consumption of any other source of probiotic strains. The main limitation of this study was the high drop-out rate in our placebo group. This study was therefore slightly underpowered to the same extent as the two previous studies when using endoscopy as a primary endpoint.[37,38] A few patients were reentered using the worst-case model but did not affect the final ITT results.

Mounting clinical evidence demonstrates that probiotics maintain remission in ulcerative colitis and pouchitis.[29–35] Also, the probiotics, VSL-3, prevent the development of pouchitis in patients after total colectomy and ileo-anal pouch.[29–31] Our study is the second randomized placebo-controlled trial published so far reporting the lack of efficacy of LA1 for prophylaxis of postoperative recurrence in CD patients.[37] Prantera et al first reported the lack of efficacy of *Lactobacillus rhamnosus* GG on endoscopic recurrence after surgery in 45 CD patients.[38,40] These three negative studies may therefore question the role of probiotics on postoperative recurrence in CD and one may wonder if probiotics should be further investigated in this indication. However, a single-blind study (reported in abstract form) appeared to demonstrate the greater efficacy of a combined treatment of rifaximine for 3 months followed by VSL-3 for 12 months compared with mesalamine in preventing postoperative recurrence in CD.[43] This suggests that longer antibiotic administration and the use of a mixture of probiotics may offer a better therapeutic gain. If single probiotics strains may be ineffective in a postoperative setting, two nestled prospective studies suggest that probiotics help maintain disease remission in CD. In 20 patients with CD in steroid-induced remission, 64% of patients maintained remission under the *Escherichia coli* Nissle 1917, while only 30% of patients in the placebo group maintained remission at 1 year.[36] In patients with CD in remission, the relapse rate at 6 months was 37.5% for patients receiving 5-ASA (3 g) only and 6.25% in patients receiving 5-ASA (2 g) plus *Saccharomyces boulardii* (2 × 500 mg).[39] These two trials, however, were recently challenged by a randomized-controlled clinical (RCT) by Bousvaros et al[40] demonstrating the lack of efficacy of *Lactobacilus* GG at maintaining remission in 75 CD children followed for up to 2 years. Concomitant medications, however, were allowed in this trial. Although these trials need further confirmation, the response to probiotics may be different in the prevention of disease occurrence or in the maintenance of remission: two strategies in essence dissimilar.[44]

Because probiotics are safe, perhaps not enough basic considerations have been addressed before launching and evaluating this strategy in clinical trials. In fact, several reports now shed light on fundamental mechanisms of action of probiotics after the empirical clinical observations of potential efficacy have already been made. If VSL-3 was carefully evaluated in pouchitis, perhaps the dose and mixture of probiotic strains chosen in VSL-3 do not seem to stem from extensive basic studies. Thus, the seemingly relative lack of efficacy of a single probiotics strain in postoperative CD may

be explained not only by the still unknown pharmacodynamic properties but also kinetic properties of the strain evaluated, namely, the dose (load) and the timing (period and duration of administration).[14] Also, the efficacy of VSL-3 over single probiotic strains in preventing postoperative recurrence in CD could suggest that a mixture of probiotics offers a greater therapeutic advantage. This observation (only published in abstract form), if confirmed, deserves a better understanding of the synergistic actions of multiple probiotic strains when used in combination.

The different results reported in CD and ulcerative colitis may also herald the degree of complexity in the interaction between the probiotic (bacteria) and the patient (host). In reality, it is clear from animal studies that a given bacterial strain may differentially influence the development of colitis, depending on the mouse strains. For example, *Bacteriodes vulgatus* induces colitis in HLA-B27 transgenic rats but not in IL-10 KO mice. Inversely, *E. coli* promotes colitis in IL-10 KO mice but not in HLA-B27 transgenic rats.[45–47] Also, a mouse strain can be rendered susceptible or resistant to colitis depending on the bacterial strains used.[22,46] The response to probiotics is tightly regulated by both the genetic background of the mouse and the bacteria strain. Thus, while efforts are being unified for a recognized phenotypic and genotypic classification of CD patients,[48–51] one may start the classification of probiotic strains based on their biochemical and genetic properties, as their efficacy will depend on the target population, namely, the location, behavior, and activity of the disease.

In conclusion, this RCT fails to demonstrate the efficacy of LA1 in preventing Crohn's endoscopic recurrence at 12 weeks after surgery.

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