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Short Communication

Clinical effects of Lactobacillus strains as probiotics in the treatment of irritable bowel syndrome. Results from the LAPIBSS trial: Future objectives

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Abstract

The objective of this communication is to present and analyze the recent results from the LAPIBSS study in order to improve future clinical trials on the effects of Lactobacillus strains in the treatment of irritable bowel syndrome (IBS). Using a tightly-controlled clinical trial protocol with the highest Jadad score of 5/5, the current trial aimed to demonstrate the efficacy of a 2-strain mixture of *Lactobacillus acidophilus* to improve IBS symptoms. Eighty patients diagnosed for IBS according to Rome III criteria were recruited to a multicentric, double-blinded, in parallel groups, placebo-controlled, randomized trial. Patients were provided with a daily dose of two capsules containing either two probiotic strains (5×10^9cfu/capsule) or placebo for 8 weeks. The primary endpoint was abdominal pain score assessed with a 100-mm visual analogue scale (VAS). Secondary endpoints included scores of bloating, flatus and rumbling assessed with a 100-mm VAS, a composite score that consisted of the sum of the 4 VAS scores, and the stool frequency and consistency assessed with the Bristol Stool Form Scale. Our study has failed to demonstrate a significant improvement of the primary endpoint of abdominal pain. Significant differences between groups were observed for flatus score at week 4 (P= 0.04) and week 8 (P= 0.03) and for composite score at week 8 (P= 0.04). The consumption of the 2-strain mixture of *L. acidophilus* over 8 weeks is safe, significantly decreases flatus and IBS composite scores. The significant effect on flatus could result from the species-specific homofermentative properties of *L. acidophilus* strains. The negative results on abdominal pain and the gained experience are discussed for the future clinical trials on this topic.

Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder and consists of chronic and recurrent abdominal pain associated with defecation or a change in bowel habits including diarrhea and/or constipation [1,2]. A recent systematic review performed by Chey et al. (2015) concluded that diagnosis of IBS is based on the identification of characteristic symptoms and the exclusion of other organic diseases [3]. As this review concerns medical education, its associated quiz for medical education is a useful prerequisite for physicians performing clinical trials in IBS [3]. Due to the lack of a well-established therapeutic approach, IBS patients seek alternative strategies such as probiotics [4]. Several food-associated *Lactobacillus* species have an excellent safety profile and have a "generally-regarded-as-safe" (GRAS) status, such

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as *Lactobacillus acidophilus* (*L. acidophilus*) [5]. While *L. acidophilus* is one of the most commonly dietary used bacterial species, only 2 randomized clinical trials (RCT) performed with *L. acidophilus* strains and conducted with a high-quality method have been reported in the management of IBS symptoms [5-8] .The first one was a pilot RCT including 40 patients and showed that *L. acidophilus*-SDC 2012, 2013 significantly reduced abdominal pain compared with placebo after 4 weeks of treatment[7]. Recently, a 12-week RCT performed with *L. acidophilus* NCFM showed significant improvement of abdominal pain in the subgroup of patients suffering from moderate to severe pain [8]. Using a tightly-controlled protocol firstly published as *Lactobacillus acidophilus versus placebo in the symptomatic treatment of irritable bowel syndrome* (LAPIBSS), we conducted a RCT investigating for a 2-month period the safety and efficacy of a 2-strain mixture of *L. acidophilus* to manage IBS symptoms which has provided the following positive results and conclusion [9,10]. 1/ at the end of the trial, probiotics reduced significantly flatus and composite scores, 2/ this RCT based on strain-specific properties confirmed the safety of probiotics and showed their limited efficacy to improve IBS symptoms, 3/ the beneficial effect on flatus severity could result from the species-specific homofermentive properties of *L. acidophilus* strains. The LAPIBSS protocol suggested an additional benefice of a combined treatment with two strains of the same species without known antagonist effects [9]. The rationale for combining *L. acidophilus* NCFM with a second available *L. acidophilus* strain, i.e. *L. acidophilus subsp. helveticus* LAFTI L10, was based on preclinical and clinical evidence for their strain-specific properties targeting the intestinal system [11,12]. However, taking into account the multifactorial pathophysiology of IBS, the strong placebo effect observed in this trial could warrant further study with probiotics targeting the gut-brain axis [3,4].

The LAPIBSS protocol refers to a multicentric (10 office-based general practitioner located in France and one gastroenterologist of the Rangueil University Hospital of Toulouse, France), double-blind, placebo-controlled, two-armed, parallel design, individually randomized trial, comparing probiotics with placebo in patients with IBS aged between 30 and 60 years old [9]. The current trial was performed for a maximum of 9 weeks with 4 visits planned (at points corresponding to screening, baseline, 2 control visits after 4 and 8 weeks of treatment) [9]. Patients were diagnosed for IBS according to Rome III criteria with in addition a negative coprological and inflammatory balance (negative CRP blood test) for over 6 months [9]. Other selection criteria were detailed in the LAPIBSS protocol [9].

The study product was provided in the form of vegetable capsule containing a blend of two viable lyophilized *L. acidophilus* strains: *L. acidophilus* NCFM (FDA GRAS Notice 000357, strain number ATCC SD5221, Danisco Inc. Madison, Wisconsin, United States) and *L. acidophilus subsp. helveticus* LAFTI L10 (strain number CBS 116.411, Lallemand Health Solutions, Blagnac, France). This mixture of two probiotic strains provides for each 2.5×10^9 colony-forming unit (cfu) for a total of 5×10^9 cfu per capsule. The trial dose was 2 capsules/day taken orally; one in the morning and the other one in the evening with a full glass of water half an hour before eating.

IBS symptoms of abdominal pain, bloating, flatus and rumbling were recorded by the clinical investigator for each patient at the baseline visit and at both visits (weeks 4 and 8). Each IBS symptom score was assessed with a 100-mm visual analogue scale (VAS; 0: none; 100: very severe) [13]. The composite score was the sum of 4 VAS scores (abdominal pain, bloating, flatus and rumbling) calculated for each patient.

For a relevant comparison with the LAPIBSS protocol, the Table 1 shows the characteristics of the high-quality RCT investigating the benefits of *Lactobacillus* strains on patients with IBS [8]. Only the multicentric clinical trials have been selected and reported. A similar table including the monocentric

Table 1: Characteristics of multicentric randomized clinical trials performed among irritable bowel syndrome (IBS) patients investigating the effects of *Lactobacillus* strains.

Trial	Diagnostic criteria and design	Size (*n*)	Probiotics	Daily dosage and duration	Jadad score
Niv et al. (2005) (20)	- Rome II - Multicentric study (2 centers)	54	*Lactobacillus reuteri* ATCC 55730	- 2 x 10^8cfu - 6 months	4
Ducrotté et al. (2012) (21)	- Rome III - Multicentric study (4 centers)	214	*Lactobacillus plantarum* 299v	- 1x 10^{10} cfu - 4weeks	4
Dapoigny et al. (2012) (22)	- Rome III - Multicentric study (4 centers)	50	*Lactobacillus casei rhamnosus* Lcr35	- 6 x 10^8 cfu - 4 weeks	4
Lyra et al. (2016) (8)	-Rome III - Multicentric study (2 centers)	391	*Lactobacillus acidophilus* NCFM	- 1 x 10^9or10^{10} cfu - 12 weeks	5
Sadrin et al. (2020) (9,10)	-Rome III - Multicentric study (11 centers)	80	*Lactobacillus acidophilus* NCFM *and* *Lactobacillus acidophilus subsp. helveticus* LAFTI L10	-5 x 10^9cfu -5 x 10^9cfu - 8 weeks	5

cfu: colony-forming unit.

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trials or was presented in our previously published study protocol [9].

The objective of this communication is to present and analyse the recent results from the LAPIBSS study and to improve the design of future RCT investigating the clinical effects of *Lactobacillus* strains on IBS symptoms. Using a tightly-controlled study protocol with the highest Jadad score of 5/5 (Table 1), the current trial aimed to demonstrate the efficacy of a 2-strain mixture of *L. acidophilus* to improve IBS symptoms but remains negative on the abdominal pain score used as primary endpoint (Figure 1). Significant differences between groups were observed for the following secondary endpoints: flatus score at week 4 (P=0.04) and week 8 (P=0.03) and composite score at week 8- (P=0.04) [10]. The consumption of the 2-strain mixture of *L. acidophilus* over 8 weeks is safe confirming the GRAS status of *Lactobacilli* [5]. A mode of action at the molecular level for the significant effect observed on flatus score could result from the species-specific homofermentative properties of *L. acidophilus* strains able to produce lactic acid without gas production [5]. One possible improvement of the next clinical study should be the use of an appropriate dosage of the *Lactobacillus* strains (an insufficient dosage is a limiting factor) and/or the duration of the trial (at least 12 weeks or more, up to 6 months).

The dose-response relationship with the probiotic mixture or with each stain used alone should complete this first clinical study especially because one of the two *Lactobacillus* strains, i.e. *L. acidophilus* NCFM, was chosen due to its strain-specific mechanism of action on μ_1-opioid receptor (MOR1) and cannabinoid receptor 2 (CB2) expression in intestinal epithelial cells that could be responsible for the decrease of the abdominal pain severity perceived by the patients with IBS [11]. The investigation of the dose-response relationship needs further RCT as outlined by EFSA guidelines [14]. Stool samples could be collected to ascertain compliance with a potential change in its microbial composition. This would increase the level of evidence to demonstrate the clinical effects (treatment benefits) of probiotics for IBS [14].

Another important observation and objective will be to decrease the placebo response rate as reported by the meta-analysis performed by Ford et al. (2010) [15]. The placebo effect in IBS is a constant preoccupation since the meta-analysis on the placebo response rate in IBS trials done by Patel et al. (2005) analysing the magnitude of responses in placebo arms within 11 variables [16]. Two variables that could independently decrease the placebo response were outlined consisting in using the Rome criteria and in increasing the number of visits [16].

We have taken these factors into consideration by using Rome criteria for patient enrolment and in the establishment of the number of visits during the preparation of the study protocol [9]. In our study, the available Rome III criteria were used without success since the magnitude of placebo responses remains high supporting the enrolment of IBS patients according to the recently defined Rome IV diagnosis criteria [1,10]. With regard to increasing the number of visits, it was possible in theory to extend from the minimum of 1 visit (2 weeks) to 12 visits (12 weeks) but we used 3 visits (8 weeks) in our study [9,16]. Indeed, it seems in our view difficult to extend to 1 visit/week for a health food supplement such as probiotics to implement this schedule both for office-based general practitioners and patients.

Abdominal pain for example is assessed by a VAS score which is always difficult to follow over a long-term period. Furthermore, the use of VAS remains a subjective method. Hence, an objective assessment method (by novel biomarkers)

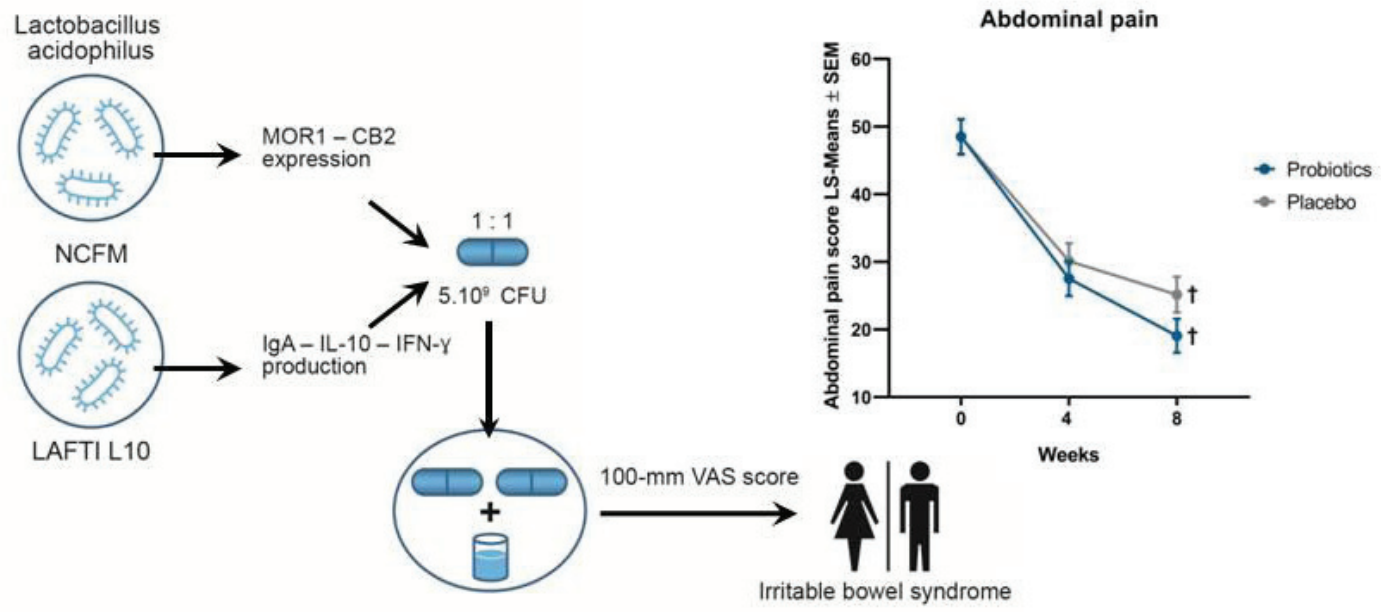

Figure 1: *Lactobacillus acidophilus* versus placebo in the symptomatic treatment of irritable bowel syndrome (LAPIBSS). The graph shows the evolution of abdominal pain scores in probiotics and placebo groups throughout the trial (within groups changes from baseline to week 8; †P <0.0001).

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is required to measure abdominal pain severity and the others IBS symptoms except for stool consistency assessed with the validated Bristol Stool Form Scale which is fulfilled by the patient itself [17].

The strong placebo effect in IBS, as evidenced by the meta-analysis done by Patel et al. [16], should be reinvestigated with its consideration as a placebo analgesia (mediated by endogeneous opioid release), with new Rome IV criteria and taking account of the potential heterogeneity of global population of patients with IBS by the achievement of RCT selecting participants according to the IBS subtypes (diarrhoea, constipation or mixed)[1]. This may entail a confounding factor and contribute to the lack of significant differences for IBS symptoms, especially for bowel-related symptoms. A better understanding of the physiological effect of probiotics in human microbiota would provide a refined rationale for their use prior to future clinical trials for IBS. Representative patients of the real-life situations and multicentric trials are also required (Table 1) [9].

The clinical effects assessment and the rationale for the use of *Lactobacillus* strains and probiotics in general could also be based on the use of validated IBS Symptom Severity Score (IBS-SSS) and IBS-related quality of life questionnaires [18-22]. Other surveys including variables diet (with dietitian), allergens, food intolerance as previously suggested for physicians [3], are also of interest for future IBS clinical protocols.

In conclusion, the therapeutic interest of *Lactobacillus* strains used as health food supplements to improve IBS symptoms remains limited by the low number of high-quality RCT and could be improved by deeper research and knowledge on the IBS.

Conflicts of interest: SS is an employee of Laboratoire Denel-Codifra (Le Chesnay, France), which supplied probiotics and the placebo for the research. The remaining authors disclose no competing interests.

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Author contributions: SS, OP,SRS and JMM designed the research study. JMM and SS wrote the manuscript.

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