Probiotics as a Novel Adjuvant Approach to Atopic Dermatitis

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Received 17 September 2014; Published online 20 September 2014

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Abstract

Objective. The aim of this observational study is to investigate the effect of *Lactobacillus rhamnosus* and *Bifidobacterium lactis* in atopic dermatitis (AD) in the context of routine clinical practice.

Materials and Methods. 107 adult subjects with documented AD receiving a symbiotic combination of *Lactobacillus rhamnosus* LR05, *Bifidobacterium lactis* BS01 and fructo-oligosaccharide (FOS) were assessed for severity of AD using the SCOring Atopic Dermatitis index (SCORAD) and Visual Analogue Scale (VAS) for AD-related global burden of the disease at baseline and after 2 and 4 months of symbiotic supplementation. Secondary evaluations involved the changes in concomitant use of corticosteroids, antihistamines drugs and calcineurin inhibitors.

Results. Treatment with *Lactobacillus rhamnosus* and *Bifidobacterium lactis* significantly decreased atopic dermatitis severity (determined by SCORAD index) after 2 and 4 months of administration, while no effect was registered on the VAS score. In addition a decrease in consumption of corticosteroids, antihistamines drugs and calcineurin inhibitors was found.

Conclusion. The supplementation of *Lactobacillus rhamnosus* LR05, *Bifidobacterium lactis* BS01 and fructo-oligosaccharide (FOS) had a positive effect with a significant reduction in SCORAD index and concomitant decrease in the use of corticosteroids, antihistamines drugs (after 2 and 4 months of treatment) and calcineurin inhibitors (after 4 months of treatment). Our data support the need of future studies to further investigate the positive effect of *Lactobacillus rhamnosus* LR05, *Bifidobacterium lactis* BS01 and fructo-oligosaccharide (FOS) symbiotic combination in the management of AD, with particular focus on strain-specific effects.

Keywords: *Lactobacillus rhamnosus; Bifidobacterium lactis; Atopic Dermatitis; Clinical practice; Probiotics; Symbiotics; Multi-strain*

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1. Introduction

During the last decades the prevalence of allergic disorders (eczema, asthma and allergic rhinitis) has been substantially increasing (Asher et al., 2006). The prevalence of atopic dermatitis (AD) may vary in different countries with an increasing tendency in developed countries (Williams et al., 1999). In particular, AD in Europe and in the USA affects 10-20% of infants and 2-3% of adults (Leung et al., 2007). The cause of AD is probably associated to a variety of conditions, such as environmental and genetic factors (Cookson et al., 2002). AD is a chronic inflammatory disease of the skin (Bieber, 2008; Flohr et al., 2014) and its heterogeneous pathophysiology comprehends an imbalance in Th1/Th2 responses to allergens (Eyerich and Novak, 2013).

Probiotics are live micro-organism which produces a health benefit when administered in certain amounts to the host (Guarner F et al., 1998). Prebiotics are dietary non-digestible ingredients that selectively stimulate the growth and activity of one or a limited number of bacterial species of the intestinal flora. Symbiotic is a combination of probiotic and prebiotic. This formulation allows an increase in the survival of the probiotic organisms, because it immediately makes its substrate available for fermentation.

In the context of AD, probiotics can affect the Th1/Th2 balance by the inhibition of Th2-cytokine production and stimulation of Th1 responses (Isolauri et al., 2001).

In recent years, probiotics have been formally investigated in randomized controlled trials for the prevention and treatment of allergic disorders but their role is still unclear (Williams, 2005).

To date, the effect of *Lactobacillus rhamnosus* in the management of AD has been assessed by Kalliomaki et al. in a double-blind, placebo-controlled, randomized trial. In this trial 159 pregnant women with a family history of allergic disorders such as asthma, allergic rhinitis or eczema received placebo or *Lactobacillus rhamnosus* for 2 to 4-weeks before delivery and for a 6 month period after. The percentage of children aged 2 years old with atopic eczema was 23% in the probiotic group and 46% on placebo (p= 0.008) (Kalliomaki et al., 2001). A subgroup analysis conducted on 57 breastfed infants confirmed the benefit of a defensive effect against eczema from supplementation with *Lactobacillus rhamnosus* (Rautava, 2002). In recent trials by Wickens et al., supplementation with *Lactobacillus rhamnosus* HN001 or *Bifidobacterium lactis* HN019 to mothers and infants showed a significant protective effect only in the groups receiving the supplementation with *Lactobacillus rhamnosus* HN001 by 2 years of age (Wickens et al., 2008) and 4 years of age (Wickens et al., 2012) The reported data suggest that many probiotics may share common properties but their effect may be strain-specific (Allen et al., 2003).

Published meta-analyses suggest that probiotics may be effective in the prevention of eczema, but high heterogeneity among studies and high rates of loss to follow-up must be taken into account. In a Cochrane systematic review, which included 5 trials, a reduction relative risk (0.82; 0.70–0.95, CI 95%) associated with probiotic treatment was found (Nowak-Wegrzyn et al., 2011). Another recently published meta-analysis in which a higher number of trials were included (n=12) revealed a similar result with a relative risk of 0.79 (0.67–0.92, CI 95%) (Lee et al., 2008).
The aim of this observational study is to investigate the effect of *Lactobacillus rhamnosus* LR05, *Bifidobacterium lactis* BS01 and fructo-oligosaccharide (FOS) mixture in the routine management of AD.

2. Materials and Methods

2.1 Study Design and Participants

This is an observational study to evaluate the effect of the administration of symbiotic multi-strain mixture (*Lactobacillus rhamnosus* LR05; *Bifidobacterium lactis* BS01 and FOS) in the management of AD. The study population was comprised of patients attending 35 Italian allergy outpatient clinics for the period of April 2013 to May 2014.

An industrial combination of *Lactobacillus rhamnosus* LR05 ≥ 10⁹ UFC/sachet, *Bifidobacterium lactis* BS01 ≥ 10⁹ UFC/sachet and FOS Actilight 950P 2.5 g/sachet (Kallergen Th®; Allergy Therapeutics, Milan, Italy) was used in this study. Each subject used 1 sachet per day, containing ≥ 10⁹ of bacteria for each strain. This content is in agreement with the guidelines of the Italian Ministry of Health on probiotics (Italian Ministry of Health, 2013). In addition, the used combination was microencapsulated and able to offer a significant protection against gastric juices.

2.2 Data Recording and Questionnaire

All participants were interviewed by experienced physicians using a questionnaire developed on the basis of literature data. The questionnaire consisted of the following main sections:

- Demographic characteristics;
- Concomitant treatment with oral corticosteroids (mg/die of prednisone or other corticosteroid of equivalent potency), oral antihistamines (number of pills used in the last two months, any molecule) and topical calcineurin inhibitors (tacrolimus, number of tubes used in the last two months);
- Allergic sensitization to food or environmental allergens (mites, animal dander, molds, latex);
- Visual analogue scale (VAS) for AD-related global burden of disease (intensity of symptoms, interference with daily living activities, sleep disturbance.)

2.3 Assessments and Outcome Evaluations

AD severity was evaluated by investigators using the SCORAD (Severity Scoring of Atopic Dermatitis) index (European Task Force on Atopic Dermatitis Severity scoring of atopic dermatitis, 1993). This score is calculated using visual analysis, combining the extent and intensity of the eczema, with the practical problems caused by eczema (pruritus and sleep disturbance).

Patients were assigned to 3 eczema severity groups, in accordance with the proposal of the European Task Force for Atopic Dermatitis, as follow: mild, moderate or severe with SCORAD scores ranging from <20, 20 to 40 or >40, respectively.

The primary outcome of the study was the change in SCORAD index and VAS for AD-related global burden of disease after supplementation with *Lactobacillus rhamnosus* LR05, *Bifidobacterium lactis* BS01 and FOS.
At baseline visit (T0) and after 2 months (T1) and 4 months (T2) of supplementation with *Lactobacillus rhamnosus* LR05, *Bifidobacterium lactis* BS01 and FOS, patients were re-evaluated for SCORAD and VAS for AD-related global burden of disease.

### 2.4 Statistical Analyses and Calculations

Comparisons were made by Student’s unpaired t-test. A two-tailed P value <0.05 was considered significant. The McNemar test was used to compare the effect of *Lactobacillus rhamnosus* LR05, *Bifidobacterium lactis* BS01 and FOS mixture administration between any two time points (T0, T1 and T2) on SCORAD index. Descriptive statistics were conducted using Excel Microsoft Office. Statistical analyses were performed using PSPP (psppire.exe 0.8.3-g5f5de6; A program for the analysis of sampled data; Free Software Foundation; GNU GENERAL PUBLIC LICENSE Version 3, 29 June 2007).

### 3. Results

A total of 107 subjects (64% female and 36% male) were evaluated at T0/T1 and 79 were checked at T2 with a dropout rate of 26% (Figure 1). At baseline the average age of participants was 27 years. Comorbidity such as urticaria, food allergy, oral allergy syndrome, and drug allergy were recorded in 21%, 9%, 8% and 2% respectively while the distribution of allergic sensitization was very heterogeneous among the different patients and there was no clear prevalence of a specific sensitization.

![Patient drop out during difference period of the study](image)

**Fig. 1.** Patient drop out during difference period of the study

The number of patients with a SCORAD value of >40 and 20-40 significantly decreased after treatment at T1 and at T2 (p<0.0001 and p<0.01 respectively) compared to baseline T0, indicating
a positive effect on skin condition (extent, intensity, and subjective assessment) (Figure 2). The number of patients with a SCORAD value of <20 increased after treatment at T1 and T2 compared with baseline T0 (Figure 2).

Fig. 2. SCORAD distribution of study population at T0 (n = 107), T1 (n = 107) and T2 (n = 79). There was a significant decrease of numerosity in SCORAD groups >40 and 20-40 at T1 and T2 compared to T0 (p<0.0001 and p<0.01 respectively), and a concomitant increase of numerosity in the less severe SCORAD <20 group.

Fig. 3. Mean VAS score at T1 and T2 compared to baseline T0 (T1 vs T0 p=0.22 ; T2 vs T0 p=0.35)
By contrast changes in mean VAS score at T1/T2 visits were not significantly different compared to baseline T0 (4.45±0.28, p=0.22 and 4.84±0.35, p=0.35 respectively vs 4.74±0.32), (Figure 3).

The concomitant use of corticosteroids in the last 2 months significantly decreased from 4.97±1.01 mg/die of prednisone at T0 to 1.18±0.43 at T1 and to 0.34±0.19 at T2 (p<0.0001, Figure 4).

![Fig. 4. Use of corticosteroids in the last 2 months (prednisone or other corticosteroid of equivalent potency, mean±se) (T2 vs T0 p<0.0001).](image)

The concomitant use of antihistamines in the last 2 months significantly decreased from 28.07±2.96 pills in the last 2 months at T0 to 20.01±2.52 at T1 and finally to 12.09±2.67 at T2 (p<0.0001, Figure 5). No differences were detected in the number of calcineurin inhibitors tubes used at T1, while there was a statistically significant decrease at T2 compared to T0 (p=0.01, Figure 6).
Fig. 5. Use of antihistamines drugs (number of pills – any molecule, mean ± se) in the last 2 months (T2 vs T0 p<0.0001).

Fig. 6. Use of topical calcineurin inhibitors in the last 2 months (number of tubes, mean ±se) (T2 vs T0 p=0.01; T1 vs T0 p=ns).
4. Discussion

Direct evidence of specific *Lactobacillus rhamnosus, Bifidobacterium lactis* strain activity in the control of AD symptoms are well described in literature with a number of studies using *Lactobacillus rhamnosus* or *Bifidobacterium lactis* separately.

Our data suggest a potential positive effect of symbiotic multi-strain (Kallergen Th®; Allergy Therapeutics, Milan, Italy), composed of *Lactobacillus rhamnosus* LR05, *Bifidobacterium lactis* BS01 and FOS, administered to patients suffering from AD during the four-months observation period.

We analyzed a number of aspects for their possible association with AD, including the co-morbidities and allergen sensitizations identified as clinically relevant, the response to symptomatic treatment. Of the total of 107 subjects (with an average age of 27 years) who were evaluated at T0/T1, 79 were checked at T2; the dropout rate of 26% is acceptable given that this is an observational study. Comorbidity such as urticaria, food allergy oral allergy syndrome, drug allergy and the distribution of allergic sensitization were very heterogeneous among the different patients and there was no clear prevalence of a specific sensitization.

Based on the results from our study, the regular administration of this specific symbiotic multi-strain combination of *Lactobacillus rhamnosus* LR05, *Bifidobacterium lactis* BS01 and FOS may provide an opportunity to obtain a positive effect on AD with a significant reduction in severity after 2 and 4 month of treatment compared to baseline, suggesting the importance of the strain-specific effects of *Lactobacillus rhamnosus* LR05 and *Bifidobacterium lactis* BS01.

The concomitant decrease of administration of oral antihistamine drugs, oral corticosteroids and calcineurin inhibitors during treatment with this symbiotic multi-strain combination could be interpreted as indirect evidence of the beneficial effect of *Lactobacillus rhamnosus* LR05, *Bifidobacterium lactis* BS01 and FOS mixture in the management of AD.

Of notice, the symbiotic multi-strain formulation used in the present study contained ≥ 10⁹ bacteria for each strain (at the end of the 2 years shelf-life). Moreover, the utilization of microencapsulated products capable of offering a considerable protection against gastric juice and the addition of prebiotic FOS could be important factors ensuring a better colonization of the intestinal tract with an increased number of viable bacteria, and therefore positively influencing the effect of *Lactobacillus rhamnosus* LR05 and *Bifidobacterium lactis* BS01.

Our data support the hypothesis that an adequate symbiotic multi-strain supplementation can be suggested as a novel adjuvant approach to AD symptoms, and *Lactobacillus rhamnosus* LR05 and *Bifidobacterium lactis* BS01 are relevant candidates for this purpose. Further studies and randomized trials with larger patient populations are needed to confirm this positive effect with particular focus on strain-specific outcomes, usefulness of concomitant prebiotic and probiotic supplementation, dose optimization, microencapsulation, and other relevant manufacturing specifications.
Acknowledgements

The authors acknowledge the PANATAD Study Group: Appino Antonella, Bassini Massimo, Bernardini Elena, Borrelli Paolo, Bramè Barbara, Bussolino Claudia, Carbonara Anna Maria, Caruso Maria, Catelli Luca, Coppo Paola, Daniele Saverio, De Serio Alessandra, Della Valle Daniela, Brienza Tiziana, Di Rienzo Businco Andrea, D’Ippolito Giannamaria, Facchetti Susanna, Fanelli Valentina, Favero Elisabetta Favro Mauro, Ferrarini Ettore, Frasin Lucretia Adina, Fuiano Nicola, Gandus Stefano, Iadarola Giuseppe, Maiuolo Antonio, Marraccini Paolo, Nebiolo Franco, Nenna Saverio, Ingrassia Antonino, Ortolani Valeria, Rossi Renato Enzo, Turatello Franca.
The authors also would like to acknowledge Dr. Valentina Franco for her writing and editorial assistance and Dr. Guido Fedele for assisting in biostatistics.

Conflict of Interests

Filippo Fassio received consultancy fees from Allergy Therapeutics Italia.

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