Journal of Microbiology, Immunology and Infection (2017) 50, 684–692

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ORIGINAL ARTICLE

Evaluation of efficacy and safety of *Lactobacillus rhamnosus* in children aged 4–48 months with atopic dermatitis: An 8-week, double-blind, randomized, placebo-controlled study

Yi-Jie Wu [a], Wei-Fong Wu [b,c], Chia-Wei Hung [b], Ming-Shiu Ku [a,d], Pei-Fen Liao [a], Hai-Lun Sun [a,d], Ko-Hsiu Lu [d], Ji-Nan Sheu [a,d], Ko-Huang Lue [a,d,e,*]

[a] *Department of Pediatrics, Chung-Shan Medical University Hospital, Taichung City, Taiwan, ROC*
[b] *Taipei City Hospital, Ren-Ai Branch, Taipei City, Taiwan, ROC*
[c] *Siyuan Hospital, Taipei City, Taiwan, ROC*
[d] *School of Medicine, Chung Shan Medical University, Taichung City, Taiwan, ROC*
[e] *Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan, ROC*

Received 27 December 2014; received in revised form 25 August 2015; accepted 8 October 2015
Available online 27 November 2015

KEYWORDS
atopic dermatitis;
efficacy;
Lactobacillus rhamnosus

Abstract *Objective:* The main objective of this study was to evaluate the efficacy and safety of *Lactobacillus rhamnosus* in children aged 4–48 months with atopic dermatitis.
Methods: The design of this study was a two-center, double-blind, randomized, and placebo-controlled study with two parallel groups to evaluate the efficacy and safety profile of *L. rhamnosus* in children aged 4–48 months with atopic dermatitis diagnosed using Hanifin and Rajka criteria and with a Scoring of Atopic Dermatitis (SCORAD) $\geq$ 15 at enrollment. The duration of this study was 8 weeks with a total of five visits. The enrolled patients were allocated into either a treatment group (one ComProbi capsule containing *L. rhamnosus* a day) or a control group (one capsule of placebo a day) at a ratio of 1:1. The primary endpoint was to compare the mean change from baseline in SCORAD after 8 weeks of treatment. The other secondary end points were to compare the following: the mean changes from baseline in SCORAD at post-baseline visits, the frequency and total amount of the use of corticosteroids during the 8-week treatment, the frequency of atopic dermatitis and the symptom-free duration, the mean

* Corresponding author. Institute of Allergy, Immunology, and Rheumatology, Department of Pediatrics, Chung Shan Medical University Hospital, Number 110, Section 1, Jianguo North Road, Taichung City 40201, Taiwan, ROC.
E-mail address: cshy095@csh.org.tw (K.-H. Lue).

http://dx.doi.org/10.1016/j.jmii.2015.10.003

changes from baseline in Infant Dermatitis Quality of Life Questionnaire at Week 4 and Week 8, and the mean changes from baseline in the Dermatitis Family Impact Questionnaire at Week 4 and Week 8.

Results: The mean changes in SCORAD from baseline at Week 8 was -21.69 ± 16.56 in the *L. rhamnosus* group and -12.35 ± 12.82 in the placebo group for the intent-to-treat population ($p = 0.014$). For the per-protocol population, the mean change of SCORAD from baseline was -23.20 ± 15.24 in the *L. rhamnosus* group and -12.35 ± 12.82 in the placebo group ($p = 0.003$). Significant differences were demonstrated between groups at Week 8 in intensity in the intent-to-treat population and per-protocol population. Throughout the period, the amount of topical corticosteroids used showed no difference between groups. No significant difference was noted in the overall symptom-free durations compared with the placebo group. Infant Dermatitis Quality of Life Questionnaires and Dermatitis Family Impact Questionnaires scores improved significantly at Week 4 and Week 8 but did not reach statistical significance. Adverse events were documented in 14/33 patients in the *L. rhamnosus* group (42.42%, 35 events) and in 15/33 placebo patients (45.45%, 37 events).

Conclusions: The results of this study indicated that *L. rhamnosus* was effective in decreasing symptoms of atopic dermatitis after an 8-week treatment by comparing the mean change of SCORAD from baseline with a placebo ($p < 0.05$). The reduction in SCORAD resulted from a consistent decrease in all components of SCORAD. Patients who took *L. rhamnosus* for 8 weeks expressed less SCORAD in the three components: area of affected skin, intensity of atopic dermatitis, and patient symptoms, with a significant decrease in the mean change of intensity from baseline compared with placebo.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease with various degrees of remission and relapsing courses which, in nearly half of cases, has an allergic origin. Skin barrier due to a genetic defect plays an important role in AD. Mutations of the *filaggrin* gene, located in the epidermal differentiation complex, have been identified as a strong predisposing factor for AD.[1] The skin inflammation can be caused by a variety of triggers, including allergens, food allergens, dust mites, weather changes, temperature changes, and stress. It affects about 5—20% of children worldwide and the incidence is increasing year by year;[2–4] and the same trend was also noted from 1.3% in 1974 up to 12.9% in 2007 in Taiwan.[5] AD is becoming a major problem in industrialized countries.[2,3]

The treatment strategies of childhood AD include traditional topical corticosteroids, a topical calcineurin inhibitor, phototherapy, and immunosuppressants.[6–8] All these treatment methods are useful and the onset is fast. However, the side effects must be monitored for longterm use. Side effects such as skin atrophy, changes in pigmentation, and easy bruising were noted, especially in vulnerable infants and children.

Allergic diseases are associated with a shift in T helper (Th1/Th2) cytokine balance toward a Th2 response. Probiotics can inhibit the Th2 response, especially early in life, while stimulating the production of Th1 cytokines, such as interferon gamma.[9–12] In addition, decreases in regulatory T cells, which are crucial regulators of the immune response, have been reported in patients with AD, and their numbers are inversely correlated with immunoglobulin E (IgE), eosinophilia, and interferon gamma levels.[13,14] Probiotics upregulated the generation of regulatory T cells, which migrated to inflammation sites and suppressed disease progression in mice.[15] When ingested, probiotics may have a positive effect in the treatment or prevention of specific diseases,[16] and have been shown to modulate the mucosal immune response and reduce gastrointestinal inflammation in infants with food allergies.[17] Suggested mechanisms of probiotics include: (1) stimulation of epithelial mucin production;[18] (2) enhanced production of secretory IgA;[19–21] and (3) alleviation of intestinal inflammation by stimulation of anti-inflammatory cytokines.[22,23] Atopic children have been reported to harbor more *Clostridia* and fewer *Bifidobacteria* and *Lactobacilli* in their gut flora than nonatopic children.[24] Probiotics can potentially modulate the toll-like receptors and the proteoglycan recognition proteins of enterocytes, leading to activation of dendritic cells and a Th1 response.[24] Therefore, as an alternative treatment, probiotics[7,25] are suggested to prevent and treat allergic diseases, such as AD and allergic rhinitis, and even in that context their clinical use is controversial. The main objective of this study is to evaluate the effect of probiotics, *Lactobacillus rhamnosus*, in treating children aged 4—48 months suffering from AD.

Materials and methods

Patient and study design

The design of this study was a two-center, double-blind, randomized, and placebo-controlled study with two