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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

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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

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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

parallel groups to evaluate the efficacy and safety profile of *L. rhamnosus* in children aged 4—48 months with AD diagnosed using Hanifin and Rajka criteria and with a Scoring of Atopic Dermatitis (SCORAD) $\geq$ 15 at enrollment. The study was conducted at two sites, Chung Shan Medical University Hospital and Taipei City Hospital, Ren-Ai branch. 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 capsule of ComProbi containing 350 mg *L. rhamnosus* (MP108) and maltodextrin a day; CY Biotech, Taipei, Taiwan] or a control group (one capsule of maltodextrin only a day) at a ratio of 1:1. For patients who could not swallow capsules, parents were instructed to mix the powder in water, milk, breast milk, or food heated to $<$40°C. The patients with clinically evident infection in skin lesions, severe asthma or acute asthma attack within 3 months, autoimmune disease, immunodeficiency, exposure to phototherapy, or having used systemic corticosteroids within 1 month, antihistamine within 7 days, or topical calcineurin inhibitor within 1 month were all excluded. Rescue medication, Cutivate cream (GlaxoSmithKline, Durham, U.K.), the topical corticosteroid, was provided to each patient in case of uncontrolled symptoms. It was used on an as-needed basis, as and when symptoms arise (on demand). When it was used, the patients' legally acceptable representatives were asked to record the frequency of use in diary cards. The amount of remaining rescue medication was monitored at each visit.

Clinical evaluation

Evaluation of each component of SCORAD was standardized by giving examples of the area counting method, rule of nine, and examples of the intensity in each symptom. Evaluation of subjective symptoms was standardized by a visual analog scale with a line of 10 cm, which is typically used.

The primary efficacy end point of this study was to compare the mean change of SCORAD after the 8-week treatment. The secondary efficacy end points were the following: (1) to compare the mean changes of SCORAD at postbaseline visits; (2) to compare the frequency and total amounts of the use of corticosteroids during the 8-week treatment; (3) to compare the frequency of AD and the symptom-free duration; (4) to compare the mean changes from baseline in Infant Dermatitis Quality of Life Questionnaire (IDQOL) at Week 4 and Week 8; and (4) to compare the mean changes from baseline in Dermatitis Family Impact Questionnaire (DFI) at Week 4 and Week 8. Intent-to-treat (ITT) population means patients who take at least one dose of study medication and have at least one efficacy measurement. Per-protocol (PP) population means a patient of ITT with a drug compliance rate over 80%. The compliance was evaluated based on numbers of the returned medication.

Statistical methods

The study was designed to investigate the superiority of *L. rhamnosus* compared with a placebo control based on the mean change of SCORAD score from baseline after an 8-week treatment. The primary endpoint was analyzed with the Mann—Whitney test based on a one-tailed test with a significance level of 0.025. If the related p value is less than 0.025, the superiority will be demonstrated. Two-sided tests of significance were used with a significance level of 0.05 for secondary endpoint analysis. The continuous secondary efficacy variables were performed by means of a t test. The difference between the two treatments was given along with its 95% confidence interval. Statistical analysis for categorical secondary efficacy variables was performed by means of Chi-square test or Fisher's exact test.

Results

Characteristics of the study population

This randomized, double-blind, placebo-controlled study was conducted at two sites in Taiwan to investigate the efficacy and safety of *L. rhamnosus* (MP108) in children (aged 4—48 months) with AD. At baseline visit (Visit 1), a total of 67 patients were screened for eligibility and assigned to either the *L. rhamnosus* (MP108) group or placebo group randomly at a ratio of 1:1 for 8 weeks.

During the study period, five patients discontinued the study, one was excluded due to investigator's concern, and the others were withdrawn because of taking prohibited medications. Therefore, 66 patients who had taken at least one dose of the study drugs were included in the safety population. Among the 66 patients who had at least one evaluable data point for efficacy assessment were included in the ITT population. The 62 patients who fulfilled the ITT definition, had a primary efficacy measurement, without any protocol violations, and with a drug compliance rate $\geq$ 80%, were categorized as the PP population. A detailed disposition is presented in Figure 1.

No significant difference was observed in the demographic and baseline characteristics such as age, height, and weight (Table 1). The treatment compliance between the two groups was also not found to be statistically significant.

Though the SCORAD for the placebo group showed more severity than for the *L. rhamnosus* group, no significant differences were noted in SCORAD between the groups.

The SCORAD and each component of SCORAD obtained at baseline and posttreatment visits are demonstrated in Figures 2 and 3. A significant reduction in both SCORAD and each component of SCORAD was observed in both groups from Week 2. However, no significant differences were observed between the groups.

The analysis for primary efficacy endpoint

The primary efficacy was assessed through the SCORAD index which concerned lesion spread, intensity, and subjective symptoms.

Table 2 presents the results of the mean change from baseline in SCORAD after an 8-week treatment for both populations. At the end of Week 8, the severity of AD tended to reduce in both groups significantly. The mean change in SCORAD from baseline on the 8th week was -21.69 ± 16.56 in the *L. rhamnosus* (MP108) group and

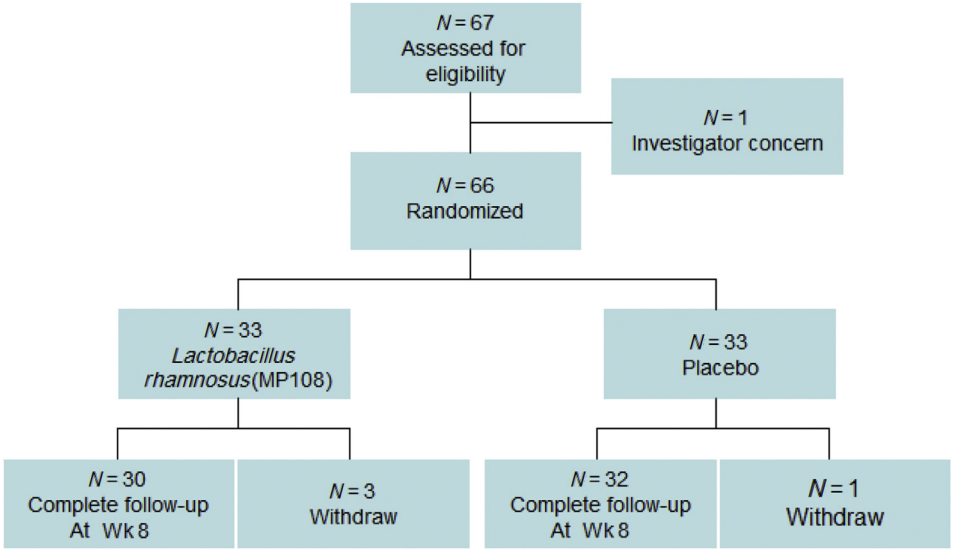

Figure 1. Trial profile showing patient population analyzed for efficacy of the probiotics.

−12.35 ± 12.82 in the placebo group for the ITT population patients ($p = 0.005$). For the PP 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 ($p = 0.002$).

Analysis for mean changes of SCORAD components from baseline at Week 8 is provided in Table 3. Significant improvements were observed as reductions in the skin surface with AD, intensity of AD, and subjective symptoms in both groups. The mean changes from baseline at Week 8 in surface area, intensity, and subjective symptoms were −13.66 ± 14.42 versus −7.21 ± 8.99 (*L. rhamnosus* vs. placebo, $p = 0.2510$), −3.91 ± 3 .57 versus −2.06 ± 2.77 (*L. rhamnosus* vs. placebo, $p = 0.0121$), and −5.47 ± 5.32 versus −3.69 ± 4.25 (*L. rhamnosus* vs. placebo, $p = 0.0858$) in the ITT population. For the PP population, the mean changes were −14.40 ± 14.49 versus −7.21 ± 8.99 in surface area (*L. rhamnosus* vs. placebo, $p = 0.1786$), −4.13 ± 3.55 versus −2.06 ± 2.77 in intensity (*L. rhamnosus* vs. placebo, $p = 0.0053$) and −5.93 ± 4.52 versus −3.69 ± 4.25 (*L. rhamnosus* vs. placebo, $p = 0.0545$) in subjective symptoms score.

Table 1 Summary of demographics of the intent-to-treat population and per-protocol population.

		ITT population		PP population	
		LR, $n = 33$	Placebo, $n = 33$	LR, $n = 30$	Placebo, $n = 32$
Age (y)	Mean ± SD	1.5 ± 1.1	1.8 ± 1.1	1.4 ± 1.1	1.8 ± 1.1
	Median	1.0	1.8	0.9	1.8
	Range	(0.3, 3.5)	(0.3, 3.9)	(0.3, 3.5)	(0.3, 3.9)
	95% CI	(0.3, 3.5)	(1.4, 2.2)	(1.0, 1.8)	(1.4, 2.3)
	p[a] (95% CI)	0.241 (−0.9, 0.2)		0.144 (−1.0, 0.1)	
Sex	Male, *n* (%)	25 (75.8)	19 (57.6)	24 (80.0)	18 (56.3)
	Female, *n* (%)	8 (24.2)	14 (42.4)	6 (20.0)	14 (43.7)
	p[b] (95% CI)	0.158		0.064	
Weight (kg)	Mean ± SD	10.6 ± 3.0	11.5 ± 3.4	10.5 ± 3.0	11.6 ± 3.4
	Median	10.0	10.0	9.9	10.3
	Range	(6.2, 17.0)	(7.5, 21.0)	(6.2, 17.0)	(7.5, 21.0)
	95% CI	(9.6, 11.7)	(10.4, 12.7)	(9.3, 11.6)	(10.4, 12.8)
	p[a] (95% CI)	0.258 (−2.5, 0.7)		0.180 (−2.8, 0.5)	
Height (cm)	Mean ± SD	78.2 ± 12.9	82.9 ± 11.7	77.1 ± 12.7	83.0 ± 11.8
	Median	75.0	81.5	72.0	81.8
	Range	(60.0, 103.0)	(63.0, 112.0)	(60.0, 103.0)	(63.0, 112.0)
	95% CI	(73.6, 82.8)	(78.8, 87.1)	(72.4, 81.8)	(78.8, 87.3)
	p[a] (95% CI)	0.122 (−10.8, 1.3)		0.062 (−12.2, 0.3)	

[a] *t* test.
[b] Chi-square test.
CI = confidence interval; ITT = intent to treat; LR = *Lactobacillus rhamnosus*; PP = per-protocol; SD = standard deviation.

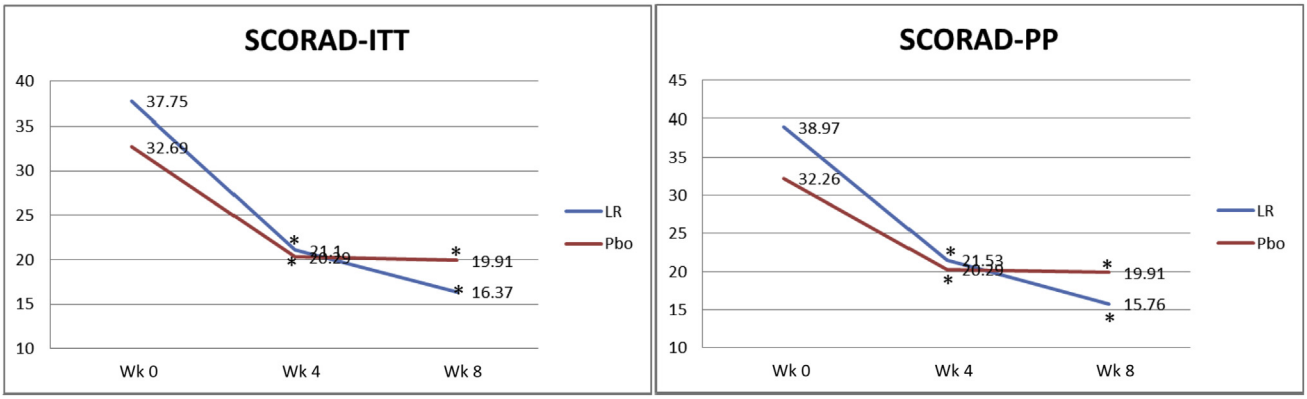

Figure 2. The comparison of Scoring of Atopic Dermatitis between the treatment groups during treatment in the intent-to-treat population and per-protocol population. * Statistically significant. Statistical method: paired *t* test (within group). ITT = intent-to-treat; LR = *Lactobacillus rhamnosus*; Pbo = placebo; PP = per-protocol; SCORAD = Scoring of Atopic Dermatitis.

In summary, statistical significance was observed in mean change of SCORAD after the 8-week treatment between the groups in ITT and PP populations. Furthermore, statistically significant differences were found in mean changes in intensity between the groups in ITT and PP populations.

The analysis for secondary efficacy endpoints

Secondary efficacy endpoints included comparing the following: the mean changes from baseline in SCORAD, frequency and total amount of use of topical corticosteroids during the 8-week treatment, frequency of AD and the symptom-free duration, mean changes from baseline in IDQOL at Week 4 and Week 8, and mean changes from baseline in DFI at Week 4 and Week 8.

As shown in Table 4, the mean changes in SCORAD at Week 2, Week 4, and Week 6 were also analyzed. For the ITT population, patients receiving *L. rhamnosus* (MP108) were found to experience greater reduction in SCORAD scores, with the values of -13.34 ± 13.10, -16.65 ± 10.68, and -20.50 ± 13.94 versus -10.12 ± 9.00, -11.97 ± 9.62, and -13.42 ± 10.37 in the placebo group at Visit 2 (Week 2), Visit 3 (Week 4), and Visit 4 (Week 6), respectively. With regard to the PP population, the mean changes in SCORAD compared with baseline at Visit 2, Visit 3, and Visit 4 in the *L. rhamnosus* (MP108) group were -14.51 ± 13.11, -17.44 ± 10.60, and -21.36 ± 13.79 versus -10.29 ± 9.09, 11.97 ± 9.62, and 13.42 ± 10.37 in the placebo group, respectively. Mean change in SCORAD reach obviously decreased in the *L. rhamnosus* group compared to the placebo group from Visit 6 in the ITT population and Visit 4 in the PP population.

During the study, the total amount of topical corticosteroids used in the *L. rhamnosus* (MP108) group and the placebo group were 5.87 ± 7.48 g versus 4.73 ± 5.48 g for the ITT population, and 6.01 ± 7.77 g versus 4.49 ± 5.52 g for the PP population, with no significant differences between the groups for the two populations. The frequency of topical corticosteroid use showed no significant differences (data not shown).

The overall symptom-free durations for AD are 0.58 ± 0.27 versus 0.65 ± 0.25 (*L. rhamnosus* vs. placebo) for the ITT population, and 0.59 ± 0.26 versus 0.65 ± 0.26 for the PP population. After treatment with *L. rhamnosus*, no significant difference was noted at each post-treatment visit compared with the placebo (data not shown).

Compared with the baseline, the mean changes in DFI (Table 5) at Week 4 and Week 8 for the ITT population and PP population showed a decline. DFI reduced significantly at Week 4 and Week 8 along with the treatment period in both groups. However, no statistically significant differences were observed between the groups. As for IDQOL (Table 6), we also recorded at Week 4 and Week 8. Mean changes from baseline declined in the ITT population and PP population, but no statistically significant differences were noted.

Assessment of safety

The vital signs, including blood pressures, pulse rate (or heart rate), respiratory rate, and ear temperature, were summarized by descriptive statistics as well as the mean change from baseline. No significant difference was noted for values of vital sign, pulse rate, respiratory rate, and body temperature at each posttreatment visit between the groups. Also, most of the changes in physical examinations did not reach significant difference. Besides, adverse events were monitored and data showed no relation to our study products (data not shown).

Discussion

The role of probiotics in the treatment of AD remains controversial. There are several studies published. Some studies[25–29] suggested that there was a statistically significant decrease in SCORAD after probiotics ingested by infants or children with AD for 1 month or 2 months compared with that after placebo, while some studies[26,30,31] showed that SCORAD was significantly reduced after treatment with *Lactobacilli* only in children with IgE-associated AD, i.e., treatment with *Lactobacilli* may alleviate AD symptoms in IgE-sensitized infants but not in non-IgE-sensitized infants. In the study by Rosenfeldt et al,[26] the effect of probiotics in AD treatment was more pronounced in patients with a

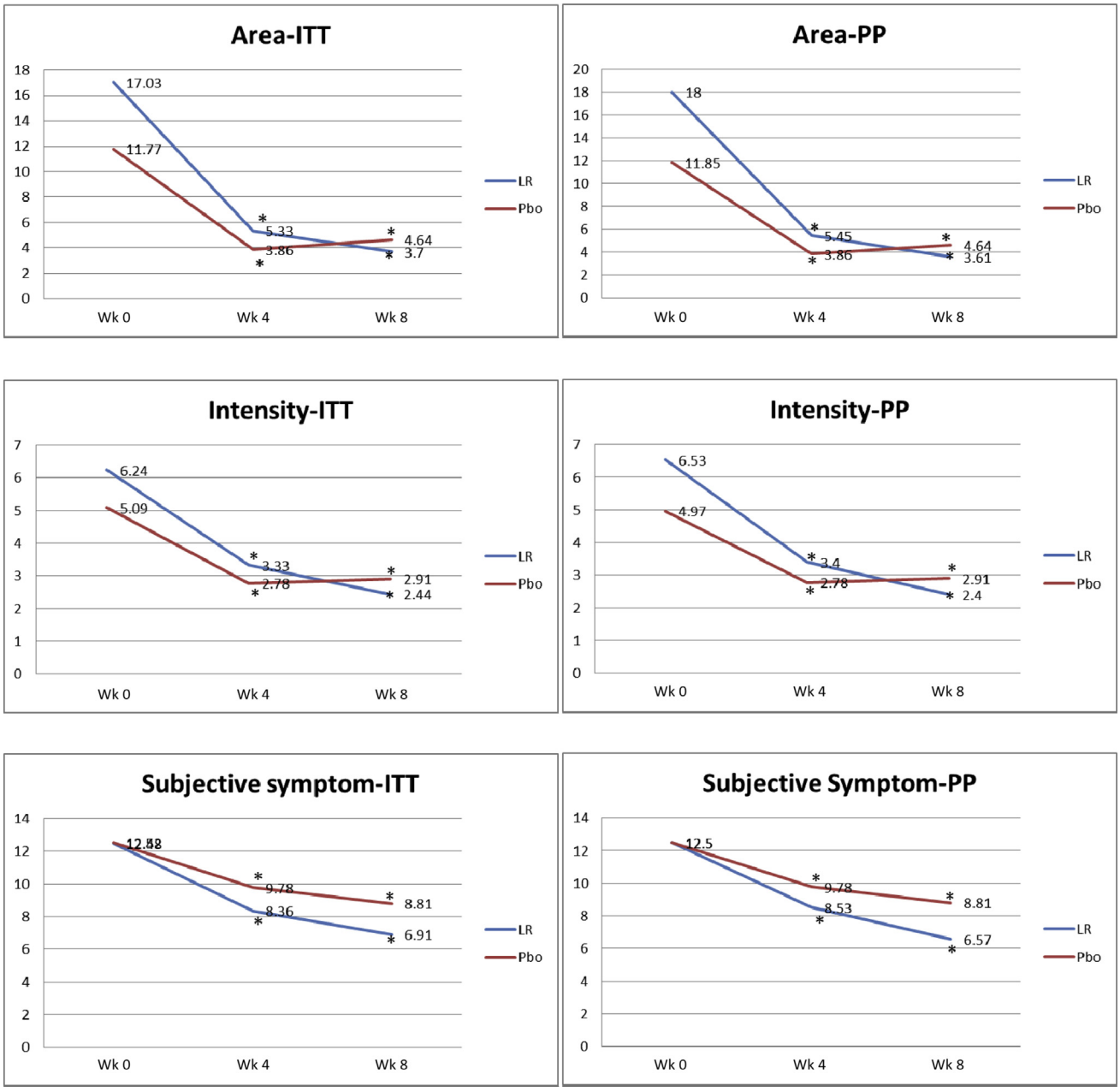

Figure 3. The comparison of Scoring of Atopic Dermatitis items between the treatment groups during treatment in the intent-to-treat population and per-protocol population. * Statistically significant. Statistical method: paired *t* test (within group). ITT = intent-to-treat; LR = *Lactobacillus rhamnosus;* Pbo = placebo; PP = per-protocol.

positive skin prick test response and increased IgE levels. However, in some studies,[32–34] the change in SCORAD was not statistically significant between probiotic- and placebo-treated children. Therefore, the effect of probiotics on AD treatment was controversial.

There is some evidence that intestinal inflammation and disruption of the intestinal barrier function is involved in the pathogenesis of AD.[35] Probiotics have been shown in a number of studies to alleviate intestinal inflammation. *Lactobacillus* species showed the most potent inhibitory activity against the growth of *Staphylococcus aureus*, which was found to be one of the causes of exacerbation of AD.[36] Therefore, probiotics may have a beneficial role in AD treatment due to the inhibitory effect on *S. aureus*. In the study by Iemoli et al,[35] probiotics were shown to be well tolerated, and resulted in the colonization of gut microbiota and beneficial clinical effects in AD, which suggests that probiotic supplements could be a beneficial adjunct therapy for treating AD. In another study,[37] probiotic bacteria enhanced murine and human intestinal epithelial barrier functions. Other mechanisms that may be due to the effect of *Lactobacillus* species in reducing allergen-induced skin inflammation is by regulating interleukin (IL)-4 and IgE. In an animal study,[38] probiotic strains

Table 2 Mean change from baseline in Scoring of Atopic Dermatitis after an 8-week treatment.

Mean change in SCORAD[a]	ITT population		PP population	
	LR (MP108)	Placebo	LR (MP108)	Placebo
Mean ± SD	−21.69 ± 16.56	−12.35 ± 12.82	−23.20 ± 15.24	−12.35 ± 12.82
Median	−18.19	−10.97	−18.86	−10.97
p[b]	0.005*		0.002*	
(95% CI)	(−16.75, −1.94)		(−18.00, −3.72)	

[a] SCORAD = Area/5 + 7 × intensity/2 + subjective symptoms.
[b] Mann–Whitney (between groups).
* Statistically significant.
CI = confidence interval; ITT = intent to treat; LR = *Lactobacillus rhamnosus*; PP = per-protocol; SCORAD = Scoring of Atopic Dermatitis; SD = standard deviation.

Table 3 Mean change from baseline in the components of Scoring of Atopic Dermatitis after an 8-week treatment.

Components of SCORAD		ITT population		PP population	
		LR (MP108)	Placebo	LR (MP108)	Placebo
Area	Mean ± SD	−13.66 ± 14.42	−7.21 ± 8.99	−14.40 ± 14.49	−7.21 ± 8.99
	p[a]	0.2510		0.1786	
Intensity	Mean ± SD	−3.91 ± 3.57	−2.06 ± 2.77	−4.13 ± 3.55	−2.06 ± 2.77
	p[a]	0.0121*		0.0053*	
Subjective symptom	Mean ± SD	−5.47 ± 5.32	−3.69 ± 4.25	−5.93 ± 4.52	−3.69 ± 4.25
	p[a]	0.0858		0.0545	

[a] Mann–Whitney test (between groups).
* Statistically significant.
CI = confidence interval; ITT = intent to treat; LR = *Lactobacillus rhamnosus*; PP = per-protocol; SCORAD = Scoring of Atopic Dermatitis; SD = standard deviation.

isolated from *kimchi* suppress house dust mite-induced dermatitis in an NC/Nga mouse, which suggests that *Lactobacilli* inhibiting AD probably resulted from altering the balance of the Th1/Th2 ratio. In the study by Kalliomaks et al,[39] probiotics were proven to be effective in the prevention of early atopic disease in children with high risk.

Table 4 Mean change in Scoring of Atopic Dermatitis at 2nd, 4th, and 6th weeks in the intent-to-treat population and per-protocol population.

Mean change in SCORAD		ITT population		PP population	
		LR (MP108)	Placebo	LR (MP108)	Placebo
Wk 2	Mean change	−13.34	−10.12	−14.51	−10.29
	p[a]	0.25		0.15	
Wk 4	Mean change	−16.65	−11.97	−17.44	−11.97
	p[a]	0.07		0.04*	
Wk 6	Mean change	−20.50	−13.42	−21.36	−13.42
	p[a]	0.03*		0.01*	

[a] Mann–Whitney test (between groups).
* Statistically significant.
ITT = intent to treat; LR = *Lactobacillus rhamnosus*; PP = per-protocol; SCORAD = Scoring of Atopic Dermatitis.

Our study suggests a positive effect of probiotic supplementation in patients with AD. There is a clinical observation also favoring this theory with the demonstration that probiotic supplements could alleviate atopic eczema in children.[40]

Our data showed a greater decrease in the mean SCORAD score for the ITT population than for children from the placebo group at Week 8 (−21.69 vs. −12.35, respectively; $p = 0.014$). The same result was noted in the PP population (−23.20 vs. −12.35, respectively; $p = 0.002$; Table 2). Each of the SCORAD items (intensity score, subjective itch score, and extent) were analyzed separately (Table 3).

Besides each component of the SCORAD, the area and intensity decreased after 8 weeks of treatment and reached the level of significance ($p < 0.05$) in the ITT and PP populations. We also saw a mean change of SCORAD that decreased from Week 4 and reached the level of significance and the outcome persisted to Week 8 (Table 4). IDQOL and DFI scores decreased from baseline in the probiotic group and placebo group, but our data are not statistically significant. Use of topical corticosteroids during the 8-week trial period in the *L. rhamnosus* (MP108) group and the placebo group showed no significant difference.

Although a significantly greater reduction of SCORAD was seen in the *L. rhamnosus* group than in placebo group, the SOCRAD were similar between the groups at Week 8. That might explain why there is no difference in IDQOL and DFI

Table 5 Mean change of Dermatitis Family Impact Questionnaire at Week 4 and Week 8 in the intent-to-treat population and per-protocol population.

Mean change of DFI		ITT population		PP population	
		LR(MP108)	Placebo	LR(MP108)	Placebo
Wk 4	Mean change	−4.2	−4.3	−4.3	−4.3
	p[a]	0.57		0.54	
Wk 8	Mean change	−6.0	−5.4	−6.2	−5.4
	p[a]	0.61		0.46	

[a] Wilcoxon signed rank test (between groups).
DFI = dermatitis family impact questionnaires; ITT = intent to treat; LR = *Lactobacillus rhamnosus*; PP = per-protocol.

scores. However, the onset of probiotics may be much more significant when treated for more than 8 weeks, which is one of our limitations—lack of longterm follow up. Due to the fluctuating nature of AD, the disease activity can fluctuate widely in the short term. Another limitation is lack of other laboratory data evaluation, total IgE, or IL-4, which can evaluate the allergic constitution. Serum levels of cytokines can provide a more objective evaluation. A possible limitation of our study is that patients were allowed to use topical corticosteroids. Because corticosteroids are the mainstay treatment of AD, it would be unethical to withhold this treatment. Therefore, the combined treatment may be practical and the synergistic effect was observed in our study. However, corticosteroid use was carefully monitored and collected during the treatment period. In our study, not only SCORAD, but also DFI and IDQOL were evaluated for efficacy. Actually, life quality can also be one way to present the severity of AD and can be used for efficacy evaluation. Vital signs and any adverse effects were documented at each visit for safety evaluation. Those patients with other severe allergic disease or who were under medication with immunosuppressants were excluded, and thus the influence of latent variables on efficacy was decreased. The probiotic efficacy in AD was demonstrated by the decreased SCORAD. Both efficacy and safety were reported. Our study implies that the effect of probiotics was not attributable to dose or duration of probiotic supplementation, as these parameters were similar in children who did not finish the course of probiotics, which can be noted through similar results in ITT and PP populations.

Table 6 Mean change of Infant Dermatitis Quality of Life Questionnaires at Week 4 and Week 8 in the intent-to-treat population and per-protocol population.

Mean change of IDQOL		ITT population		PP population	
		LR (MP108)	Placebo	LR (MP108)	Placebo
Wk 4	Mean change	−2.97	−2.47	−3	−2.47
	p[a]	0.71		0.63	
Wk 8	Mean change	−3.28	−3.38	−3.53	−3.38
	p[a]	0.71		0.65	

[a] Wilcoxon signed rank test (between groups).
IDQOL = Infant Dermatitis Quality of Life Questionnaire; ITT = intent to treat; LR = *Lactobacillus rhamnosus*; PP = per-protocol.

In summary, administration of probiotic, *L. rhamnosus*, to children aged 4—48 months with AD was associated with the improvement in severity of AD and the product safety was demonstrated. Our results are in accordance with the results from experimental studies, as well as those reported in previous clinical trials. Further studies may address the effects of probiotic supplementation in a longterm period.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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