Lactobacillus salivarius plus fructo-oligosaccharide is superior to fructo-oligosaccharide alone for treating children with moderate to severe atopic dermatitis: a double-blind, randomized, clinical trial of efficacy and safety

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Summary

Background Some probiotics can ameliorate childhood atopic dermatitis (AD). Prebiotics have also shown some efficacy, although when combined with probiotics as synbiotics, their efficacy may improve.

Objective We compared the effects of Lactobacillus salivarius and fructo-oligosaccharide (synbiotic) with fructo-oligosaccharide alone (prebiotic) on children with moderate to severe AD.

Methods We randomly assigned 60 children aged 2–14 years with moderate to severe AD [SCORing AD (SCORAD) > 25] to a treatment (synbiotic) or a control (prebiotic) group (30 per group). They received one capsule twice daily for 8 weeks containing either L. salivarius plus fructo-oligosaccharide (treatment) or fructo-oligosaccharide only (control). SCORAD indices were monitored at weeks 0, 4, 8 and 10 (post-treatment). Laboratory results and AD medication use were also monitored.

Results Baseline demographic and clinical characteristics and SCORAD scores were similar between the two groups. At 8 weeks, the treatment group SCORAD scores (27·4 ± 12·7) were significantly lower than for the controls (36·3 ± 14·9) (P = 0·022); this difference remained at 10 weeks. At 8 weeks, treatment group AD intensity was significantly lower (P = 0·013); more children had mild AD in the treatment group (52%; 14/27) than the control group (30%; 8/27) (P = 0·024). Medication use frequency and eosinophil cationic protein levels were significantly reduced in the treatment group at 8 weeks compared with 4 weeks.

Conclusion A synbiotic combination of L. salivarius plus fructo-oligosaccharide is superior to the prebiotic alone for treating moderate to severe childhood AD. However, continued follow-up will be necessary to ascertain long-term benefits.

The incidence of atopic dermatitis (AD) among children has increased dramatically in recent decades, particularly in Western countries.1 However, these trends have also become apparent in Asian countries that have experienced rapid economic growth and urbanization, such as Taiwan.2 According to the hygiene hypothesis, these populations have experienced changes in environmental and living conditions that may have had effects on altering immune system regulatory components and/or responses.3 Altering the education of the immune system, especially in early life, could lead to aberrant immune system responses to otherwise benign antigenic challenges (i.e. allergens), with a corresponding increase in atopic disorders, including AD.

Recent work suggests that alterations in the intestinal microflora possibly contribute to deviations in immune system education and the propensity for atopic disease.4,5 Studies have investigated if it is possible to overcome these alterations in the intestinal microflora, which might in turn produce beneficial...
effects either for preventing or ameliorating AD. Two of these strategies include using dietary supplements with prebiotics and ingesting benign, presumably commensal bacteria, as probiotics.

A prebiotic, such as galacto- or long-chain fructo-oligosaccharide, is an indigestible dietary component that may have beneficial effects by selectively stimulating the growth and/or activities of one or more gut bacterial species.\(^6\) Used as dietary supplements, prebiotics have shown some possible effects for preventing atopic disease, although overall the results are inconclusive.\(^7\) According to the Food and Agriculture Organization of the United Nations, probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.\(^8\) Probiotics, particularly various Lactobacillus species, have shown significant effects on preventing or treating AD in children.\(^9,10\) However, results have varied, as these effects appear to be bacterial strain-specific.

A third strategy has recently arisen that includes combining a prebiotic with a probiotic, a so-called synbiotic.\(^11\) Although only a few studies have been conducted, synbiotics had effects superior to a prebiotic alone for treating AD\(^11\) and was superior to a placebo for ameliorating atopic disease.\(^12\) In a randomized, controlled study, infants with AD received either an extensively hydrolysed formula with Bifidobacterium breve M-16V and a galacto-/fructo-oligosaccharide mixture (Immuno-\(\beta\)fortis\(^12,13\); Dumex, Singapore) or the same formula without synbiotics for 12 weeks.\(^13\) Although the synbiotic showed no improvements in AD severity compared with the placebo, it did alter infants’ intestinal microflora. Thus, synbiotic combinations may have some synergistic effects, although results appear to be strain-specific for the particular probiotic used.

A bacterial species used as a probiotic should exhibit immune-stimulating properties. This has been shown for Lactobacillus salivarius,\(^14–16\) which has not previously been tested for possible beneficial effects on AD in children. Thus, we investigated if a synbiotic combination of L. salivarius and fructo-oligosaccharide had better effects on children with moderate to severe AD than fructo-oligosaccharide alone.

### Methods

#### Study subjects and treatment schedule

Sixty children aged 2–14 years were recruited from the Taipei Veterans General Hospital, Taipei, Taiwan. They fulfilled the diagnostic criteria of AD developed by Hanifin and Rajka.\(^17\) They had moderate to severe AD [SCORing AD (SCORAD) > 25]\(^17\) and persistently showed AD symptoms for at least 4 days before diagnosis.

The children were randomized into two groups (synbiotic or prebiotic group; 30 per group) in a double-blind manner using a computer-generated, blocked randomization list provided by ProMD Biotech Co., Ltd (Tainan, Taiwan). A block size of four was used, and stratified according to sex, age and diagnosis of moderate to severe AD. To ensure consistency, the same investigator (K.G.W.), who was blinded to group assignments, enrolled patients and performed all SCORAD assessments at weeks 0, 4, 8 and 10.

For the synbiotic group, each capsule contained 475 mg fructo-oligosaccharide plus 25 mg live probiotic [\(2 \times 10^9\) colony forming units (CFU) L. salivarius]. For the control group, each capsule contained 475 mg fructo-oligosaccharide plus 25 mg corn starch. Each child took one capsule orally of synbiotic or prebiotic twice daily for eight consecutive weeks. The synbiotic and prebiotic products, which were identical in appearance, odour and taste, were delivered in numbered packages directly to the parents according to the randomization list. The code was opened only after all data were analyzed. The supplier regularly checked the viability of the bacteria in the capsules. The parents were instructed to bring the remaining products to the study unit and not to feed their children other probiotic preparations during the intervention.

The children were not preselected. During a 2-week run-in period, blood was drawn and the sera from all the participating patients were positive (specific IgE antibodies > 0.35 kU L\(^{-1}\)) against at least one of six common allergens (see Laboratory tests below). During the trial period, routine therapy for patients with AD remained unchanged, which included continuing use of topical corticosteroids and topical calcineurin inhibitors. We used Nerisone\(^\text{®}\) fatty ointment (0.1%) with medium potency (1 g contained 1 mg of difflunisolide valerate; Intendis Manufacturing S.p.A., Via E. Schering, Milan, Italy). A topical calcineurin inhibitor (pimecrolimus cream 1%) was used for skin lesions on the face and inguinal areas. There were no statistically significant differences between arms with respect to corticosteroid potency at the inclusion stage or during the study. Those patients who received systemic steroid therapy (e.g. oral steroid administration) or had SCORAD scores ≤ 25 were discontinued from the trial.

This study was approved by the ethics committee of our hospital and written informed consent was received from the children’s parents or guardians who had knowledge of the children’s medical history.

#### Lactobacillus and placebo capsule preparation

We used L. salivarius PM-A0006, which was verified to modulate immune responses,\(^14\) provided by the Bioresource Collection and Research Center, Food Industry Research and Development Institute, Ministry of Economic Affairs, Taiwan (http://www.bcrc.firdi.org.tw/index.do). Lactobacillus salivarius PM-A0006 with probiotic characteristics was initially isolated from the intestinal tracts of normal, healthy humans using an IHTD system [interferon (IFN) High Throughput Detecting System; ProMD Biotech Co., Ltd]. A high-density culture system was used to produce freeze-dried powder containing L. salivarius PM-A0006 at concentrations over \(10^{11}\) CFU g\(^{-1}\). Each capsule (500 mg) contained > \(2 \times 10^9\) CFU of L. salivarius plus fructo-oligosaccharide. Prebiotic capsules contained fructo-oligosaccharide only. All capsules were stored at < 4 °C by ProMD Biotech Co., which has Current Good Manufactur-
Efficacy assessments

Demographic data were collected 1 week before entering the trial.

Clinical efficacy was the primary outcome for this study and was evaluated using SCORAD scores at weeks 0, 4, 8 and 10 (2 weeks after completing therapy). SCORAD scores the extent of the body surface area that is involved (0–100%); intensity is the sum of individual scores for erythema, oedema/papules, oozing/crusts, excoriation, lichenification, and skin dryness (each 0–3; maximum 18); and subjective symptoms including pruritus and sleep loss (assessed by a parent on a visual analogue scale, 0–10 points each; maximum 20). The range of the SCORAD scores is 0–103. AD severity was classified based on SCORAD scores as mild (< 25), moderate (25–50), or severe (≥ 50).18,19

As a secondary outcome, quality of life was assessed during the trial using 13 items, including skin symptoms (pruritus or oedema; skin itch at specific times or seasons of the year; eczema-like symptoms on face and hands behind the knees; feeling itchy and uncomfortable after eating certain foods), activity limitations (unable to do general activities; unable to do continuous exercise), sleep disturbances (unable to sleep due to itching; night-time arousal due to itching; difficulty in staying asleep), and daily activity disturbances (affected routine or class work; unable to concentrate on work or study; affected social activities; disturbances of normal life) as well as times of topical medication use (topical steroids and topical calcineurin inhibitors). Each item was divided into a five-point scale: 0, none; 1, seldom (< 3 times/month); 2, sometimes; 3, usually; 4, every day. These items were recorded daily in a diary by the parents and were reviewed by the investigators at weeks 0, 4 and 8.

To determine if AD would relapse after the interruption of treatment, the patients were asked to revisit 2 weeks after the completion of therapy (week 10) for SCORAD values and laboratory tests.

Laboratory tests

Before interventions, peripheral blood samples were drawn for measurements of serum allergen-specific IgE against six common allergens using a Pharmacia CAP system (Pharmacia Diagnostics AB, Uppsala, Sweden): house dust mites (Dermatophagoides pteronyssinus and Dermatophagoides farinae), dog dander, cat dander, milk and egg white. Serum total IgE and eosinophil cationic protein (ECP) were assayed by UniCAP FEIA (Pharmacia Diagnostics AB) at weeks 0 and 8. Full blood cell counts with differential counts (FBC/DC) were determined at weeks 0, 8 and 10. Total eosinophil counts (TEC) were determined using a Coulter LH 750 haematology analyser (Beckman Coulter, Fullerton, CA, U.S.A.). Laboratory test results were also used as secondary outcomes.

Possible side-effects

Any adverse effects, such as diarrhoea, abdominal pain, skin rash, or others, during the study period were recorded.

Statistical analysis

For this randomized, blinded trial study, no power calculations were made before conducting the trial. However, we stopped recruiting patients after 60 children were recruited, and estimated the study’s power based on this sample size. The study’s estimated power was based on assuming that the percentage of subjects for whom a 50% reduction of SCORAD index scores at week 8 was superior in the treatment (symbiotics) group than the control (prebiotics) group. The observed percentages were 70% and 26% for the treatment and control groups, respectively. The observed power was 92.8% at a significance level of α = 0.05.

Results for continuous variables are given as mean ± SD or median with interquartile range (IQR: Q1–Q3). Results for categorical variables are given as numbers (n) and percentage (%). Group comparisons used two-sample t-tests, Mann–Whitney U-tests, or Pearson χ² tests, as appropriate. A paired t-test was used for changes within a group. The changes in SCORAD index scores from baseline were given as mean (SD) for both groups and evaluated with a linear mixed model to identify group and time effects. All statistical assessments were two-tailed at the α = 0.05 level of significance. Statistical analyses used SPSS 15.0 software (SPSS Inc., Chicago, IL, U.S.A.).

Results

Patient characteristics

A total of 60 patients with AD aged 2–14 years were screened and randomized into two groups: 30 in a treatment group (symbiotics) and 30 in a control group (prebiotics). All patients’ sera were positive for at least one of six common allergens (specific IgE antibodies > 0.35 kU L⁻¹). In the symbiotics (treatment) group, three patients received steroids for acute disease flares. In the prebiotics (control) group, one patient did not meet an acceptable SCORAD score (score < 25), one refused to continue, and one received steroids for acute disease flare. These withdrawals occurred before the treatment period commenced. Hence, 27 patients in each group were retained for evaluations and were available for the intention-to-treat analysis.

Table 1 summarizes the demographics, and baseline clinical and laboratory results by group. Overall, there were no significant differences in demographic or clinical characteristics.
between the groups at baseline (week 0). The treatment group included 17 male and 10 female subjects, and the control group included 12 male and 15 female subjects. The average ages were 7.8 years (SD 3.5) and 6.9 years (SD 3.4) for the treatment and control groups, respectively. Regarding severity of AD, the average SCORAD index scores at baseline (week 0) were 60.2 (SD 12.0) and 54.2 (SD 14.5) for the treatment and control groups, respectively. In the treatment group, seven patients (26%) had moderate AD and 20 (74%) had severe AD. In the control group, 11 patients (41%) had moderate AD and 16 (59%) had severe AD.

Changes in atopic dermatitis severity

Figure 1 shows AD clinical severity for the treatment (synbiotics) and control (prebiotics) groups over time based upon SCORAD index scores. Figure 1a shows the changes in SCORAD index scores from baseline at weeks 4 and 8, and Figure 1b shows the trends with time of SCORAD index scores at weeks 0, 4 and 8. The treatment group showed more changes in the SCORAD index scores from baseline at weeks 4 and 8. SCORAD index scores in the treatment group were significantly lower than in the control group at week 8 \( (P < 0.05) \). Figure 1c shows the percentage of patients in each category of severity (mild, moderate and severe) at weeks 0, 4 and 8. Overall, the treatment (synbiotics) group showed greater improvements in AD clinical severity than the control (prebiotics) group. In particular, although both groups included patients with moderate or severe AD at baseline (week 0), at 8 weeks the percentages with mild AD severity were significantly different between the two groups: 52% (14/27) in the treatment group and 30% (eight of 27) in the control group \( (P = 0.024) \) (data not shown).

Changes in clinical and laboratory results

Table 2 shows the clinical SCORAD parameters for the treatment and control groups after treatment at week 8. Compared with baseline (week 0), both groups showed improvements (compare with Table 1). At week 8, intensity (one of the SCORAD parameters) was significantly different between the groups: treatment group median (IQR) 6 (4–8) vs. control group median (IQR) 8 (7–12) \( (P = 0.013) \). In addition, the average total SCORAD scale scores were significantly different between the groups: treatment group 27.4 ± 12.7 vs. control group 36.3 ± 14.9 \( (P = 0.022) \) (Table 2).

The SCORAD index scores significantly decreased over time in both the treatment and control groups based upon a linear mixed model \( (P < 0.001 \text{ for both groups}) \). However, the reduction rate of > 50% in SCORAD scores at week 8 was significantly increased over time for the treatment group, but not the control group \( (P = 0.006 \text{ for treatment group and } P = 0.068 \text{ for the control group}) \).

At week 8, the median serum ECP was 5.2 (IQR 3.4–14.1) in the treatment group and 12.4 (IQR 6.4–37.4) in the control group, but these were not significantly different between the two groups.

### Table 1 Demographics and baseline characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Treatment group (n = 27)</th>
<th>Control group (n = 27)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), ( ^{a} ) mean ± SD</td>
<td>7.8 ± 3.5</td>
<td>6.9 ± 3.4</td>
<td>0.366</td>
</tr>
<tr>
<td>Sex (M/F), ( ^{b} ) n</td>
<td>17/10</td>
<td>12/15</td>
<td>0.172</td>
</tr>
<tr>
<td>Allergic rhinitis, yes, ( ^{c} ) n (%)</td>
<td>23 (85)</td>
<td>21 (78)</td>
<td>0.484</td>
</tr>
<tr>
<td>Asthma history, yes, ( ^{d} ) n (%)</td>
<td>4 (15)</td>
<td>5 (19)</td>
<td>1.000</td>
</tr>
<tr>
<td>Topical steroid usage, yes, ( ^{e} ) n (%)</td>
<td>24 (89)</td>
<td>25 (93)</td>
<td>1.000</td>
</tr>
<tr>
<td>WBC ( ^{f} ) ( (10^6 \text{ } L^{-1}) ), median (IQR)</td>
<td>8.8 (7.6–10.1)</td>
<td>9.1 (7.5–10.3)</td>
<td>0.431</td>
</tr>
<tr>
<td>RBC ( ^{g} ) ( (10^6 \text{ } L^{-1}) ), median (IQR)</td>
<td>4.51 (4.3–4.7)</td>
<td>4.66 (4.4–5.0)</td>
<td>0.200</td>
</tr>
<tr>
<td>HB ( ^{h} ) ( g \text{ } dL^{-1} ), median (IQR)</td>
<td>12.9 (12.6–13.9)</td>
<td>12.9 (12.6–13.9)</td>
<td>0.835</td>
</tr>
<tr>
<td>Platelets ( ^{i} ) ( (10^9 \text{ } L^{-1}) ), median (IQR)</td>
<td>347 (303–422)</td>
<td>334 (305–385)</td>
<td>0.359</td>
</tr>
<tr>
<td>TEC ( ^{j} ) ( (10^6 \text{ } L^{-1}) ), median (IQR)</td>
<td>720 (300–1100)</td>
<td>622 (400–816)</td>
<td>0.828</td>
</tr>
<tr>
<td>ECP ( ^{k} ) (μg L(^{-1})) , median (IQR)</td>
<td>25.5 (13.3–42.7)</td>
<td>35.6 (8.1–63.4)</td>
<td>0.931</td>
</tr>
<tr>
<td>Total IgE ( ^{l} ) (IU mL(^{-1})) , median (IQR)</td>
<td>1237 (512–3827)</td>
<td>1339 (303–4933)</td>
<td>0.842</td>
</tr>
<tr>
<td>SCORAD parameters, mean (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extent ( ^{m} )</td>
<td>21.6 (11.2–48.6)</td>
<td>15.1 (9.0–21.4)</td>
<td>0.109</td>
</tr>
<tr>
<td>Intensity ( ^{n} )</td>
<td>15 (12–16)</td>
<td>14 (10–15)</td>
<td>0.074</td>
</tr>
<tr>
<td>Subjective – pruritus ( ^{o} )</td>
<td>4 (3–5)</td>
<td>4 (3–4)</td>
<td>0.284</td>
</tr>
<tr>
<td>Subjective – sleep loss ( ^{p} )</td>
<td>2 (1–4)</td>
<td>1 (1–3)</td>
<td>0.283</td>
</tr>
<tr>
<td>SCORAD scale, ( ^{q} ) mean ± SD</td>
<td>60.2 ± 12.0</td>
<td>54.2 ± 14.5</td>
<td>0.104</td>
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<td>Moderate, ( ^{r} ) n (%)</td>
<td>7 (26)</td>
<td>11 (41)</td>
<td>0.248</td>
</tr>
<tr>
<td>Severe, ( ^{s} ) n (%)</td>
<td>20 (74)</td>
<td>16 (59)</td>
<td></td>
</tr>
<tr>
<td>Total score of QOL, ( ^{t} ) mean ± SD</td>
<td>22.0 ± 11.7</td>
<td>21.1 ± 11.3</td>
<td>0.778</td>
</tr>
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</table>

IQR, interquartile range (Q1–Q3); WBC, white blood cell count; RBC, red blood cell count; HB, haemoglobin; TEC, total eosinophil count; ECP, eosinophil cationic protein; SCORAD, SCORing Atopic Dermatitis; QOL, quality of life. Results were compared using \(^{a}\)two-sample t-test; \(^{b}\)Pearson \( \chi^2 \) test; or \(^{c}\)Mann–Whitney U-test.
Fig 1. Changes in SCORing for Atopic Dermatitis (AD) (SCORAD) index scores. (a) Line-plot of the changes in SCORAD index scores from baseline by group. Changes in SCORAD scores are given as means ± SD (error bars) and group comparisons were made using two-sample t-tests. No significant results were found. (b) Dispersion of SCORAD scales over time by group during the study period. Results are mean ± SD (error bars). A linear mixed model was used to compare the SCORAD scales over time and group effects. *P < 0.05 indicates significant difference between the two groups and **P < 0.001 indicates significant change over time. (c) Bar chart of percentages in each AD severity category (mild, moderate or severe). Comparisons of severity between groups used Fisher’s exact test. Overall, there were no significant differences between the two groups at each time point during the treatment period (P = 0.248, 0.518, 0.055 at weeks 0, 4 and 8, respectively). *The percentage of mild AD was significantly higher in the treatment group compared with the control group (P = 0.024).

Table 2 SCORing Atopic Dermatitis (SCORAD) parameters after treatment at week 8

<table>
<thead>
<tr>
<th>SCORAD parameters</th>
<th>Treatment group</th>
<th>Control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 27)</td>
<td>(n = 27)</td>
<td></td>
</tr>
<tr>
<td>Extent</td>
<td>4.5 (2.2–11.2)</td>
<td>7.3 (4.1–13.7)</td>
<td>0.373</td>
</tr>
<tr>
<td>Intensity</td>
<td>6 (4–8)</td>
<td>8 (7–12)</td>
<td>0.013</td>
</tr>
<tr>
<td>Subjective – pruritus</td>
<td>2 (1–4)</td>
<td>2 (2–3)</td>
<td>0.712</td>
</tr>
<tr>
<td>Subjective – sleep loss</td>
<td>1 (1–2)</td>
<td>1 (1–1)</td>
<td>0.659</td>
</tr>
<tr>
<td>SCORAD scale, mean ± SD</td>
<td>27.4 ± 12.7</td>
<td>36.3 ± 14.9</td>
<td>0.022</td>
</tr>
</tbody>
</table>

IQR, interquartile range (Q1–Q3). Results were compared using *Mann–Whitney U-test or †two-sample t-test.

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the groups. For other clinical outcomes, such as total scores for quality of life (QOL) and medication use at week 8, no significant differences were found between the groups (data not shown).

Table 3 shows comparisons of the frequencies of medication use, total scores of QOL and ECP levels for the treatment and control groups between week 4 and week 8. For the treatment group, frequency of medication use \( (P = 0.007) \) and ECP levels \( (P = 0.002) \) were significantly decreased at the end of study. There were no significant changes in medication use and total scores of QOL for the control group. However, ECP levels were significantly decreased at week 8 in control group \( (P = 0.01) \).

**Side-effects**

Two patients in the synbiotics group initially had mild diarrhea, but tolerated the treatment well thereafter.

**Discussion**

The major finding of our study was that a synbiotic combination of a putative probiotic \( L. \) salivarius preparation with the prebiotic fructo-oligosaccharide was superior to the prebiotic alone for alleviating the severity of AD symptoms in young children (aged 2–14 years) with moderate to severe disease. This was based on significant changes of SCORAD scores and not due to natural variations in childhood AD. Sistek et al.\(^{20} \) defined normal variations of stable AD as \( \leq 11 \) points on the SCORAD scale after monitoring scores during a pretrial period. Brouwer et al.\(^{21} \) assumed that only individual changes in SCORAD values of 15 points should be considered clinically significant after taking into consideration inter- and intra-observer variability. Thus, a cut-off of 15 SCORAD points indicates a meaningful clinical change in severity, and the SCORAD changes in our study were more than 15 points.

Additionally, although it has been shown that this bacterial strain had immune-modulating effects in vitro,\(^{6,14–16} \) to our knowledge this is the first report that \( L. \) salivarius might be of use as a therapeutic for childhood AD. It should also be noted that the prebiotic fructo-oligosaccharide alone did have some beneficial effects on AD severity. However, as in previous studies with probiotics or prebiotics, the effects that we observed may be considered as only modest.

It has been argued that alterations in the intestinal microflora, especially in early life, is a predisposing factor to the susceptibility to atopic disorders.\(^{4,5} \) Thus, it has been assumed that by somehow overcoming these alterations in microflora, either by introducing noninfectious bacterial species (probiotics) or dietary components that selectively stimulate the growth and activities of certain bacteria (prebiotics), this susceptibility may be reduced.\(^{22} \) Some obvious questions are which organisms or dietary components should be used and in what combinations?

In a review of 13 randomized (placebo)-controlled trials (RCTs) on the use of probiotics for treating or preventing AD, Betsi et al.\(^{23} \) found that some probiotics, such as \( L. \) rhamnous GG, were effective for preventing AD, but did not significantly change most markers of inflammation. A systematic review by Boyle et al.\(^{24} \) concluded that probiotics could not be recommended for use in treating eczema, although there was significant heterogeneity among the study results they reviewed due, most likely, to probiotic strain-specific effects. In their meta-analysis of probiotics use in paediatric AD, Michail et al.\(^{9} \) concluded that probiotics had only a modest role for treating AD, and that the effects were most beneficial for moderately severe rather than mild disease. In another meta-analysis, Lee et al.\(^{10} \) concluded that probiotics were more efficacious for preventing rather than treating AD.

Similarly, in a review of prebiotics, including short-chain galacto- and long-chain fructo-oligosaccharides, Fanaro et al.\(^{6} \) concluded that these dietary supplements could selectively stimulate the growth of certain bacteria in the intestinal microenvironment, such as bifidobacteria and lactobacilli, while suppressing the growth of pathogens. Yet, in a review of clinical studies that used prebiotics alone, by Osborn and

<table>
<thead>
<tr>
<th>Variables</th>
<th>Treatment</th>
<th>Control</th>
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<tbody>
<tr>
<td></td>
<td>Week 4</td>
<td>Week 8</td>
</tr>
<tr>
<td>Frequency of medication use (times/month)</td>
<td>31.3 ± 16.8</td>
<td>23.5 ± 19.1</td>
</tr>
<tr>
<td>P-value*</td>
<td>0.007*</td>
<td>0.085</td>
</tr>
<tr>
<td>Scale of quality of life</td>
<td>16.9 ± 12.4</td>
<td>14.2 ± 12.4</td>
</tr>
<tr>
<td>P-value</td>
<td>0.086</td>
<td>0.964</td>
</tr>
<tr>
<td>Serum ECP</td>
<td>39.3 ± 39.8</td>
<td>17.2 ± 26.4</td>
</tr>
<tr>
<td>P-value</td>
<td>0.002*</td>
<td>0.010*</td>
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</tbody>
</table>

P-values for treatment and control were derived using either \(^*\)paired \( t \)-test for comparisons within group (month 1 vs. month 2) or \(^b\)Mann–Whitney \( U \)-test as serum ECP was not normally distributed. \(^*P < 0.05\), significantly different within group (month 1 vs. month 2).
Sinn, the authors concluded that there was insufficient evidence to recommend their use as dietary supplements for children in terms of preventing allergic diseases. However, there have been too few studies on possible beneficial effects of prebiotics on atopic diseases.

In a review of probiotic and prebiotic use in paediatric practice, Morais and Jacob suggested that adding probiotics or prebiotics to infant formula early in life might be beneficial for preventing these atopic disorders, but that more studies were needed to clarify this. Also, regarding synbiotic combinations of probiotics and prebiotics, Tang concluded that synbiotics showed promise, but that more studies were needed regarding optimal doses, specific strains and the optimal timing for using these preparations. Again, all of these reviews noted that the effects, if any, were modest at best.

Thus, our intent in this preliminary investigation was to determine if a synbiotic combination showed more efficacy than a prebiotic alone for treating moderate to severe AD. Although we did not include a placebo group, several previous reports have demonstrated that a prebiotic alone did have some beneficial effects on AD severity and had protective effects against both allergic manifestations and infections.

In this light, combinations of prebiotics, that selectively promote the growth of certain bacterial species and their activities, and probiotics, that elicit immune-modulating effects, may be a more effective strategy. This synbiotic strategy was used by Passeron et al. who compared the clinical efficacies of a combination of L. rhamnous Lcr35 plus a prebiotic and a prebiotic alone for children 2 years and older with mild to severe AD. Based on SCORAD scores, both the synbiotic combination and the prebiotic were effective for reducing the severity of AD. At 3 month’s follow-up, however, they found no differences in SCORAD improvements for their synbiotic and prebiotic groups.

In contrast, in our study, which used a synbiotic combination of L. salivarius plus a prebiotic (fructo-oligosaccharide), we found a significant difference in total SCORAD scores after 8 weeks of treatment between the synbiotic and prebiotic only groups. By comparison, our study and that of Passeron et al. used children of the same age group (> 2 years) with AD. However, our study also followed various laboratory results, such as ECP while Passeron et al. did not. In confirmation of in vitro results, L. salivarius also appears to have in vivo immune-modulating activities.

A limitation of our study is that we may not have followed up our patients for a sufficiently long period. While the effects of our synbiotic combination appeared to remain at 2 weeks after the end of the treatment protocol, additional follow-ups will be necessary to evaluate more fully its efficacy. In addition, our study population may have been too small. However, as described in Methods, the statistical power to observe significant effects for this population was 92.8% (α = 0.05). Thus, even with these small numbers, our statistical results were good.

In conclusion, we have shown that a novel strain, L. salivarius PM-A0006, had therapeutic efficacy for treating children with moderate to severe AD when used in a synbiotic combination with a prebiotic, fructo-oligosaccharide. During a short treatment period, the synbiotic combination showed superior efficacy for ameliorating the severity of AD compared with the prebiotic alone.

What's already known about this topic?
- Dietary regimens can alter immune responses.
- Some probiotics ameliorate childhood atopic dermatitis to some extent.

What does this study add?
- This study demonstrates that a synbiotic combination of a probiotic (Lactobacillus salivarius) and a prebiotic (fructo-oligosaccharide) is superior to the prebiotic alone for treating children with moderate to severe atopic dermatitis.

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