Is the effect of probiotics on atopic dermatitis confined to food sensitized children?

D. Sistek*, R. Kelly*, K. Wickens*, T. Stanley†, P. Fitzharris‡ and J. Crane*

Wellington Asthma Research Group, Department of Medicine, School of Medicine and Health Sciences, Wellington, New Zealand, †Department of Paediatrics, School of Medicine and Health Sciences, Wellington, New Zealand and ‡Department of Respiratory Medicine & Allergy, Guy’s Hospital, London, UK

Correspondence:
Julian Crane, Department of Medicine, School of Medicine, PO Box 7343, Wellington, New Zealand.
E-mail: crane@wnmeds.ac.nz

Summary

Background Probiotics have previously been shown to reduce the severity of atopic dermatitis (AD) in infants and children.

Objective To examine the effect of two probiotics (Lactobacillus rhamnosus and Bifidobacteria lactis) on established AD in children.

Subjects and methods Atopic children with current dermatitis received $2 \times 10^{10}$ colony forming units/g of probiotic ($n = 29$) or placebo ($n = 30$). Both were given daily as a powder mixed with food or water. SCORing Atopic Dermatitis (SCORAD; developed by the European Task Force on Atopic Dermatitis) a measure of the extent and severity of AD, was assessed at baseline, 2 and 12 weeks after starting treatment and 4 weeks after treatment was discontinued.

Results SCORAD geometric mean score at baseline was 26.0 (21.9–30.8) in the probiotic group and 35.1 (28.9–42.8) in the placebo group ($P = 0.02$). After adjustment for these between-group baseline differences there was no significant improvement in AD at 12 weeks, SCORAD geometric mean ratio: 0.80 (95% confidence level (CI) 0.62–1.04, $P = 0.10$). Among the food sensitized children, there was an improvement in those treated with probiotics, SCORAD geometric mean ratio: 0.73 (95% CI 0.54–1.00, $P = 0.047$).

Conclusion In this study a combination of Lactobacillus rhamnosus and Bifidobacteria lactis improved AD only in food sensitized children.

Keywords atopic dermatitis, probiotics, SCORAD

Submitted 3 February 2005; revised 21 December 2005; accepted 27 January 2006

Atopic dermatitis (AD) is a common disease of childhood, sometimes persisting into adulthood. The prevalence of reported current symptoms of AD in New Zealand children aged 6–7 years is 15%, and a history of any symptoms of AD is reported by almost a third of parents of children in this age group [1]. The causes of AD are unknown but many cases particularly in early childhood are associated with sensitization to food proteins. Children who are atopic and develop dermatitis are at significantly increased risk of developing atopic asthma and rhinitis in later childhood [2].

Two lines of argument have led to studies of the relationship between bowel flora and allergic disease. Firstly, lower counts of Enterococci and Bifidobacteria in infancy have been found in atopic vs. non-atopic children and these differences precede sensitization [3, 4]. The early colonization of the bowel with probiotic bacteria such as Enterococci and Bifidobacteria are hypothesized to more effectively mature the gut mucosal immune system and promote tolerance to non-bacterial antigens. Secondly, increased gut permeability may lead to increased exposure to food antigens and has been associated with AD [5]. Probiotics may decrease this permeability and thus decrease systemic exposure to food antigens.

Isolauri et al. [6] have previously reported an improvement in SCORing Atopic Dermatitis (SCORAD) index in milk-allergic infants with mild AD following probiotic supplemented hydrolysed whey formula. Recently, Rosenfeldt et al. [7] in a cross-over study have shown an improvement in SCORAD in older children with AD treated with probiotics, but the improvement was only significant in atopic children. We have examined the
effect of a combination of probiotics in atopic children with dermatitis.

Subjects and methods

Children with previously diagnosed eczema were recruited from the greater Wellington area in New Zealand between March and July 2002, predominantly from a paediatric hospital clinic. All children met the UK diagnostic criteria for atopic eczema [8]. The inclusion criteria were, age between 1 and 10 years, AD present for at least 6 months before inclusion and atopy as shown by at least one positive skin test (weal size ≥ 3 mm) or one positive RAST (≥ 0.7 kU/L) test to any common food or environmental allergens. SCORAD of ≥ 10 and stable AD (a change in SCORAD of not more than 11 points between visits 1 and visit 2). If the AD was not stable, the children were seen for an extra visit 2 weeks later. Children were excluded if they had used oral corticosteroid therapy, oral immunosuppressive therapy or antibiotic treatment currently or in the previous month, or if they had been diagnosed with any immune deficiency disease and past or current malignancy.

Study design

Children were randomly assigned to treatment or placebo groups, using computer-generated random numbers. The treatment group received $2 \times 10^{10}$ colony forming units/g of probiotics (Lactobacillus rhamnosus and Bifidobacteria lactis) supplied by Fonterra Co-operative Group Ltd. The control group received a placebo consisting of microcrystalline cellulose, that looked and tasted the same as the probiotic. The powder was given once daily mixed in drink or food. A small number of the older children took the powder in its opaque capsule. The viability of the probiotics was tested monthly. Both subjects and investigators were blind to the treatment groups.

The study lasted for 18 weeks. There were five scheduled visits: 2 weeks before starting the treatment (visit 1), at the beginning of the treatment (visit 2), then 2 weeks (visit 3) and 12 weeks (visit 4) after starting the treatment and 4 weeks after discontinuation of treatment (visit 5). Parents received two phone calls during the treatment period to check on progress and compliance (6 and 9 weeks after the beginning of the treatment). At each visit the severity of the child’s AD was evaluated using the SCORAD index.

Questionnaire

All parents answered a questionnaire (visit 1) about AD and a history of allergic disease for their child, family history of allergic diseases and current oral or topical medication.

During the 16 weeks of the study parents were asked to complete a weekly diary of medication use, health problems and the presence and severity of AD in the child to aid recall for the questionnaire at the study visits. A final questionnaire which covered medication, other allergic diseases, changes in life style or housing during the study was completed at the end of treatment.

SCORing Atopic Dermatitis index

The SCORAD system was used to assess the severity of the dermatitis [9]. The criteria used are the extent of AD on the body surface, the severity of the different skin lesions (erythema, oedema/papulation, oozing/crusts, excoriation, lichenification and dryness) and two subjective symptoms (itchiness and sleep loss). All SCORAD assessments were done by either the research nurse or the research fellow. Before the study both observers independently scored children at paediatric and dermatology clinics until there was a high level of agreement on each parameter of SCORAD. The study was approved by the Wellington Regional Ethics Committee and written informed consent obtained from all parents or care givers.

Statistical analysis

Data analysis was conducted using SAS version 8 (SAS Institute Inc., Cary, NC, USA). As SCORAD values were log normally distributed, analyses were performed on logged data. Analysis of variance or covariance (with the baseline SCORAD as a covariate) was conducted to assess changes in SCORAD from baseline and between study groups. Differences in treatment effect over time were examined using the interaction of treatment group and time term. As there were repeated measures individuals were nested within a treatment group. All analyses were by intention to treat.

Results

From the 82 children recruited, 62 were eligible. Of the 20 ineligible children, 10 had negative skin prick tests (SPTs), seven had a SCORAD under 10, two had their AD improve to a SCORAD less than 10 between the first and the second visit, and one child was receiving oral prednisone for AD at the first visit. Two children withdrew before and one child withdrew after starting treatment, see Fig. 1. A further 10 children discontinued active treatment; eight (three from the treatment group and five from the placebo group) after using oral corticosteroids for between 3 and 10 days during the treatment phase (for exacerbations of asthma), one child because of non-compliance (placebo group) and one child because the mother chose to use non-study probiotics (treatment group). For all these
children a final SCORAD was assessed at the end of treatment, week 12. Table 1 shows baseline measurements for each study group. The groups were similar in their demographic composition and family history of allergy. However, baseline differences in past oral steroid use and SCORAD scores indicate that by chance the groups were unbalanced with regard to AD severity.

During active treatment, there was a significant reduction in geometric mean SCORAD by 2 weeks, in the probiotic group with a further reduction by the end of treatment. There was a non-significant reduction in the placebo group. One month after treatment cessation, the reduction in SCORAD was smaller but remained significant in the probiotic group, Table 2. SCORAD had improved by the end of treatment in 23/29 children actively treated and 19/30 children in the placebo group ($P = 0.18$). The effect of the probiotic was greater among food sensitized children. SCORAD had improved in 18/19 children actively treated but only 15/24 children in the placebo group ($P = 0.01$). In children who were not sensitized to food allergens (but sensitized to environmental allergens) there was no improvement seen with the probiotics, Table 2.

After adjusting for baseline differences, the end of treatment geometric mean SCORAD values were not significantly lower in the treatment group than the placebo group among the total population but remained significantly lower among food sensitized children. These effects were not sustained 1 month after treatment ceased, Table 3. The further addition of age to this model, did not alter the effect estimates, suggesting that these findings are independent of age. Controlling for oral corticosteroid use during the study did not alter the effect estimates (data not shown). Analysis of individual SCORAD components (extent, intensity and pruritis) showed that each component followed a similar pattern.

The use of antibiotics during the study did not vary with study group – 10 (34%) in the probiotic group and 12 (40%) in the placebo group. Topical steroid use at the end of the treatment phase was the same in each group ($n = 21$) and was the same as at baseline. At the end of the study parents were asked whether they thought their child had received probiotics or placebo. Fifteen parents could not offer an opinion. Of the 31 who thought they had received placebo, 16 had received the probiotics and 15 placebo. Of the 13 who thought they had received probiotics, eight had and five had received placebo, suggesting that subjects remained blind to their treatment group during the study.

![Fig. 1. Consort statement: participant progress.](image-url)
Discussion

Before commencing the study probiotics had only been studied in infants with AD. Our purpose in undertaking this small study was to examine the combined effects of two probiotics on AD among a group of older atopic children aged 1–10 years. Sample size was based on the German population study of Schafer et al. [10] where the median SCORAD was 21.4 (SD = 0.45). With 27 subjects in each group and a 30% level of reduction in SCORAD the study had 80% power of finding a difference at the 5% level and this was considered clinically worthwhile.

Comparison of geometric mean ratios of SCORAD at each time-point compared with baseline (Table 2) shows a significant reduction in SCORAD for all probiotic-treated children, and a non-significant reduction for children receiving placebo. When children were stratified into food sensitized and non-food sensitized groups the effect of the probiotics was greater in children with food sensitization.

However, despite randomization, by chance, the placebo group had higher mean baseline SCORAD than the treatment group, and were more likely to have received oral corticosteroids previously (Table 1). When we adjusted for these baseline differences (Table 3), a significant improvement was observed for the food sensitized children only, at the end of the study period (12 weeks). In retrospect we could have reduced these baseline differences by block randomizing subjects by severity. The difference in response between the food sensitized and environmental allergen sensitized children was striking, but should be interpreted cautiously because this subgroup analysis was not based on an a priori hypothesis. All 16 children who were classified as having atopy to environmental allergens only, had been tested to wheat, whole milk, egg, fish and peanut. There remains the possibility that some non-food-sensitised children may have shown sensitization to uncommon foods. Our results are similar to those recently reported by Rosenfeldt et al. [7] for atopic children but in our study the benefit appears to be confined to those sensitized to food antigens.

Table 1. Baseline characteristics of study population by study group

<table>
<thead>
<tr>
<th></th>
<th>Probiotic (n = 29)</th>
<th>Placebo (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>15 (52)</td>
<td>17 (57)</td>
</tr>
<tr>
<td>Age (median, range)</td>
<td>3.8 (1.1–10.6)</td>
<td>4.4 (1.1–10.9)</td>
</tr>
<tr>
<td>Family history of allergic disease</td>
<td>27 (93.1)</td>
<td>25 (83.3)</td>
</tr>
<tr>
<td>Food sensitized</td>
<td>19 (65.5)</td>
<td>24 (80.0)</td>
</tr>
<tr>
<td>Asthma</td>
<td>8 (27.6)</td>
<td>15 (50)</td>
</tr>
<tr>
<td>Hayfever</td>
<td>11 (37.9)</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>Current topical steroids</td>
<td>21 (72.4)</td>
<td>21 (70.0)</td>
</tr>
<tr>
<td>Oral steroids ever</td>
<td>4 (13.8)</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>SCORAD</td>
<td>26.0 (21.9–30.8)</td>
<td>35.1 (28.9–42.8)</td>
</tr>
<tr>
<td>Extent</td>
<td>20.5 (15.0–28.0)</td>
<td>34.1 (25.3–46.0)</td>
</tr>
<tr>
<td>Intensity</td>
<td>4.3 (3.6–5.2)</td>
<td>5.8 (4.7–7.2)</td>
</tr>
<tr>
<td>Pruritis</td>
<td>2.6 (0.9–7.7)</td>
<td>4.4 (3.6–5.3)</td>
</tr>
<tr>
<td>Food sensitized</td>
<td>N = 19</td>
<td>N = 24</td>
</tr>
<tr>
<td>SCORAD</td>
<td>26.7 (21.2–33.3)</td>
<td>36.4 (29.0–45.8)</td>
</tr>
<tr>
<td>Extent</td>
<td>21.5 (14.4–32.2)</td>
<td>36.6 (25.6–52.4)</td>
</tr>
<tr>
<td>Intensity</td>
<td>4.4 (3.5–5.6)</td>
<td>6.0 (4.7–7.6)</td>
</tr>
<tr>
<td>Pruritis</td>
<td>1.9 (0.3–10.3)</td>
<td>4.4 (3.5–5.6)</td>
</tr>
<tr>
<td>Non-food sensitized</td>
<td>N = 10</td>
<td>N = 6</td>
</tr>
<tr>
<td>SCORAD</td>
<td>24.7 (17.9–34.0)</td>
<td>30.4 (18.3–50.4)</td>
</tr>
<tr>
<td>Extent</td>
<td>18.6 (10.3–33.8)</td>
<td>25.7 (14.7–44.9)</td>
</tr>
<tr>
<td>Intensity</td>
<td>4.1 (2.8–6.1)</td>
<td>5.0 (2.6–9.7)</td>
</tr>
<tr>
<td>Pruritis</td>
<td>4.6 (3.0–7.1)</td>
<td>4.1 (2.4–6.8)</td>
</tr>
</tbody>
</table>

* P ≤ 0.05
CI, confidence interval; SCORAD, SCORing Atopic Dermatitis.

Table 2. Geometric mean ratios of SCORAD values at each time point compared with baseline

<table>
<thead>
<tr>
<th>SCORAD</th>
<th>Baseline</th>
<th>2 weeks after treatment commenced</th>
<th>End of treatment (12 weeks)</th>
<th>End of study (16 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total probiotic</td>
<td>1.00</td>
<td>0.77 (0.63–0.94) P = 0.009</td>
<td>0.65 (0.52–0.79) P &lt; 0.001</td>
<td>0.78 (0.63–0.96) P = 0.02</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.00</td>
<td>0.83 (0.68–1.01) P = 0.06</td>
<td>0.85 (0.69–1.03) P = 0.09</td>
<td>0.85 (0.69–1.05) P = 0.13</td>
</tr>
<tr>
<td>Food sensitized</td>
<td>N = 43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probiotic</td>
<td>1.00</td>
<td>0.72 (0.57–0.91) P = 0.006</td>
<td>0.59 (0.47–0.75) P &lt; 0.0001</td>
<td>0.76 (0.59–0.97) P = 0.03</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.00</td>
<td>0.88 (0.71–1.08) P = 0.22</td>
<td>0.86 (0.70–1.06) P = 0.16</td>
<td>0.83 (0.66–1.05) P = 0.12</td>
</tr>
<tr>
<td>Non-food sensitized</td>
<td>N = 16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probiotic</td>
<td>1.00</td>
<td>0.86 (0.57–1.29) P = 0.46</td>
<td>0.76 (0.51–1.14) P = 0.17</td>
<td>0.83 (0.55–1.27) P = 0.38</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.00</td>
<td>0.66 (0.39–1.11) P = 0.11</td>
<td>0.79 (0.47–1.33) P = 0.36</td>
<td>0.89 (0.53–1.52) P = 0.67</td>
</tr>
</tbody>
</table>

SCORAD, SCORing Atopic Dermatitis.
results suggest that any beneficial effect of probiotics in AD may be related to local effects on the gastrointestinal tract. A number of studies have shown AD to be associated with gastrointestinal symptoms and pathological abnormalities, including symptoms associated with specific food challenges [11]. Cafarelli et al. [12], have recently shown that diarrhoea, vomiting and regurgitation are more common amongst children with AD particularly those sensitized to food antigens. Probiotics have been shown to enhance the intestinal mucosal barrier and reduce the increased permeability associated with food sensitivity [13], and enhance gut-specific IgA [14]. Probiotics have also been shown to reduce the allergenicity of dietary antigens and to promote the secretion of anti-inflammatory cytokines such as IL-10 [15, 16].

In this study a combination of probiotics decreased the severity of AD in a subgroup of children sensitized to food but had no effect on children sensitized to environmental allergens.

Acknowledgements
This study was supported by a grant from the Health Research Council of New Zealand.

References

Table 3. Geometric mean SCORAD ratios of probiotic to placebo at each time point, adjusted for baseline differences

<table>
<thead>
<tr>
<th>SCORAD</th>
<th>2 weeks after treatment</th>
<th>End of treatment (12 weeks)</th>
<th>End of study (16 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>0.98</td>
<td>0.80</td>
<td>0.97</td>
</tr>
<tr>
<td>(0.75–1.28)</td>
<td>(0.62–1.04)</td>
<td>(0.74–1.29)</td>
<td></td>
</tr>
<tr>
<td>P = 0.88</td>
<td>P = 0.10</td>
<td>P = 0.86</td>
<td></td>
</tr>
<tr>
<td>Food sensitized</td>
<td>0.88</td>
<td>0.73</td>
<td>0.99</td>
</tr>
<tr>
<td>(0.65–1.20)</td>
<td>(0.54–1.00)</td>
<td>(0.71–1.39)</td>
<td></td>
</tr>
<tr>
<td>(n = 43)</td>
<td>P = 0.42</td>
<td>P = 0.047</td>
<td>P = 0.96</td>
</tr>
<tr>
<td>Non-food</td>
<td>1.32</td>
<td>0.96</td>
<td>0.92</td>
</tr>
<tr>
<td>sensitized</td>
<td>(0.72–2.38)</td>
<td>(0.53–1.75)</td>
<td>(0.51–1.68)</td>
</tr>
<tr>
<td>(n = 16)</td>
<td>P = 0.36</td>
<td>P = 0.90</td>
<td>P = 0.78</td>
</tr>
</tbody>
</table>

SCORAD, SCORing Atopic Dermatitis.

Journal compilation © 2006 Blackwell Publishing Ltd, Clinical and Experimental Allergy, 36 : 629–633