

CORRESPONDENCE

Follow-up of probiotic *Lactobacillus GG* effects on allergic sensitization and asthma in infants at risk

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Introduction

Atopic eczema is an early step towards allergic asthma. Many studies examined the preventive and modulatory effects of probiotics, which have been observed especially in IgE-associated allergic disease. Our primary study examined the impact of placebo-controlled probiotic food supplementation on atopic dermatitis, allergic sensitization, and bronchial asthma when given to 6–24 month old infants at an increased risk of atopic disease [1]. To study long-term effects, we followed-up our cohort until the fourth year of life.

Methods

Our primary investigator-initiated prospective study had supplemented children, with at least two episodes of wheezing and a first degree family history of atopic disease with a six-month food supplementation of *Lactobacillus (L.) rhamnosus strain Goldbach & Gasseri ATCC 53103* (LGG, 10^{10} cfu) or placebo. Here, we followed-up our study population for another 1.5 years, i.e., an average of 26 months after the intervention terminated. We documented asthma-related clinical events: asthma exacerbations defined as cough and wheeze, associated hospitalizations, use of inhaled steroids- and beta-agonists, systemic steroids, and antibiotics. Children underwent a physical examination including determination of the severity scoring of atopic dermatitis (SCORAD), and sensitization for respiratory allergen was measured by total and antigen specific IgE assays (cat epithelia, house dust mite (Der pt. and far.), birch pollen, timothy pollen, horse epithelia, and alternaria), eosinophilic granulocytes, and eosinophilic cationic protein (ECP). Rhinoconjunctivitis was documented in a diary. We used SPSS for

Windows® version 11.0 (SPSS Inc., Chicago, Illinois/USA). The U-test (Mann-Whitney and Kruskal-Wallis) was performed for between-group comparison. Results are expressed as means with 95% confidence intervals. Nonparametric tests were two-tailed. Probability (*P*) values < 0.05 were considered as statistically significant.

Result

Population

Of the 100 subjects who had completed the primary study, our per-protocol analysis encompassed 56% (39 in the LGG group, 17 after placebo). The rest was lost-to-follow-up due to high fluctuation in the Frankfurt area.

Asthma-related events

Again, we could not find significant differences of asthma-related events during our follow-up (see table). With an average of about 1.5 obstructive episodes per year, both groups were within the normal range of mild asthmatics in this age frame. Children after LGG tended to require slightly more inhaled betamimetics: 12.7 (4.91–20.6) vs. 3.75 (2.02–9.52) days, *P* = 0.08.

Rhinoconjunctivitis

Allergic complaints were significantly more frequent after placebo (23.5% of the intervention group) than after LGG (10.3 %; *P* = 0.03).

Atopic eczema and allergic sensitization

In our group with only mild eczema, we also found no differences of SCORAD-indices during further follow-up. Total IgE levels continued being higher after placebo 52.0 (19.8–84.2) than after LGG 17.0 (5.79–39.8); *P* = 0.09. The significant differences of aeroallergen-specific cumulative IgE still persisted during this further follow-up: 2.38 (1.63–6.40) after LGG vs. 42.1 (10.7–73.6) after placebo; *P* = 0.0006.

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Results

	LGG	Placebo	P
Number of subjects (female:male)	39 (12:27)	17 (5:12)	NA
Age at follow-up (months)	42.0 (40.3–43.7)	44.0 (39.8–48.2)	0.37
Time since end of intervention (months)	28.0 (24.0–32.0)	24.0 (20.8–27.2)	0.43
Household smoking (index*)	0.38 (0.29–0.94)	0.18 (0.01–0.36)	0.19
SCORAD	4.70 (0.45–9.84)	0.71 (0.50–1.98)	0.19
Eos	0.21 (0.19–0.29)	0.28 (0.18–0.38)	0.39
IgE (U/ml)	17.0 (5.79–39.8)	52.0 (19.8–84.2)	0.09
cum. spec. IgE (/ml)	2.38 (1.63–6.40)	42.1 (10.7–73.6)	0.0006
ECP [U/ml]	14.2 (2.00–26.4)	18.5 (9.44–27.6)	0.39
Asthma exacerbations/year (number)	1.41 (0.68–2.14)	1.53 (0.15–3.21)	0.43
Allergic complaints (% of intervention group)	10.3	23.5	0.03
Cough (days)	15.6 (7.57–25.5)	13.6 (2.58–29.9)	0.40
β -mimetics (days)	12.7 (4.91–20.6)	3.75 (2.02–9.52)	0.08
Inhalative steroids (days)	3.97 (0.60–7.33)	8.00 (0.81–24.8)	0.22
Emergency medication (no. of doses)	0.22 (0.02–0.45)	0.43 (0.33–1.18)	0.23
Antibiotics for bronchitis (days)	2.90 (1.04–4.77)	4.92 (0.23–9.60)	0.17
Hospitalized for bronchitis/pneumonia (days)	0	0	NA

*1 = 1 parent occasionally, 2 = 2 parents occasionally, 3 = 1 parent regularly, 4 = both parents regularly.

LGG, Lactobacillus GG; SCORAD, severity scoring of atopic dermatitis; eos, eosinophilic granulocytes; IgE = immunoglobuline E; ECP, eosinophilic cationic protein; emergency medication, steroidal suppositories; NA, not applicable.

Discussion

When young children grew older, an underlying atopic disposition is closely associated with recurrent wheezing and airway symptoms. Besides household exposure to cigarette smoke, early sensitization towards aeroallergens is a major risk-factor for the long-term development of bronchial asthma. Also lung function impairment increases with high amounts of specific IgE antibody levels. Our primary study revealed a positive impact of six months of oral supplementation with probiotic *Lactobacillus rhamnosus* GG on sensitization with aeroallergens even six months after the end of the intervention. Even after another one and a half year of follow-up, in the fourth year of age, we consistently observed less allergic sensitization after probiotic food supplementation as expressed by lower total IgE and cumulative specific IgE, reaching statistical significance for the latter. This goes with a recent study, which revealed an amelioration of the symptom-medication score in Japanese pre-school children with atopic dermatitis after eight weeks of *L. acidophilus* L-92 or placebo [2]. Another trial from the Ukraine treated 90 children 1–3 years old with eight weeks of a mixture of *L. acidophilus* DDS-1 and *Bifidobacterium lactris* UABLA-12 or placebo, resulting in significant clinical improvement and corresponding lymphocyte subset changes in peripheral blood [3].

When looking for rhinoconjunctivitis, our children after probiotic food supplementation had significantly less complaints compared to placebo. This was in line with a recent Swiss trial, where four weeks of *L. paracasei* ST11 in adults with allergic rhinitis improved subjective nasal congestion and down-regulated pro-inflammatory IL-5 [4].

So far, probiotic food supplementation has failed to induce positive impacts on airway disease. While data from animal studies were promising, showing reductions of airway reactivity following probiotic food supplementation, our findings are in line with other trials in humans, where no protective long-term effects as to wheezing and airway inflammation could be detected [5]. In our trial, subjects after probiotic food-supplementation even tended to require more beta-mimetic inhalation. In parallel, subjects belonging to the verum group kept being more exposed to cigarette smoke in the household, with its known negative impact on airways. Our follow-up examination has the limitation that the per-protocol analysis only encompassed 56% of the population which had completed the primary study. Interestingly, more placebo-recipients had dropped-out of the primary study, and also the follow-up evaluation included a larger group of probiotic-fed children. This might be an expression of the individual patients' and parents' satisfaction with the double-blind intervention.

Conclusion

In young children with atopic disposition and recurrent wheeze, six months of oral *L. rhamnosus* GG food supplementation had no long-term beneficial effect on airway symptoms also in the fourth year of life. Even two years after the end of the intervention, we consistently observed moderate positive effects on allergic sensitization. Further studies are needed to investigate long term benefits.

References

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