

Feeding a soy formula to children with cow's milk allergy: The development of immunoglobulin E-mediated allergy to soy and peanuts

Klemola T, Kalimo K, Poussa T, Juntunen-Backman K, Korpela R, Valovirta E, Vanto T. Feeding a soy formula to children with cow's milk allergy: The development of immunoglobulin E-mediated allergy to soy and peanuts.

Pediatr Allergy Immunol 2005; 16: 641–646. © 2005 Blackwell Munksgaard

Peanut allergy has been associated with the intake of soy milk or a soy formula. We studied the development of immunoglobulin E antibodies specific to soy and peanuts and of allergic reactions caused by peanuts, in children with confirmed cow's milk (CM) allergy fed either a soy formula or an extensively hydrolyzed formula (EHF). One hundred and seventy infants with documented CM allergy (CMA) were randomly assigned to receive either a soy formula or an EHF. The children were followed to the age of 4 yr. Peanut-specific immunoglobulin E was measured at the age of 4. A detailed history of the occurrence of allergic reactions caused by peanuts was recorded by the parents. Soy-specific immunoglobulin E antibodies were measured at the time of diagnosis and at the ages of 1, 2 and 4 yr. Immunoglobulin E antibodies to soy (≥ 0.35 kU/l) were found in 22 of 70 children fed the soy formula, and in 14 of 70 of the children fed the EHF ($p = 0.082$). In an open challenge with soy at the age of 4, no immediate reactions were observed. One of 72 children from the soy group had a delayed reaction. Immunoglobulin E antibodies to peanuts (≥ 0.35 kU/l) were found in 21 of 70 children fed the soy formula and 17 of 69 infants fed the EHF ($p = 0.717$). The incidence of reported peanut allergy in the soy group was two of 72 (3%) and four of 76 (5%) in the EHF group ($p = 0.68$). Development of immunoglobulin E-associated allergy to soy and peanuts was rare in our study group of milk allergic children. The use of a soy formula during the first 2 yr of life did not increase the risk of development of peanut-specific immunoglobulin E antibodies or of clinical peanut allergy.

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Key words: soy allergy; peanut allergy; cow's milk allergy; immunoglobulin E-mediated reactions; prospective randomized controlled clinical trial

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Accepted 16 August 2005

Allergies to peanuts and tree nuts cause the majority of severe food-induced anaphylactic reactions (1, 2). The prevalence of peanut allergy is reported to have doubled in young children over the past decade (3, 4). Highly atopic children and children with a family history of peanut allergy are at risk of developing peanut allergy (4–6). Soybean and peanuts belong to the

legume family, and immunological cross-reactivity can occur among legumes (7, 8). It has been suggested that the consumption of soy by infants and the use of skin creams containing peanut oil may be a risk factor for development of peanut allergy (9).

The purpose of this prospective randomized study was to discover whether feeding soy

formula as opposed to extensively hydrolyzed formulas (EHF) to children with cow's milk allergy (CMA) increases the risk of the development of peanut- and soy-specific immunoglobulin E antibodies or the development of adverse reactions caused by soy or peanuts during the first 4 yr of age.

Material and methods

Subjects

The study initially comprised 170 children with CMA (99 boys, 71 girls). The mean age at the time of diagnosis of the allergy was 7 months, range 2–11 months. CMA was diagnosed by means of a double-blind placebo-controlled food challenge (DBPCFC) in all the subjects except in four patients who had a history of an anaphylactic reaction and showed positive immunoglobulin E antibodies to cow's milk. Details of the study patients and the diagnostic procedure have been reported earlier (10, 11).

The infants were randomized to receive either an extensively hydrolyzed formula (EHF; 90 infants; PeptidiTutteli®, Valio Ltd., Helsinki, Finland) or a soy protein based formula (80 infants; SoijaTutteli®, Valio Ltd.) according to a computer-generated randomization list, as reported earlier (11). Neither the parents nor the investigators were told which formula was given to which infants, and the blinding was shown to be successful (11). Cow's milk (CM) products were eliminated from the infants' diets until tolerance to CM was confirmed in the challenge test (12). During their first 2 yr, either a soy-based or an extensively hydrolyzed formula was given instead of CM products. During the first year the infants were given no soy protein products other than the randomized formula. Other food items, which on the basis of clinical history and/or skin prick tests, might cause hypersensitivity reactions, were also avoided. The subjects were prospectively followed at the ages of 2, 3 and 4 yr with a clinical examination and with an open challenge to assess the development of tolerance to CM.

Specific immunoglobulin E antibodies

Immunoglobulin E antibodies to soy protein and to peanuts were determined using the Pharmacia CAP System™ FEIA (Pharmacia, Uppsala, Sweden) according to the manufacturer's instructions. The cut-off level for the presence of immunoglobulin E antibodies was 0.35 kU/l. Serum samples for the measurement of

immunoglobulin E to soy were available from 137 children at the time of randomization, from 140 at 1 yr, 143 at 2 yr and 140 children at the age 4 yr. Immunoglobulin E to peanuts was measured in 58 infants at the time of randomization, and in 139 children at the age of 4.

Allergy to soy and peanuts

Data on food allergy from the study children was collected prospectively by means of a questionnaire filled in by the parents during the follow-up visits at the age of 18 months, and at 2, 3 and 4 yr. Parents were asked questions about food avoidance and whether their children had had adverse reactions caused by the soy or the peanuts. If no reactions from soy were suspected at the age of 4 yr, the parents were advised to feed the child a normal portion of soy in the form of soy-based ice cream or yoghurt before the follow-up visit. Children with suspected adverse reactions from soy were investigated in the outpatients clinic with an open soy challenge.

Children were not systematically challenged with peanuts at the age of 4. Adverse reactions caused by peanuts at the age of 4 yr were recorded through the questionnaire and by interviewing the parents.

Statistical methods

This study was part of a larger investigation which examined the effects of a soy formula and an extensively hydrolyzed whey formula on nutritional status and growth in infants with CMA. The sample size of the study was not based on the incidence of detectable (≥ 0.35) peanut or soy immunoglobulin E or of clinical peanut allergy.

However, assuming that at the age of 4 the prevalence of detectable immunoglobulin E to peanuts was 25% in the EHF group and 46% in the soy formula group [odds ratios (OR) = 2.60], the sample size per group necessary to detect the anticipated statistically significant OR of 2.60 (9) (type I error 0.05, power 80%) was 78 infants. It was also calculated that with the predefined sample size ($n = 90$ in the EHF group and $n = 80$ in the soy formula group) the power would be 83% to detect the statistically significant OR of 2.60. The power of 83% was sufficient to start the study.

The primary outcome variables were two: the proportion of children with positive (≥ 0.35 kU/l) immunoglobulin E antibodies to soy and proportion of children with positive immunoglobulin E antibodies to peanuts, at the age of 4 yr.

The secondary outcome variables were adverse reactions to soy and peanuts at the age of 4 yr. The 95% confidence intervals for prevalences were calculated using exact binomial distribution. Univariate and multivariate logistic regression analyses were performed to compare the soy formula group (soy) with the EHF group as to immunoglobulin E (≥ 0.35 kU/l) to soy and to peanuts. The results are given with OR with 95% confidence intervals. The chi-squared test was used for other categorical variables. The Pearson correlation was calculated to describe the association between serum levels of peanut- and soy-specific immunoglobulin E. The distributions of immunoglobulin E variables were skewed to the right and were logarithmically transformed before analysis.

Ethical consideration

Written informed consent was obtained from all the parents. The study was approved by the Joint Commission on Ethics of Turku University and Turku University Central Hospital, Turku, Finland, and by the commission on Ethics of the Skin and Allergy Hospital, Helsinki, Finland.

Results

The drop-out rate during the 4-year follow-up was eight of 80 (10%) in the soy formula group, and 14 of 90 (16%) in the EHF group.

Immunoglobulin E antibodies to soy

Before the randomization to soy formula or EHF, eight of 67 (12%) in the soy group and 10 of 70 (14%) in the EHF group had detectable (≥ 0.35 kU/l) immunoglobulin E antibodies to soy. The total prevalence was 13% (95% CI: 7–19%). By the age of 1 yr, the frequency of

positive immunoglobulin E to soy had increased to 15 of 68 (22%) in the soy group, while it remained constant (14%) in the EHF group. At the age of 2 yr, an increase in the frequency of positive immunoglobulin E antibodies to soy was observed in both groups. At the age of 4, 22 of 70 (31%) of the children in the soy group and 14 of 70 (20%) in the EHF group had detectable immunoglobulin E to soy. At the 4 yr of age, when the soy formula group was compared with the EHF group, the baseline-adjusted OR was 2.28 (95% CI: 0.90–5.76, $p = 0.082$). The OR for the ages from 1 to 4 yr, with and without baseline-adjustments, are given in Table 1.

Reported allergic reactions caused by soy

At the age of 4 no immediate reactions caused by soy products were reported by the parents. One child of the 72 children in the soy group was reported to have a delayed reaction (gradual worsening of atopic eczema) caused by the soy. The reaction was confirmed by an open 4-day challenge with soy. The child had no immunoglobulin E antibodies to soy. No adverse reactions to soy were reported from the children in the EHF group at the age of 4 yr.

Immunoglobulin E antibodies to peanuts

Immunoglobulin E to peanuts was measured in 58 children before the randomization to soy formula or EHF (Table 1). The frequency of detectable Immunoglobulin E to peanuts was six of 28 (21%) in the soy group, and three of 30 (10%) in the EHF group. The total prevalence was 16% (95% CI: 7–27%). At the age of 4 yr immunoglobulin E to peanuts was measured in 139 children. The frequency of positive (≥ 0.35 kU/l) immunoglobulin E antibodies to peanuts was not significantly different in the two

Table 1. The prevalence and 95% confidence interval of positive immunoglobulin E antibodies (≥ 0.35 kU/l) to soy and to peanuts. The soy formula group was compared with the EHF group using the logistic regression analysis. The analysis was performed with and without adjustment for baseline Immunoglobulin E

	Prevalence in the soy formula group		Prevalence in the EHF group		Without baseline adjustment			Baseline adjusted		
	n (%)	95% CI	n (%)	95% CI	OR	95% CI	p-value	OR	95% CI	p-value
Immunoglobulin E to soy ≥ 0.35 kU/l										
Baseline	8/67 (12)		10/70 (14)							
1 yr	15/68 (22)	13–34	10/72 (14)	7–24	1.75	0.73–4.23	0.211	2.32	0.67–8.07	0.186
2 yr	15/71 (21)	12–32	11/72 (15)	8–26	1.49	0.63–3.50	0.366	1.52	0.50–4.58	0.461
4 yr	22/70 (31)	21–44	14/70 (20)	11–31	1.83	0.85–3.97	0.124	2.28	0.90–5.76	0.082
Immunoglobulin E to peanuts (≥ 0.35 kU/l)										
Baseline	6/28 (21)		3/30 (10)							
4 yr	21/70 (30)	20–42	17/69 (25)	15–36	1.31	0.62–2.77	0.479	1.27	0.35–4.61	0.717

groups (soy formula group 21 of 70, 30%; EHF group 17 of 69, 25%). When the soy formula group was compared with the EHF group, the OR was 1.31 (95% CI: 0.62–2.77, $p = 0.479$). The baseline adjustment changed the OR only slightly in a subgroup with baseline immunoglobulin E to peanuts (OR = 1.27, $n = 55$). When detectable immunoglobulin E to soy at 4 yr was also included as a categorical explanatory variable, the OR for Soy formula vs. EHF decreased to 0.46 (95% CI: 0.12–1.84, $p = 0.274$) and detectable immunoglobulin E to soy turned out to be the dominant factor (OR = 134.9, $p < 0.001$). The interaction between the formula groups and immunoglobulin E to soy was non-significant ($p = 0.896$).

Association between the serum levels of soy- and peanut-specific immunoglobulin E at the age of 4

The correlation between the logarithmically transformed serum levels of peanut- and soy-specific immunoglobulin E at the age of 4 yr was 0.875 ($p < 0.001$; Fig. 1). In 92% (95% CI: 86–96%) of the cases these two methods gave identical results (both < 0.35 or both ≥ 0.35 kU/l; Table 2).

The percentage of positive immunoglobulin E to peanuts was significantly ($p < 0.001$) higher in the group with positive immunoglobulin E to soy (31 of 35, 89%) than in the group with negative immunoglobulin E (seven of 103, 7%).

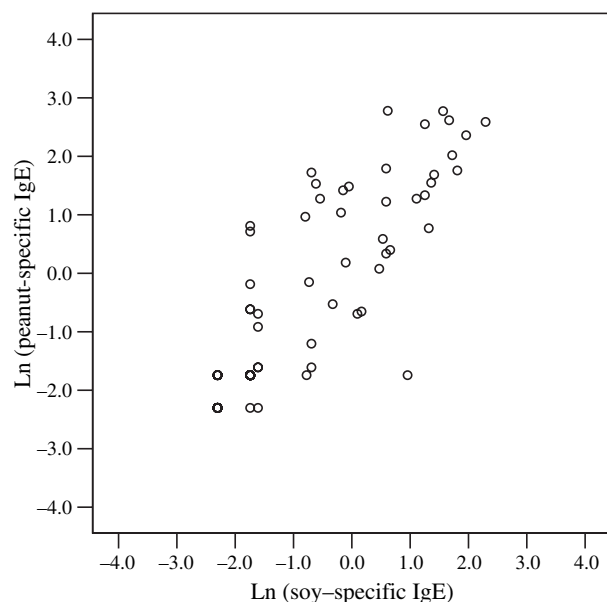


Fig. 1. The relationship between the peanut-specific IgE and the soy-specific IgE at the age of 4 yr ($r = 0.875$, $p < 0.001$, $n = 138$).

Table 2. The association between Immunoglobulin E antibodies (≥ 0.35 kU/l) to soy and to peanuts at the age of 4 yr

	Immunoglobulin E to peanuts (kU/l) < 0.35 (%)	Immunoglobulin E to peanuts (kU/l) ≥ 0.35 (%)	Total (%)
Immunoglobulin E to soy (≥ 0.35 kU/l)			
< 0.35	96 (93)	7 (7)	103 (100)
≥ 0.35	4 (11)	31 (89)	35 (100)
Total	100 (72)	38 (28)	138 (100)

Reported allergic reactions caused by peanut

Parents of six of 148 children [2 from the soy group and 4 from the EHF group ($p = \text{NS}$)] reported that their children had had adverse reactions to peanuts. The relative risk (RR) was 1.89 (95% CI: 0.36–10.00) when the rate of adverse reactions to peanuts in the EHF group was compared with the soy formula group. Reported symptoms were immediate in three subjects: urticaria in one subject, lip swelling in another, and itching with erythema in the third. A delayed reaction (eczema) was reported in three children. Of these six subjects, only one child had detectable immunoglobulin E antibodies (0.5 kU/l) to peanuts. One additional child was reported to have suffered from wheezing after eating pistachios; she had since then avoided all nuts and peanuts. Forty-one of the 148 children had never knowingly eaten products that contained peanuts (20 of 72 in the soy group, 21 of 76 in the EHF group). Of these, nine of 20 in the soy group and eight of 21 in the EHF group had positive immunoglobulin E antibodies to peanuts.

Discussion

We have previously shown that adverse reactions to a soy formula occur in 10% of infants with CMA (11). Only a small proportion of these adverse reactions to soy formula are immunoglobulin E-mediated. Feeding a soy formula as opposed an EHF to infants with CMA may slightly increase the risk of sensitization (prevalence of immunoglobulin E antibodies) to soy at the age of 4 yr, but the difference was not statistically significant ($p = 0.082$). Clinically important adverse reactions to soy at the age of 4 yr were uncommon: one child had a delayed worsening of atopic eczema in an open challenge, and no immediate or severe adverse reactions to soy were observed.

As reactions to soy cannot be predicted based on skin prick test results (13), and immunoglobulin E levels to soy did not exceed 30 kU/l (90%

predictive decision point; 14) in any of the subjects, the subjects were not excluded from the soy group or the follow-up if they had a positive skin prick test or specific immunoglobulin E to soy. Therefore no exclusion from the follow-up was made based on allergy test results or a previous adverse reaction from the soy formula.

It has been suggested that the consumption of soy by infants may be a risk factor in the development of peanut allergy (9). Soy protein-based formulas are commonly used by children with CMA. Our study is the first prospective randomized follow-up study to investigate whether a soy formula fed to CM allergic children has any effect on the development of immunoglobulin E-antibodies to peanuts or the occurrence of allergic reactions caused by peanuts. Reported reactions to peanuts were not more common among children fed soy formula compared with those fed an EHF, and there were no significant differences in the development of immunoglobulin E antibodies to peanuts between the groups. However, immunoglobulin E antibody levels to soy correlated significantly with immunoglobulin E antibodies to peanuts. This may partly be explained by the similar immunoglobulin E-binding properties of peanut-derived Ara h 3 and soy glycinin (8, 15). Soybean proteins also cross-react with birch pollen and may even cause severe allergic reactions in patients allergic to birch pollen (16, 17). The amount of the main cross-reacting allergen, Gly m 4, in soy food products depends a great deal on the degree of food processing (17).

Sensitization to soy and to inhalant allergens increases with age, at least until the age of 5 yr, whereas sensitization to more common food allergens (egg, CM) peaks at the age of 1 year (18). One reason for this may be that immunoglobulin E antibodies to soy cross-react with pollen allergens and reflect sensitization to pollen rather than to soy itself.

In our study the formula (soy or EHF) consumed by CM allergic children did not have any effect on the development of the immunoglobulin E response to peanut allergens. There was also no difference in the history of allergic reaction caused by peanuts.

Development of immunoglobulin E-associated allergy to soy and peanut was rare in our study group of milk allergic children. The reported prevalence of nut allergy in a general population under 5 yr of age is 1% (3, 4). We studied children with CM allergy who are at greater risk of the development of nut allergy. Six of 148 (4%) of the study children reported an allergic reaction caused by peanuts by the age of 4 yr.

Immunoglobulin E to peanut was detected in only one of these subjects. The use of soy formula during the first 2 yr of life did not significantly increase the risk of development of soy- or peanut-specific immunoglobulin E antibodies at the age of 4 yr. We consider that soy formulas are safe alternatives to EHF for CM allergic infants.

Acknowledgments

We would like to thank Drs Antti Koivikko and Pirkko Syvänen, and Marja Marja-aho and Janette Räikkönen, the two nurses who worked on the study, for assisting with DBPCFCs. Pellervo Marja-aho PhD helped greatly in the collection of data.

Funded by the Social Insurance Institution, Helsinki, Finland, Turku University Hospital, Turku, Finland, Helsinki University Hospital, Helsinki, Finland, and Valio Ltd, Helsinki, Finland.

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