

A randomized trial of the acceptability of a daily multi-allergen food supplement for infants

To the Editor,

Many studies demonstrate the protective benefits of early dietary introduction and consistent inclusion of allergenic foods in infant diets, including those at increased risk.¹ While some recommendations encourage early food introduction for all infants, even those at higher risk,² adherence to a consistent, multifood dietary inclusion protocol can be difficult in infants and children.³ Multiple studies justify a minimally adequate daily dose of food allergenic protein, even in children with a food allergy.^{4,5} This study evaluates the acceptability by parents/caregivers (parents) and tolerability by infants of a daily, single-dose, powdered food supplement containing 30 mg of protein from each of the 16 commonly allergenic foods.

The blinded, randomized, controlled 28-day trial recruited healthy infants in the United States, without severe eczema, aged 5-11 months at enrollment. Eligibility was determined by an on-line questionnaire administered to a parent. Infants were excluded if they were born at <37 weeks' gestation or had parent-reported severe eczema, a health condition lasting ≥ 3 months, ≥ 2 hospitalizations since birth, or a prior or current specialist diagnosis of food allergy. If more than one eligible infant lived in a household, parents selected one infant. The consented parents received study instructions via email and study materials by mail.

All study documents were reviewed by the Northwestern University (NU) Institutional Review Board and deemed exempt under Category 6 of the Code of Federal Regulations, Title 45, Part 46.⁶ The study was not subject to the Federal Drug Administration's premarket review or approval as a food additive because content of both the placebo and the supplement was certified as Generally Regarded As Safe. The study is registered on ClinicalTrials.gov as "Introduction and Maintenance of Still Eating Protein Blends in Support of Infant Nutritional Goals," Registration # NCT03667118.

Households were randomized, using Research Randomizer in a 1:1 ratio, to placebo or food supplement. Parents were instructed to mix or sprinkle a single-dose packet of powder into a small amount of liquid, soft, or solid food and feed it to their infant once a day, observe their infant for 2 hours for any reaction/symptom ("symptom"), and record in an online daily diary any symptom and any medication or medical care received for the symptom. For any reported symptom,

a blinded investigator called the parent to confirm the timing of the symptom and to determine whether it was in fact an IgE-type reaction.

The powdered placebo was a commercially compounded blend of flax seeds, sugar, and 400 IU of vitamin D with natural coloring. The powdered food supplement was a patented,⁷ commercially compounded blend of 30 mg of each of the 16 most common allergenic foods (peanut, soy, almond, cashew, hazelnut, pecan, pistachio, walnut, wheat, oat, milk, egg, cod, shrimp, salmon, and sesame), 400 IU of vitamin D, sugar, and natural flavoring. The food supplement composition and levels of each allergenic protein were developed to support safe ingestion in a non-food-allergic population, while providing a dietary training exposure capable of generating immunomodulatory benefits, based on studies of therapeutic oral immunotherapy for food allergy that demonstrate equivalent efficacy using low doses of protein.^{4,5,8}

The primary outcome was the difference in proportion of infants with a reported symptom(s) within 2 hours of ingestion in the supplement vs placebo arms. Sample size calculation was based on the 4% difference in reported symptoms in the EAT study⁹ and 11% difference from data submitted for the patent.⁷ The primary end-point would be achieved if the supplement caused no more than 5% more symptoms compared to the placebo (non-inferiority margin of 5%). A sample size of 125 infants per arm was calculated and deemed sufficient for a 4% proportion difference with a 0.05 significance level and 80% power with a 5% non-inferiority margin.

Two-sample t tests and chi-square test statistics were used for continuous and categorical variables. After the trial, a non-inferiority, intention-to-treat analysis using Wald's tests was conducted at the ingestion and child levels with margins of 0.05 to 0.01. In an exploratory analysis, we tested the hypothesis that the proportion of reported symptoms between groups was equal.

A total of 705 infants were randomized to the placebo (339) or food supplement (366); trial completion was equivalent for both arms (88%; 298 and 321, respectively) with 10% in each arm withdrawing (4 in both groups) or being withdrawn (37 and 41, respectively) due to non-compliance with recording in the daily diary. No infants were withdrawn due to any symptoms or reactions.

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TABLE 1 Demographic and clinical characteristics of enrolled infants

	Placebo	Food supplement	Total
Demographics			
Age at enrollment (mean in months)	7	7	7
Sex (F)	50%	52%	51%
Parent/caregiver race			
White not Hispanic (%)	51%	51%	51%
Black not Hispanic (%)	30%	31%	31%
Hispanic (%)	12%	9%	11%
Family income (% < \$75 000/y)	47%*	57%*	52%*
Parent/caregiver education (% with college degree)	66%	66%	66%
Clinical characteristics			
Mostly being fed breast milk (%)	28%	25%	26%
Overall reported infant's health (% excellent)	93%	92%	92%
Eczema			
Mild (%)	1%	2%	2%
Moderate (%)	3%	2%	2%
Sibling with food allergy/severe eczema/chronic condition for >3 mo (%)	7%	5%	6%

*Significant chi-square test of association between groups, $P = .0156$.

TABLE 2 Proportion of infants with any self-reported symptom during the trial period

Symptoms (any)	Food supplement (n = 321) (%)	Placebo (n = 298) (%)	Proportion difference	Proportion equivalence P-value	Non-inferiority P-value at .05 margin
Any symptom	11.5	10.7	0.0079	.755	.048
Rash	1.9	3.0	-0.0115	.356	<.0001
Cough	0.6	1.7	-0.0105	.222	<.0001
Stuffy nose	0.9	1.0	-0.0007	.927	<.0001
Diarrhea	3.1	2.0	0.0110	.384	.001
Throw-up/spit-up	4.7	3.4	0.0132	.403	.010
Other symptoms	1.6	1.3	0.0022	.823	<.0001

TABLE 3 Proportion of ingestions with self-reported symptom during the trial period

Symptom (any)	Food supplement (8803 ingestions) (%)	Placebo (8087 ingestions) (%)	Proportion difference	Proportion equivalence P-value	Non-inferiority P-value at .01 margin
Any symptom	0.75	0.64	0.0011	.404	<.0001
Rash	0.08	0.25	-0.0017	.008	<.0001
Cough	0.02	0.10	-0.0008	.048	<.0001
Stuffy nose	0.03	0.06	-0.0003	.413	<.0001
Diarrhea	0.40	0.09	0.0031	<.0001	<.0001
Throw-up/spit-up	0.20	0.14	0.0700	.279	<.0001
Other symptoms	0.06	0.05	0.0100	.836	<.0001

Table 1 shows the demographic and clinical characteristics of the infants. There were no significant racial/ethnic differences between the two groups, although the proportion of black infants was higher and that of Hispanic infants was lower than the proportion of each group born in the United States (15% and 23%, respectively) in 2016.

The supplement group had a slightly higher proportion of infants with a family income \geq \$75 000/y ($P = .016$).

There were 8803 supplement and 8087 placebo ingestions. The non-inferiority of the supplement is supported at a margin of 5% (11.5% vs 10.7%; $P < .05$) of having at least one reported symptom (Table 2).

A two-sided test of equivalence of the proportions between the two groups was accepted ($P = .76$), meaning there was no significant difference between the groups in the proportion of any specific reported symptoms. Of the supplement and placebo ingestions, 0.75% and 0.64%, respectively, had a reported symptom (Table 3). The non-inferiority of the supplement is supported at a margin of 1% ($P < .0001$) (Table 3). No infant had any IgE-type reaction to the supplement or received any related prescribed medication or medical care.

This trial strongly suggests that feeding a single daily dose of a multiple allergenic protein food supplement to healthy infants is accepted by parents, given the high trial completion rate. The absence of any reported IgE-type reactions or need for medication or medical care supports tolerability in infants. The null hypothesis in a non-inferiority analysis of the proportion of reported symptoms was rejected.

Infants with severe eczema because current guidelines require introduction of allergenic foods under physician care, as well as infants with a food allergy diagnosis, were excluded.

Limitations of the study include a 28-day trial only; inability to verify ingestions in a clinical setting and, instead, reliance on daily diary entries; and possible under- or over-parent-reporting of symptoms and/or allergic reactions (although unlikely for a serious allergic reaction such as anaphylaxis, prescribed medication, or medical care).

This is the first study to show acceptability by parents and tolerability by healthy infants of a daily serving of a powdered food supplement that includes the 16 most common allergenic food proteins, thus offering an acceptable and tolerable option to achieve early, consistent dietary exposure to potential food allergens in healthy infants. Given the acknowledged role of a diverse diet in immune diversification,¹⁰ tolerability of a highly diverse protein blend is a plausible avenue for further exploration, related to the "multiplicity-of-effect" mechanism of dietary exposure to a wide range of allergenic food proteins, of the supplement's potential to decrease the risk of food allergy.

CONFLICT OF INTEREST

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