Acceptability and Tolerability of a Daily Multi-Allergen Food Supplement for Infants

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BACKGROUND

- **Many studies demonstrate 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, multi-food 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 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.**

RESEARCH OBJECTIVES

The goals of this study were to:

- **Evaluate the safety of a blend of 16 common allergenic proteins (peanut, soy, almond, cashew, hazelnut, pecan, pistachio, walnut, wheat, oat, milk, egg, cod, shrimp, salmon, sesame), combined with 400 IU of Vitamin D into a food supplement powder;**
- **Assess the acceptability of parents to feed their infant a daily dose of the powder;**
- **Show that the food supplement is well tolerated by infants; and**
- **Learn about aspects of the food supplement that are more or less attractive to infants and parents.**

METHODS

Population: Healthy, full-term infants, 5-11 months of ages at enrollment, without parent-reported severe eczema, food allergy, or hospitalization ≥ 2 times since birth or taking medication chronic condition lasting ≥ 3 months.

Sample: Recruited from a national, web-enabled research panel.

Protocol: 28-day randomized trial to food supplement or placebo, consisting of

- **Feeding their infant one packet (approximately 1 tbsp) of the placebo or food supplement powder to once daily;**
- **Observing their infant for 2 hours after the feeding;**
- **Recording any allergic type reaction, including anaphylaxis, occurring within 2 hours after ingestion in an online daily diary; and**
- **Recording any other symptoms (e.g., diarrhea, rash, vomiting).**

Biomarker Sub-Study

- **Convenience sample of infants, randomized to the food supplement arm, whose parents continued to feed their infant food supplement after the end of the trial;**
- **Blood samples drawn at baseline, 4 months, and 8 months after ingestion of food supplement for total serum IgE, allergen-specific IgE, and IgG4 antibody levels; and**
- **If needed, infant would undergo an oral food challenge of the 3 common allergenic foods, milk, egg, and peanut.**

RESULTS

Enrollment, Randomization, and Completion

- **A total of 705 infants were randomized to the placebo (339) or food supplement (366) arms;**
- **NO infants were withdrawn due to any symptoms or reactions;**
- **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 online daily diary.**

RESULTS CONTINUED

Demographic and Clinical Characteristics

- **Table 1 shows the demographic and clinical characteristics of the infants.**
- **There were no significant racial/ethnic differences between the two groups; although**
  - **The food supplement group had a slightly higher proportion of infants with a family income ≥ $75,000/year in (p=0.016).**

Symptoms and Reactions During the Placebo Only and Trial Periods

- **There were 8,803 supplement and 8,087 placebo ingestions:**
  - **NO infant had any IgE-type reaction to the supplement or received any related prescribed medication or medical care**
- **There was no significant difference between the groups in the proportion of any specific reported symptoms, and**
  - **The non-inferiority of the food supplement is supported at a margin of 5% (11.5% versus 10.7%; p<0.05) of having at least one reported symptom (Table 2).**
- **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<0.0001) (Table 3).**

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF ENROLLED INFANTS

		Placebo	Food Supplement	Total
DEMOGRAPHIC	Age at enrollment (mean in months)	7	7	7
	Sex (female)	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/year)	47%*	57%*	52%*
	Parent/Caregiver Education (% with college degree)	66%	66%	66%
CLINICAL	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 months (%)	7%	5%	6%

**Significant X2 test of association between groups, p=0.0156*

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 0.05 Margin
Any symptom	11.5%	10.7%	0.0079	0.755	0.048
Rash	1.9%	3.0%	-0.0115	0.356	<0.0001
Cough	0.6%	1.7%	-0.0105	0.222	<0.0001
Stuffy nose	0.9%	1.0%	-0.0007	0.927	<0.0001
Diarrhea	3.1%	2.0%	0.0110	0.384	0.001
Throw-up/spit-up	4.7%	3.4%	0.0132	0.403	0.010
Other symptoms	1.6%	1.3%	0.0022	0.823	<0.0001

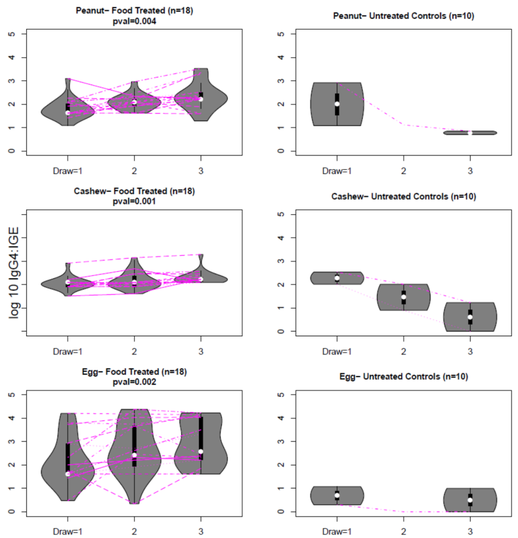
TABLE 3. PROPORTION OF INGESTIONS WITH SELF-REPORTED SYMPTOM DURING THE TRIAL PERIOD

Symptom (Any)	Food Supplement (8,803 ingestions)	Placebo (8,087 ingestions)	Proportion Difference	Proportion Equivalence P-Value	Non Inferiority P-Value at 0.01 Margin
Any symptom	0.75%	0.64%	0.0011	0.404	<0.0001
Rash	0.08%	0.25%	-0.0017	0.008	<0.0001
Cough	0.02%	0.10%	-0.0008	0.048	<0.0001
Stuffy nose	0.03%	0.06%	-0.0003	0.413	<0.0001
Diarrhea	0.40%	0.09%	0.0031	<0.0001	<0.0001
Throw-up/spit-up	0.20%	0.14%	0.0700	0.279	<0.0001
Other symptoms	0.06%	0.05%	0.0100	0.836	<0.0001

Sub-Study Plasma Biomarkers and Food Challenge

- **Among 18 infants in the sub-study, on average, 3 blood samples were obtained at 12, 17, and 22 months of age. Specific IgG4 antibody response increased for peanut, cashew, and egg compared to age-matched controls (p<0.05) – the specific IgG4/IgE ratio increased over time.**
- **No significant changes in specific IgE antibody levels were observed (Figure 2).**
- **No infants had any reported allergic reaction to the food supplement or to any food and, therefore, none met the criteria to undergo a food challenge.**

FIGURE 2: SUB-STUDY VERSUS CONTROL COMPARISON OF IGG4/IGE RATIO BY TYPE OF COMMON ALLERGENIC FOOD



CONCLUSIONS

- **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,[5] 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.**

1. Tran MM, Lefebvre DL, Dai D, et al. Timing of food introduction and development of food sensitization in a prospective birth cohort. Pediatr Allergy Immunol. 2017;28(5):471-477.
2. Greenhawt M. The National Institutes of Allergy and Infectious Diseases sponsored guidelines on preventing peanut allergy: A new paradigm in food allergy prevention. Allergy Asthma Proc. 2017;38(2):92-97.
3. Perkin MR, Logan K, Tseng A, et al. Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants. N Engl J Med. 2016;374(18):1733-1743.
4. Kulis M, Yue X, Guo R, et al. High- and low-dose oral immunotherapy similarly suppress pro-allergic cytokines and basophil activation in young children. Clin Exp Allergy. 2019;49(2):180-189.
5. Sampath V, Nadeau KC. Newly identified T cell subsets in mechanistic studies of food immunotherapy. J Clin Invest. 2019;129(4):1431-1440.

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