Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective

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Background: Oral immunotherapy (OIT) is an effective experimental food allergy treatment that is limited by treatment withdrawal and the frequent reversibility of desensitization if interrupted. Newly diagnosed preschool children may have clinical and immunological characteristics more amenable to treatment.

Objective: We sought to test the safety, effectiveness, and feasibility of early OIT (E-OIT) in the treatment of peanut allergy.

Methods: We enrolled 40 children aged 9 to 36 months with suspected or known peanut allergy. Qualifying subjects reacted to peanut during an entry food challenge and were block-randomized 1:1 to receive E-OIT at goal maintenance doses of 300 or 3000 mg/d in a double-blinded fashion. The primary end point, sustained unresponsiveness at 4 weeks after stopping early intervention oral immunotherapy (4-SU), was assessed by double-blinded, placebo-controlled food challenge either upon achieving 4 prespecified criteria, or after 3 maintenance years. Peanut-specific immune responses were serially analyzed. Outcomes were compared with 154 matched standard-care controls.

Results: Of 40 consented subjects, 3 (7.5%) did not qualify. Overall, 29 of 37 (78%) in the intent-to-treat analysis achieved 4-SU (300-mg arm, 17 of 20 [85%]; 3000 mg, 12 of 17 [71%], $P = .43$) over a median of 29 months. Per-protocol, the overall proportion achieving 4-SU was 29 of 32 (91%). Peanut-specific IgE levels significantly declined in E-OIT-treated children, who were 19 times more likely to successfully consume dietary peanut than matched standard-care controls, in whom peanut-specific IgE levels significantly increased (relative risk, 19.42; 95% CI, 8.7-43.7; $P < .001$). Allergic side effects during E-OIT were common but all were mild to moderate.

Conclusions: At both doses tested, E-OIT had an acceptable safety profile and was highly successful in rapidly suppressing allergic immune responses and achieving safe dietary reintroduction. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: *Oral immunotherapy, desensitization, sustained unresponsiveness, early intervention, peanut allergy, randomized clinical trial*

Over the last 20 years, peanut allergy has become a global public health problem affecting now 1.5% to 3% of children.[1,2] The lack of therapeutic options is a substantial unmet need. In previous randomized studies of children grade-school age and older, oral immunotherapy (OIT) has shown promise as an immunomodulatory treatment that can provide a margin of safety protecting against a potentially life-threatening accidental exposure.[3-6] Yet because little evidence for cure exists, even OIT successes must continue vigilance with strict dietary restrictions and self-injectable epinephrine. Furthermore, up to 20% cannot tolerate the treatment and there is substantial potential for relapse if treatment is interrupted.[7] However, we previously showed that long-term treatment response was significantly associated with lower peanut-specific IgE (psIgE) levels at study entry. These subjects achieved "sustained unresponsiveness (SU)" to peanut after 5 years of treatment with goal maintenance doses of 4 g/d, permitting them to stop OIT and safely introduce peanut-containing

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Abbreviations used
AE: Adverse event
DBPCFC: Double-blinded, placebo-controlled food challenge
E-OIT: Early intervention oral immunotherapy
4-SU: Sustained unresponsiveness at 4 weeks after stopping early intervention oral immunotherapy
IQR: Interquartile range
ITT: Intent-to-treat
LEAP: Learning Early About Peanut Allergy
OFC: Oral food challenge
OIT: Oral immunotherapy
psIgE: Peanut-specific IgE
psIgG$_4$: Peanut-specific IgG$_4$
SPT: Skin prick test
SU: Sustained unresponsiveness

foods into the diet.[8] This result suggests that the strength of allergic sensitization at baseline may largely influence durable OIT treatment success.

Although it is now known that the production of food-specific IgE frequently begins in infancy,[9-11] T-cell receptor affinity is weak[12] and GATA-3 expression unstable.[9] IgE production is further driven by progressive intensification of T_H2 cytokine expression over the first 2 years of life, and is strongly correlated with the clinical expression of allergic disease.[13-15] In the approximately 80% of affected patients for whom peanut allergy persists as a lifelong disease, psIgE production has been shown to increase over the first 5 years of life.[15,16] Taken together, these data suggest that the allergic program requires time to fully differentiate, and in the food allergy context, does so in the absence of oral exposure. We postulated that targeting newly diagnosed young peanut-allergic children would provide the best opportunity to enhance the clinical effectiveness of OIT as an immunomodulatory and disease-modifying treatment by interrupting allergic priming before its full maturation. We termed this approach early intervention oral immunotherapy (E-OIT).

To test whether E-OIT would safely enhance favorable long-term outcomes and explore an effective dose range, we designed a randomized, double-blinded clinical trial of low-dose and high-dose peanut E-OIT among recently diagnosed peanut-allergic children aged 9 to 36 months and compared outcomes to a control group of untreated peanut-allergic patients. Our primary hypothesis was that 70% or more participants receiving low-dose E-OIT would achieve SU to 5 g of peanut protein during a double-blinded, placebo-controlled food challenge (DBPCFC) performed 4 weeks after discontinuing OIT.

METHODS

Study design

This single-center clinical trial was appropriately registered[17] and carried out in accordance with the principles of the Declaration of Helsinki and the local ethics committee. Following written informed parental consent, eligible participants underwent a qualifying baseline open oral food challenge (OFC) to 4 g of peanut protein (see this article's Methods section in the Online Repository at www.jacionline.org). Those who demonstrated clear objective evidence of an IgE-mediated allergic reaction were block-randomized 1:1 to receive low-dose (target maintenance dose, 300 mg/d peanut protein) or high-dose (3000 mg/d peanut protein) E-OIT. All randomized subjects represent the intent-to-treat (ITT) population. After an initial-day escalation, all subjects in both groups updosed to a 3000 mg/d target maintenance dose in a double-blinded fashion before undergoing up to 2 exit DBPCFCs. Study product for the low-dose group consisted of 300 mg peanut flour plus 2700 mg of placebo filler. Further details about the investigational product and dosing schedule can be found in this article's Methods section. All participants, site investigators, and study coordinators were blinded to treatment assignment. Efficacy, safety, and immunological data were all analyzed in blinded fashion.

The primary end point was the proportion of ITT subjects achieving sustained unresponsiveness at 4 weeks after discontinuing early intervention oral immunotherapy (4-SU), defined as the ability to consume 5 g of peanut protein without dose-limiting symptoms during an exit DBPCFC followed by 1 additional serving size feeding of peanut fed openly. As discussed further in this article's Methods section, we prespecified an analysis of a matched standard-care control group to compare the frequency of peanut consumption in the diet following OIT or standard care (ie, allergen avoidance). Key secondary end points included the proportion of subjects achieving desensitization, the frequency of treatment-related adverse events (AEs) in each group, and longitudinal immunologic changes.

Study population

We recruited children aged 9 to 36 months inclusive who were peanut-allergic or peanut-sensitized. Peanut-allergic children were enrolled within 6 months of a convincing first allergic reaction following oral exposure to a peanut-containing food, and had a psIgE level of more than 0.35 kU_A/L and/or a peanut skin prick test (SPT) wheal diameter of 3 mm or more above that with the negative control. Children with no known history of peanut ingestion and psIgE level of 5 kU_A/L or more were also eligible. Exclusion criteria included life-threatening peanut anaphylaxis (eg, involving hypoxia, hypotension, or neurological compromise); wheat/oat allergy; severe atopic dermatitis according to the clinical judgment of the investigator (eg, requiring systemic therapy); asthma requiring more than medium-dose inhaled corticosteroids as per the National Heart, Lung, and Blood Institute asthma guidelines; and participation in an interventional food allergy study within 1 year.

Standard-care control group

A control cohort (N = 154), matched on inclusion and exclusion criteria, was retrospectively collected from a pediatric allergy clinic database at Johns Hopkins (see this article's Methods section). These children were treated consistent with standard of care National Institute of Allergy and Infectious Disease clinical guidelines[18] and the routine practice patterns of the attending physician(s). For example, not all diagnoses were routinely confirmed with OFC when the history was suggestive, and open OFCs were offered according to the judgment of the attending physician when he or she deemed natural tolerance likely to have occurred. Key clinical and immunologic variables were extracted from case histories by research assistants and were verified by the same pediatric allergist (C.K.), who was unaware of the trial results. IgE levels at Johns Hopkins were measured by ImmunoCAP (Thermo Fisher, Waltham, Mass).

Food challenge assessments

OFC techniques are described further in this article's Methods section. End points were assessed with two 5-g exit DBPCFCs, the first at the end of treatment to confirm desensitization. If successful, the OIT was stopped and the DBPCFC repeated after 4 weeks of peanut abstinence to test for 4-SU. The protocol allowed for end-point assessment on achievement of prespecified benchmarks (at least 12 months in the maintenance phase; psIgE $\leq$ 15 kU_A/L; SPT $\leq$8 mm; and no severe peanut-related symptoms in the previous 6 months). All subjects not meeting these benchmarks were assessed for 4-SU once they completed a 36-month maintenance phase.

Mechanistic studies

SPTs were performed and PsIgE, total IgE, and peanut-specific IgG$_4$ (psIgG$_4$) levels were measured as previously described.[19,20]