



From the Pages of allergywatch®

Recent advances in food allergy prevention and treatment



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Oral Immunotherapy to Peanut Shows Promise Under Age 3

For children with peanut allergy, oral immunotherapy (OIT) may provide a margin of safety against accidental exposure, but its use is limited by a high rate of interrupted treatment. Recent reports have suggested that starting OIT in newly diagnosed children at a young age might interrupt the process of allergic priming. The authors report a randomized, double-blind trial of this early intervention OIT approach in preschool children. The study included 40 children, aged 9 to 36 months, with suspected or known peanut allergy. All received peanut OIT, with a target maintenance dose of 300 or 3,000 mg/d. Treatment continued until the children met four specified criteria, or until they completed 3 years of maintenance therapy. Double-blind, placebo-controlled food challenge was performed to assess sustained unresponsiveness at 4 weeks after stopping OIT (4-SU). Outcomes were compared to those in a retrospective group of 154 matched children receiving standard care. Thirty-seven children qualified for the OIT protocol. On intention-to-treat analysis, median follow-up 29 months, 4-SU was achieved in 85% of the 300 mg target group and 71% of the 3,000 mg group. On per-protocol analysis, 91% of children met the primary outcome. Allergic side effects of OIT were common but mild to moderate. Early intervention OIT led to a significant reduction in peanut-specific IgE, compared to a significant increase in the comparison group. Successful peanut introduction was 19 times more likely to be achieved in children receiving OIT. Treatment failure was more likely for children with

higher peanut-specific IgE levels. The results support the safety and effectiveness of an early intervention OIT approach for preschool-aged children recently diagnosed with peanut allergy. Both low and high-dose OIT are associated with high rates of sustained responsiveness and modulation of allergic immune responses. With further study, early OIT “has the potential to further transform the standard of care in the post-LEAP era,” the authors conclude.

Comments from David M. Lang, MD: We have seen a surge in the prevalence of peanut allergy, for which the lack of management options other than strict avoidance poses an unmet need. This study, focusing on children less than 3 years old, assessed the efficacy of peanut OIT in a randomized, blinded fashion. There was no placebo group; the 40 children enrolled were compared with 154 matched controls who received standard care. Almost all patients had adverse events, but they were generally mild and the rate of systemic reactions requiring epinephrine injections was much lower than published OIT studies in older children. Unfortunately, 1 of the 37 subjects developed persistent EoE. Stay tuned for more on this promising therapy but DO NOT TRY THIS AT HOME!

Vickery BP, Berglund JP, Burk CM, et al.
Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol.* 2017;139:173–181.

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Peanut OIT—Is it Safe Enough?

Oral immunotherapy (OIT) is a promising treatment for peanut allergy, but its use is limited by a significant risk of adverse events (AEs). So far, there are limited data on the safety of peanut OIT in children. The authors pooled data from previous studies to identify predictors of AEs in children undergoing OIT for peanut allergy.

The analysis included 104 children from three studies of peanut OIT. The frequency and characteristics of AEs were identified, along baseline variables associated with AE risk. The typical patient was a white male, under age 4, with a history of atopic dermatitis or other allergic diseases. Eighty percent of children had one or more AEs likely related to OIT: 72% during the buildup phase and 47% during the maintenance phase. Ninety percent of AEs occurred at home. Systemic reactions occurred in about 42% of children and gastrointestinal symptoms in 49%. Eighty-five percent of AEs were considered mild, 15% moderate, and none severe. The dropout rate was 20%, with half of these due to persistent gastrointestinal symptoms.

On adjusted analysis, AE risk was elevated for children with allergic rhinitis, incidence rate ratio (IRR) 2.9; and larger skin test wheal size, IR 1.4 per 5 mm increase. Wheal size also predicted gastrointestinal symptoms, while AR predicted systemic reactions. During OIT, 61% of children were treated for a total of 240 likely related events; antihistamines were used in 59% and epinephrine in 12%.

The results suggest a high rate of AEs in children receiving OIT for peanut allergy. Allergic rhinitis and larger wheal size are risk factors for AEs, including systemic and gastrointestinal reactions. The authors believe that additional safety studies are needed before OIT is implemented into widespread clinical practice.

High AE rates and low desensitization rates have limited the use of OIT for peanut allergy. Anti-IgE therapy with omalizumab might facilitate oral desensitization by allowing more rapid and successful escalation of allergen dose.

Thirty-seven children and adolescents with peanut allergy were randomly assigned to omalizumab (29 patients) or placebo (8 patients). After 12 weeks, patients started an initial rapid desensitization protocol, with up to 250 mg of peanut protein the first day and weekly increases up to 2,000 mg. At week 20, omalizumab was stopped and patients continued on a 2,000 mg dose. Twelve weeks later, they underwent an open challenge with 4,000 mg of peanut protein. If tolerated, they continued on the 4,000 mg daily dose.

On initial rapid desensitization, median tolerated dose was 250 mg in patients assigned to omalizumab versus 22.5 mg in the placebo group. Six weeks after stopping study treatment, 79% of patients in the omalizumab group tolerated 2,000 mg of peanut protein, compared to 12% of the placebo group. Six weeks later, 23 patients in the omalizumab group tolerated a 4,000 mg dose versus 1 patient in the placebo group. There was no significant difference in overall reaction rate, despite much higher doses of peanut protein in the omalizumab group. Omalizumab enables rapid peanut desensitization within as little as 8 weeks of peanut OIT. In most cases, including patients with high peanut-specific IgE levels, desensitization persists after omalizumab treatment is stopped. The authors call for further studies to determine which patients can benefit most from this approach to peanut OIT.

Comments from Stanley M. Fineman, MD: These two articles address the safety of OIT for peanut allergy in children. MacGinnitie et al combined data from three OIT trials and to examine whether baseline characteristics can predict the relatively high risk for AEs during the treatment. Overall there was a 20% dropout rate, with 80% experiencing AEs; 61% required treatment, 12% with epinephrine. Patients with larger skin test reactions and those with respiratory allergies had a higher incidence of AEs. The authors state that OIT for food allergies should not yet be implemented in widespread practice; they recommend allergen avoidance as the current standard of care. The study by Virkud et al suggests that omalizumab can improve the safety of OIT. This is the first report from a double-blind, placebocontrolled study using omalizumab for pretreatment and during initial updosing of OIT for peanut allergy in children and adolescents. Although the sample was small, the results were impressive: the omalizumab group tolerated ten times the dose of peanut during initial rapid desensitization. Even after stopping omalizumab, 79% of treated patients were able to tolerate 2,000 mg of peanut, compared to 12% (one patient) in the placebo group. The quest for a safe treatment for our patients with life-threatening peanut allergy continues, although we may be getting closer.

Virkud YV, Burks AW, Steele PH, et al.

Novel baseline predictors of adverse events during oral immunotherapy in children with peanut allergy. *J Allergy Clin Immunol*. 2017;139:882–888.

MacGinnitie AJ, Rachid R, Gragg H, et al.

Omalizumab facilitates rapid oral desensitization for peanut allergy. *J Allergy Clin Immunol*. 2017;139:873–881.

Three Trials with Early Introduction of Egg: HEAP, STEP and BEAT

A few previous studies have evaluated early egg introduction to prevent the development of egg allergy (EA), with mixed results. The “Hen’s Egg Allergy Prevention” (HEAP) study evaluated early egg introduction for primary prevention of EA in a general population of infants. The study included 4- to 6-month-old infants free of egg sensitization, based on specific IgE (sIgE) levels.

They were randomly assigned to receive verum egg white powder or placebo rice powder, added to weaning foods three times weekly up to age 12 months. The main study outcome was the development of egg sensitization, reflected by sIgE.

On screening, sIgE was detected in 23 of 406 infants. Food challenge confirmed EA in 16 of 17 tested infants, 11 of whom had anaphylactic reactions.

At 12 months, rates of egg sensitization were 5.6% in infants assigned to egg white powder versus 2.6% in those assigned to rice powder: relative risk (RR) 2.20. Rates of confirmed EA were 2.1% versus 0.6%, respectively: RR 3.30. Allergic symptoms related to study treatments were also more frequent in the egg white group: 7.1% versus 0.5%.

In a general population of infants at weaning age, early introduction of egg white does not prevent egg sensitization or allergy. Since many infants already have sIgE and EA, this intervention might even result in an increased number of allergic reactions, some of them severe. Screening on the basis of atopic eczema misses one-third of infants with early egg sensitization.

At a time of rising rates of egg allergy (EA), the optimal age to introduce egg into the infant’s diet remains unclear. The “Starting Time of Egg Protein” (STEP) study evaluated the effects of early egg protein introduction for primary prevention of EA in infants at high hereditary risk.

The study included 820 infants, aged 4 to 6 months, whose mothers had a history of allergic disease or sensitization. To ensure that the study was evaluating a primary prevention effect, infants with eczema were excluded. The infants were randomly assigned to receive pasteurized raw whole egg powder or rice powder daily up to age 10 months. At that time, cooked egg was introduced to the diet in both groups. At 12 months, EA was assessed by raw egg challenge and sensitization was assessed by skin prick test.

At 12 months, there was no significant difference in the development of EA: 7.0% in infants assigned to egg powder and 10.3% in the control group. Rates of confirmed allergic reactions causing early discontinuation of study treatment were 6.1% in the egg powder group versus 1.5% in the rice powder group; none of these were anaphylactic reactions. Infants in the egg group had higher egg-specific IgG4 levels at age 12 months: median 1.22 versus 0.07 mgA/L.

In 4- to 6-month-old infants at hereditary risk of allergy but without eczema, early egg introduction does not reduce the risk of IgE-mediated EA by age 12 months. Routine testing for egg sensitization does not appear necessary before introduction of egg into the diet for this group of infants.

Some trials have suggested that early introduction of egg into the diet might reduce the risk of egg allergy (EA) in infants at high risk. The “Beating Egg Allergy Trial” (BEAT) evaluated the effects of early egg introduction in infants with a family history of atopy. The study included 319 infants, aged 4 months, who had at least one first-degree relative with allergic disease. All were initially free of egg allergy, based on a skin prick test response of less than 2 mm to egg white; about one-fourth had eczema at baseline. Infants were randomly assigned to receive whole egg powder or placebo rice powder from age 4 to 8 months, at which time their diet was expanded. The main outcome was the presence of egg sensitization at 12 months, based on a skin prick test response of 3 mm or larger.

Fourteen infants had an allergic reaction to egg during the first week of the study. Twelve-month evaluation was performed in 254 infants; dropout rates were similar between groups. Rates of egg white sensitization at 12 months were 11% in the egg powder group versus 20% in the rice powder group: odds ratio 0.46. Early egg introduction was associated with an absolute risk reduction of 9.8%, with a number needed to treat of 11.

The egg powder group had higher IgG4 to egg protein and higher IgG4/IgE ratios. There was no significant difference in the rate of probable egg allergy, based on clinical, oral challenge, or skin prick test reactions: 8 cases in the egg powder group and 8 in the rice powder group.

The BEAT results suggest that early egg introduction can reduce egg white sensitization in infants at high risk of EA, including those with eczema. However, a significant percentage of these infants cannot tolerate this intervention. Introducing egg at low doses immediately after weaning might be beneficial, and does not show evidence of harm.

Comments from Stanley M. Fineman, MD: These three articles from the May issue of JACI all assessed the impact of early

introduction of egg protein in reducing the risk of developing allergy. The HEAP study recruited infants at birth and screened at 4–6 months to those with egg sIgE <0.35 kU/l assigned to either verum powder similar to raw egg or placebo. Surprisingly there was a high prevalence of egg allergy (EA), 5.7%, even before randomization. In fact, the trial was stopped early because of the relatively high rate of allergic reactions at first exposure to the verum powder. Not only did the authors conclude that consuming egg protein early did not prevent EA they advised that it may be harmful.

The STEP trial enrolled infants from atopic mothers with no eczema who were randomized at 4–6 months to either pasteurized raw egg powder or placebo. Although this was planned as a primary prevention study, there was no evidence that early egg feeding substantially reduced the risk of EA as measured by an egg challenge at 1 year. There was an impressive rise in egg sIgG4 in the egg powder treated group, but 6% stopped taking the egg powder because of allergic reactions. All children could introduce cooked egg into their diets at 10 months which may have impacted the outcomes. The authors suggest that use of cooked egg may be advisable.

The BEAT study was unique since all the infants had a family history of allergy and negative AST to egg at 4 months with 26% presenting with eczema. This was also designed as a primary prevention study with infants receiving either egg white powder or placebo at 4 months although 8.5% had reactions to the egg powder and couldn't continue. At 8 months, cooked egg could be added to the diet of all infants. The egg powder intervention resulted in EA in 10%, measured by AST positive at 12 months, compared to 20% in the group receiving placebo. There was also an impressive rise in egg sIgG4 in the treated group.

The take home message from these studies is that early intervention with cooked egg, at 4 to 6 months, is reasonable and relatively safe although it may not result in definitive reduction in egg allergy.

Bellach J, Schwarz V, Ahrens B, et al.

Randomized placebo-controlled trial of hen's egg consumption for primary prevention in infants (HEAP study). *J Allergy Clin Immunol.* 2017;139:1591–1599.

Palmer DJ, Sullivan TR, Gold MS, et al.

Randomized controlled trial of early regular egg intake to prevent egg allergy (STEP study). *J Allergy Clin Immunol.* 2017;139:1600–1607.

Tan JW, Valerio C, Barnes EH, et al.

A randomized trial of egg introduction from 4 months of age in infants at risk for egg allergy (BEAT study). *J Allergy Clin Immunol.* 2017;139:1621–1628.

Another Look at LEAP

The “Learning Early About Peanut Allergy” (LEAP) study found a lower risk of peanut allergy among high-risk children assigned to early introduction of peanut at 4 to 11 months old. Questions remain about how the response to early introduction is affected by variables such as baseline wheal size and age at introduction. These issues were addressed in a secondary analysis of publicly available LEAP datasets.

The analysis included all 640 LEAP subjects with complete available data including 60-month oral peanut challenge results. Factors affecting achievement of peanut tolerance were assessed, including baseline sensitization to peanut and egg; the presence, severity, and duration of eczema; age at peanut introduction; and gender and race.

In a multiple logistic regression model, children in the early introduction arm were nine times more likely to tolerate peanut at age 60 months: odds ratio (OR) 9.2. Other factors associated with peanut tolerance were white race, OR 2.1; older age at introduction,

OR 4.4. Peanut tolerance was less likely for children with larger peanut wheal size, OR 0.58; more severe atopic dermatitis at baseline, OR 0.98; and higher egg-specific IgE, OR 0.99.

Among children with a baseline peanut wheal size of less than 4 mm, peanut tolerance was achieved in 83% of the early introduction group versus 43% of the allergen avoidance group. In several models, peanut tolerance was more likely to be achieved with peanut introduction at 6 to 11 months, compared with 4 to 6 months. Greater eczema severity had little impact on achievement of peanut tolerance after early introduction.

In infants at high risk of peanut allergy, the effect of baseline wheal size on peanut tolerance at 60 months is much stronger in children assigned to allergen avoidance, compared to early introduction. The benefits of early introduction appear greatest when peanut is introduced at 6 to 11 months, rather than before 6 months. The authors discuss the clinical implications for early peanut introduction.

Comments from John J. Oppenheimer, MD: In this secondary analysis of the LEAP dataset, Greenhawt and colleagues found that introduction between 6 and 11 months of life was associated with a higher probability of successful peanut oral food challenge at month 60 compared with introduction before 6 months. Overall, these data strongly reinforce the risk-reducing effect of early peanut introduction, but also provide reassurance that in those patients

where there is concern of possible peanut sensitization there is a larger window of opportunity for effective peanut introduction.

Greenhawt M, Fleischer DM, Chan ES, et al.
LEAPing through the looking glass: secondary analysis of the effect of skin test size and age of introduction on peanut tolerance after early peanut introduction. *Allergy*. 2017;72:1254–1260.

Peanut Oral Immunotherapy Combined with Probiotics: Closer to a Cure?

A recent study reported promising results with a combined probiotic and peanut oral immunotherapy (PPOIT) approach in children with peanut allergy. The authors report 4-year clinical and immunologic outcomes in children assigned to PPOIT. The analysis included data from 48 of 62 children with peanut allergy randomly assigned to 18 months of PPOIT or placebo treatment. Active treatment included the probiotic *Lactobacillus rhamnosus* plus peanut oral immunotherapy; controls received two formulations of maltodextrin. Allergy outcomes, skin prick tests, and specific IgE levels were evaluated a mean of 4.2 years after the end of treatment. In the original trial, PPOIT led to higher rates of peanut desensitization and 2-week sustained unresponsiveness. At follow-up, children receiving PPOIT were more likely to have continued peanut consumption: 67% versus 4%, with a number needed to treat (NNT) of 1.6. Allergic reactions to peanut, none anaphylactic, occurred in 4 children in the PPOIT group and 6 in the placebo group. Active treatment was associated with smaller wheal size, mean 8.1 versus 13.3 mm; and a higher sIgG4:sIgE ratio, geometric mean 67.3 versus 5.2. On double-blind, placebo-controlled food challenge, 58% of the POIT group attained 8-week sustained unresponsiveness versus 7% of the placebo group: NNT 1.9. A regimen of combined peanut oral immunotherapy and probiotic treatment shows lasting clinical improvement and suppression of food-specific immune

response in children with peanut allergy. The findings suggest that “tolerance is a realistic target for food allergy treatments.” The authors plan further studies, including assessment of PPOIT’s effects on the gut microbiome.

Comments from John J. Oppenheimer, MD: This study by Hsiao and colleagues is very exciting for the allergy community. The authors demonstrated through this placebo-controlled trial that probiotics administered in tandem with peanut oral immunotherapy resulted in long-lasting peanut tolerance 4 years after discontinuation of treatment. Specifically, two-thirds of actively treated patients were able to continue regular ingestion of “moderate-to-large” amounts of peanut on a regular basis compared to 4% of the placebo treated group. This would indicate that sustained unresponsiveness can be attained. Although there are several methodological issues that must be overcome with future studies, these provocative results provide hope that a cost-effective cure for peanut allergy may be on the horizon.

Hsiao KC, Ponsonby AL, Axelrad C, et al.
Long-term clinical and immunological effects of probiotic and peanut oral immunotherapy after treatment cessation: 4-year follow-up of a randomised, double-blind, placebo-controlled trial. *Lancet Child Adolesc Health*. 2017;1:97–105.