

Advances in the management of peanut allergy (oral immunotherapy and epicutaneous immunotherapy)

Julie Wang, M.D.

ABSTRACT

Background: Peanut allergy affects up to 2% of the general population and carries not only the risk of potentially life-threatening allergic reactions but also negatively impacts day to day life for patients and their families. Advances in knowledge in immunotherapy is providing families with options for proactive treatment.

Objective: To examine the available data for oral immunotherapy (OIT) and epicutaneous immunotherapy (EPIT) for peanut allergy.

Methods: This review discusses recent studies that evaluated the safety and efficacy of OIT and EPIT to induce desensitization to peanut and identifies factors that should be considered when guiding families in treatment decisions.

Results: Results of studies have demonstrated that immunotherapy can raise the threshold of peanut allergen to induce allergic reactions for many patients, thereby potentially reducing the risk for allergic reactions and decreasing the daily burden of peanut allergy. However, adverse reactions, which range from mild to severe, are possible with immunotherapy. Shared decision-making will be important to determine the best approach for peanut allergy management for each individual and his or her family.

Conclusion: OIT and EPIT will offer patients and families more options for managing peanut allergies. Recent data from phase III studies on OIT and EPIT as well as real-world data on OIT advance the understanding of the efficacy and safety of these approaches. On-going studies aim to identify biomarkers to enhance patient selection criteria as well as develop additional therapeutic approaches.

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Peanut allergy, which affects up to 2% of the general population,^{1,2} requires allergen avoidance and preparation with emergency medication in case allergic reactions occur. The constant vigilance needed to ensure that foods are allergen safe and the unpredictability of allergic reactions, which can range from mild to severe, pose significant burdens on both patients and their families.^{3,4} Advancements in allergen immunotherapy in recent years have led to a paradigm shift in food allergy management. Differing routes of allergen delivery, including oral immunotherapy (OIT) and epicutaneous immunotherapy (EPIT), have been under investigation for inducing desensitization (increasing the threshold of allergen needed to trigger an allergic reaction while continuing on treatment).

At this time, the primary goal of treatment for many patients with food allergy is to reduce the risk of allergic reactions due to accidental exposures.⁵ By embarking on immunotherapy, many patients and families hope that desensitization will translate to reduced frequency of unpredictable allergic reactions and improvements in quality of life (QoL) and anxiety. The relevance of raising the threshold of the allergen to induce allergic reactions has been modeled for peanut. For someone who has allergic reactions after exposure to less than one-third of a peanut, raising the threshold to 300 mg (equivalent to 1 peanut) can reduce the risk of allergic reaction by >95% for foods that may contain trace levels of peanut residue.⁶

OIT

The most extensively studied approach for treating food allergy is OIT. The general approach to OIT entails an initial build-up phase, which starts at sub-threshold doses of the allergen proteins followed by incremental increases in the dose (up-dosing) under medical supervision every 1-2 weeks to a target maintenance dose, which typically ranges from 300 to 4000 mg of peanut protein. This target dose is maintained daily to achieve desensitization. Downregulation of the T-helper type 2 response results in this clinical and immunologic nonresponse.⁷

From the Division of Allergy and Immunology, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, New York

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Address correspondence to Julie Wang, M.D., Division of Allergy and Immunology, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1198, New York, NY 10029

E-mail address: julie.wang@mssm.edu

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Clinical Trial Data

The largest double-blind, placebo controlled phase III peanut OIT study used a pharmaceutical grade product.⁸ This was a multinational study that randomized 555 subjects, ranging from ages 4 to 55 years, who were randomized 3:1 to active or placebo OIT.⁸ Pediatric subjects aged 4–17 years represented the largest group ($n = 499$). The intention to treat pediatric population ($n = 496$) had a high baseline immunoglobulin E (IgE) level (median, 71 kU/L) [interquartile range, 20–202 kU/L], and 72% had a history of anaphylaxis to peanut.⁸ This study population was highly atopic: 53% with asthma and 66% had allergies to multiple foods.⁸ The target maintenance dose was 300 mg of peanut protein maintained for 24 weeks, and desensitization to 300 mg of peanut protein was achieved by 76% of the subjects.⁸

Results also demonstrated that the treatment effect can be higher than the daily maintenance dose, with 67.2% of the subjects showed a threshold increase to a single dose of 600 mg, with no dose-limiting symptoms at the exit food challenge (primary end point of the study).⁸ When reactions did occur during the food challenge assessments, the symptoms were less severe for those who received active treatment.⁸ Consistent with the data from other OIT studies, adverse events (AE) were common and occurred both during up-dosing and maintenance phases. Systemic reactions occurred in 14.2% of the active group (3.2% in the placebo group).⁸ Overall, 24.5% of the active group withdrew before the end of the study compared with 7.9% in the placebo group.⁸ Gastrointestinal symptoms were frequently reported and contributed to study discontinuations. In total, 24 subjects withdrew due to intolerable gastrointestinal (GI) symptoms, and one subject had biopsy-confirmed eosinophilic esophagitis (EoE); symptoms were reported to resolve in all cases after OIT discontinuation.⁸

OIT in Real-World Practice

Data on OIT performed in real-world practices have also been published. A single center reported their experience with 270 patients who underwent peanut OIT over 8.5 years.⁹ The majority had a history of IgE-mediated reactions to peanut (96.7%), and the mean age of the patients was 8.1 years.⁹ Similar to other OIT studies, there was a high rate of desensitization, with approximately 80% of patients successfully escalating to the target dose of 3000 mg of peanut protein during the build-up phase.⁹ Patients continued daily dosing of 2000 mg in the maintenance phase.⁹ Because OIT was performed outside of a clinical trial, the practice had the flexibility to adapt the treatment protocol over time and allowed the use different forms of peanut protein.

AEs related to OIT were common, with epinephrine-treated reactions occurring both during escalation

phases and maintenance phases in the office and at home. GI symptoms were observed, with 13.7% deemed to have “eosinophilic esophagitis-like oral immunotherapy related syndrome (ELORS).”⁹ Immediate reactions that needed epinephrine and eosinophilic esophagitis-like oral immunotherapy related syndrome occurred through the range of OIT doses.⁹ Similar to another long-term study,¹⁰ some patients experienced reactions that needed epinephrine, despite having been in the maintenance phase for several years.⁹

A recent Canadian study of real-world peanut OIT for preschool children included 270 patients.¹¹ The median age was 23.0 months (interquartile range, 15.0–33.0 months) at the start of OIT, and 94.5% of children had a previous reaction to peanut.¹¹ Ninety percent reached the maintenance dose of 300 mg of peanut protein.¹¹ The OIT process used Bamba (Osem Group, Holon, Israel), peanut flour, or powdered peanut butter (*e.g.*, peanut butter powder; PB2 Foods, Tifton, GA) or a combination.¹¹ At least one allergic reaction occurred during the OIT process for 67.8% of the patients; only 4% (10) received epinephrine for OIT-related reactions during the build-up phase.¹¹ Four patients (1.6%) developed symptoms suggestive of EoE; one underwent endoscopic evaluation and was diagnosed with EoE.¹¹ In total, 10% withdrew from the study for various reasons, including AEs and anxiety, and a child refusing to take the OIT. In this younger age group, the rate of children who reached maintenance is higher than what has been reported in other OIT studies and AE rates were lower.¹¹ The results of this study, along with a previous study of OIT in young children lend increased support for the hypothesis that immunomodulation with OIT earlier in life may be more successful.¹²

AEs of OIT have been examined in a systematic review and meta-analysis.¹³ Analysis of 12 trials ($n = 1041$; median age, 8.7 years) demonstrated an elevated risk of anaphylaxis for patients who underwent OIT, which is threefold higher than the estimated baseline risk of 7.1% in patients who were not treated (estimated risk of anaphylaxis with peanut (PN) OIT was approximately 22%; risk ratio, 3.12 [95% confidence interval {CI}, 1.76–5.55]).¹³ Study characteristics, including baseline threshold of reactivity at entry food challenge, age, and OIT regimen (starting dose, maintenance dose, treatment duration), were not associated with risk of anaphylaxis during follow-up.¹³ Two placebo controlled studies assessed effects on QoL; in this limited data, there was no significant effect of OIT on QoL (combined parents and self-report risk ratio (RR) 1.21 [95% CI, 0.87–1.69]).¹³

Although OIT does have known AEs, the results did show that OIT increases the chance of passing an oral food challenge in a controlled medical setting. However, it is unclear whether OIT treatment reduces the rates of accidental ingestions in everyday life,

which would typically occur in uncontrolled situations. Analysis of these results indicated that further explorations into safety, efficacy, and other outcomes are warranted to determine who would best benefit from this therapy. Not all allergic reactions are the same, and patients and families may view the impact of treatment-related reactions differently from reactions due to accidental exposures in less controlled settings, such as in restaurants or social situations.

EPIT

Another form of immunotherapy for peanut allergy has also moved into late-stage, large-scale trials. EPIT entails allergen delivery *via* repeated applications to the skin, which targets antigen-presenting cells in the superficial skin layers. The phase III international study included 356 children, ages 4–11 years, who were randomized 2:1 to active (250 μ g of peanut protein) or placebo patch for daily application for 12 months.¹⁴ The primary outcome was the response rate difference between the two groups. Successful treatment was deemed to be an increase in eliciting dose to 300 mg of peanut protein at the posttreatment challenge for those whose baseline eliciting dose was ≤ 10 mg of peanut protein, and an increase in eliciting dose to 1000 mg if the baseline eliciting dose was 10–300 mg.¹⁴ Enrolled subjects had a high median baseline peanut IgE level (median 77.9 kU_A/L active, median 101 kU_A/L placebo group).¹⁴ They were also highly atopic, with nearly 50% having asthma and 85% having allergies to foods other than peanut.¹⁴

In the intention to treat (ITT) analysis, the response rate was 35.3% in the active versus 13.6% in the placebo group, with a difference of 21.7% (95% CI, 12.4%–29.8%). The lower bound of the 95% CI around the responder rate difference did not cross the prespecified threshold of $\geq 15\%$, and, therefore, the study did not meet the predefined criteria to be deemed a positive study. A description of eliciting dose changes from baseline to 12 months showed that 62.6% of the active group had an increased eliciting dose and that 30.7% had no change. Among the placebo group, 28% had an increase, 33.9% had a decrease, and 38.1% had no change in the eliciting dose. AEs were common in both groups. Patch-site reactions accounted for 57.6% of the AEs in the active treatment group versus 27.1% of the placebo group. Skin reactions were most frequent in the first month, then decreased over time; most of these reactions were mild to moderate in severity. The rate of anaphylaxis was 3.4% (eight subjects). The dropout rate was 10%, and most were not attributable to AEs.

CHOOSING A TREATMENT

Consideration of the potential risks and benefits of treatment is necessary before embarking on any

medical intervention. To date, there are no clinical trials that compared the safety and efficacy of OIT and EPIT, and comparing published data is difficult due to study design differences, such as patient entry criteria and reporting of AEs. Furthermore, efficacy differences seen for OIT and EPIT may be due to the different allergen doses used and route of administration. For example, there are major dose differences between these immunotherapy approaches, which may contribute to the differences in reported efficacy and safety. The daily dose of peanut delivered by EPIT is 1/1200 of the OIT dose used in the phase III trials, and, after 3 years of EPIT, the allergen exposure level is less than one peanut (300 mg of peanut protein).¹⁵

Some factors have been noted to augment the risk of reaction to OIT, including exercise, febrile illness, concomitant nonsteroidal anti-inflammatory drug use, and dosing without food.¹⁶ Although these factors have been associated with some OIT reactions, a number of reactions have no associated factors identified.^{9,13} Analysis of EPIT data shows lower rates of AEs, the majority of which are patch-site reactions.¹⁴ Because the patch is applied for 24 hours, assessment of the relation of AEs to treatment can be difficult. Although safety seems to be higher for EPIT when compared with OIT, analysis of the data demonstrated that fewer than half of the subjects on EPIT met the efficacy end point.¹⁴

Given these notable differences between OIT and EPIT, expectations and goals of treatment for patients and families must be considered. Results of studies showed that these factors will vary from family to family.^{5,17} As an example, for some families, the unpredictability of allergic reactions in less controlled settings, such as restaurants and parties, may carry more burden than allergic reactions to OIT, which would likely occur in a more controlled setting and time frame. For other families, concern about allergic reactions that requires epinephrine treatment in any setting may weigh more heavily in the decision-making process. For these families who are risk averse, EPIT may be more appealing given the lower reported rate of anaphylaxis.

There are practical considerations to each of these treatment approaches that may further influence a practice's and/or family's choice. OIT entails an initial dosing day that often includes a few different doses to ensure a safe starting dose, followed by in-office dose escalations, typically every 2 weeks over several months, to reach the maintenance dose. Office visits can be less frequent once the maintenance dose is achieved. However, unscheduled visits will be necessary if, for example, patients have allergic reactions to home doses or if patients have to miss doses due to illness to determine a safe OIT dose to resume. Thus, the time and effort involved in the OIT process is

significant for both medical practices and families. The risk of AEs and these practical aspects of OIT have contributed to the higher dropout rates reported compared with EPIT. EPIT is applied on a daily basis, there is no dose variation, and there are no adjustments for illness, so office visits related to this therapy will generally be less frequent than for OIT.

Data on peanut OIT stem from studies that used well-characterized products from pharmaceutical or good manufacturing practice facilities as well as reports from real-world practices that used commercially available food products. Decision-making on whether a medical practice offers their patients one or both types of products for OIT will vary and may be influenced by factors such as U.S. Food and Drug Administration approval, accessibility, and insurance coverage. For EPIT, there is only one product under development, so use will be limited by when this becomes available.

Determining the effect of treatment is critical for any medical intervention. Clinical trials for OIT and EPIT have used oral food challenges to demonstrate changes in the threshold dose that triggers allergic reactions as the end point for efficacy. This may not be feasible or desirable for all patients who receive these therapies due to practice variations and/or patient and/or family preferences. Currently, there are no biomarkers that can provide reliable evidence of immunotherapy efficacy that would obviate the need for food challenges, but research is on-going in this realm. For OIT, some degree of efficacy may be assumed if a patient is routinely tolerating a daily maintenance dose. In contrast, until biomarkers are identified, physician-supervised food challenges are needed to test the treatment effect of EPIT.

Additional factors that may influence a family's decision-making of whether to pursue OIT or EPIT or to continue to maintain allergen avoidance include anxiety related to treatment dosing or AEs, taste and/or texture aversion or sensory issues, and the family's schedule. Although there is excitement about OIT and EPIT, maintaining an avoidance strategy will continue to be a preferred option for some patients with peanut allergy. Therefore, this process requires a shared decision-making approach to determine the most appropriate management plan for each individual and his or her family.

QUESTIONS TO BE ANSWERED

There are data that support that immunotherapy to peanut has the potential of raising the threshold dose of the allergen needed to trigger allergic reactions by using medically supervised food challenges as the outcome measure. However, the main goal of treatment is to increase safety in the real world in unsupervised settings. The concept of "bite-safe" is frequently discussed

because many are not expecting a cure to be able to freely eat peanut but rather are hoping that the threshold changes induced by treatment will result in no symptoms or milder symptoms if an accidental exposure occurs, despite standard precautions to avoid the allergen. It is assumed that increased thresholds during food challenge would translate to increased protection in day-to-day life, but there are no studies yet to objectively show this benefit.

Studies demonstrate the variability of threshold doses triggering reactions at food challenge.^{18,19} Immunotherapy studies to date have focused on individuals who react at low thresholds, <300 mg of peanut protein. Patients with higher thresholds of reactivity are excluded, thus the potential benefits and safety profiles of OIT and EPIT in this population may differ from the low threshold group. Data on long-term outcomes of OIT and EPIT are sparse. The median follow-up of the OIT studies included in the meta-analysis was 1 year,¹³ so it is uncertain how risk-versus-benefit discussions will change over a longer-term treatment horizon. There are limited data on OIT to other foods that suggest longer treatment may lead to improved efficacy outcomes.²⁰ There also are data on a small sample of patients who continued EPIT for a 2-year open-label extension after a phase II trial that suggests the potential for increased efficacy with longer treatment duration.²¹

There is limited data on AEs during long-term OIT. A small, single-center study reported follow-up of patients on peanut OIT for up to 5 years.¹⁰ The results demonstrate the difficulties of maintaining OIT in the long term. Over the 5 years, 5 of 12 patients who were on maintenance and participated in the long-term follow-up study discontinued OIT between months 10 and 58.¹⁰ AEs were the most common reason for discontinuation. Nearly half had allergic reactions that required epinephrine after the first year of OIT.¹⁰ Cofactors were identified in many, but not all, of these reactions. One subject had biopsy-proven EoE after developing intermittent vomiting and dysphasia at approximately month 50.¹⁰

Future studies on OIT and EPIT should also focus on patient-centered outcomes, such as QoL, economic impact, and health-care and resource utilization, which will likely influence decision-making.²² More information with regard to QoL of both the child and the parents is needed because effects may be different. Understanding the impact of treatments on these other outcomes will facilitate shared decision-making with families.

CONCLUSION

The landscape of food allergy management is undergoing tremendous change as novel treatment options become available. OIT and EPIT will offer patients and

families more choices in how they can manage peanut allergy. These approaches to desensitization may provide patients and families an increased sense of protection and control over peanut allergy, and decrease the daily burden of this disorder. Remarkably, these modes of immunotherapy just represent the tip of the iceberg when it comes to treating food allergy. There is a robust pipeline of potential therapies that are currently in various phases of development. On-going clinical trials are examining vaccines, biologics, probiotics, and other methods that may broaden options for monotherapy or act as adjuncts to increase the safety and efficacy of OIT. Researchers also continue to explore the more ambitious goal of sustained unresponsiveness or the ability to maintain an increased threshold after discontinuation of treatment, which may be achievable for some patients. Identifying biomarkers that can assist in selection of optimal treatment options on an individual basis are concurrently explored. The field of food allergy has made significant advances in recent years and will continue to do so to improve the lives of patients with food allergies and their families.

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