

Emerging Food Allergy Treatments

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ABSTRACT

Immunoglobulin E (IgE)-mediated food allergy affects up to 8% of the pediatric population and occurs when a person develops antibodies to specific food proteins resulting in immediate reaction upon ingestion of the food in question. Current treatment revolves around strict allergen avoidance and prompt treatment of systemic, anaphylactic reactions with injectable epinephrine. However, despite strict avoidance, unexpected reactions are a significant problem. Therefore, therapeutic options for treatment of food allergy are in high demand. This article focuses on emerging therapies including oral immunotherapy, sublingual immunotherapy, epicutaneous immunotherapy, and possible adjunct therapies for the treatment and desensitization of IgE-mediated food allergy. [*Pediatr Ann.* 2019;48(12):e468-e472.]

The prevalence of food allergy is rising with up to 8% of the pediatric population being affected with an allergy to at least one food.¹ Given the lack of therapies available for preventing the development of food allergy or for aid in development of attaining tolerance to the allergen, strict avoidance of the allergen while teaching families how to avoid allergen ingestion has been the primary management strategy by physicians. If accidental ingestion occurs, prompt treatment of reactions as outlined by emergency action plans is advised with use of injectable epinephrine for management of systemic, anaphylactic reactions. However, despite

strict avoidance, unexpected reactions remain a significant problem.² An estimated 12.5% of children allergic to peanut products have accidental reactions yearly.³ Although fatal food anaphylaxis is rare, it does occur despite proper use of epinephrine at an estimated rate of 0.03 to 0.3 deaths per million person years in the general population.⁴ Adding to this is the significant anxiety children, adults, and their families experience as they navigate a life of reading labels and declining play dates, birthday parties, and sleepovers due to fear of the very thing that sustains us—food. For these reasons, a therapeutic treatment option for food allergy is in high demand.

This article focuses on emerging therapies for immunoglobulin E (IgE)-mediated food allergy and will not address non-IgE-mediated food allergy or delayed-type hypersensitivities to food. IgE-mediated allergy to food occurs when one develops antibodies to specific food proteins resulting in an immediate reaction upon ingestion of the food in question. Reactions are reproducible with each exposure to that allergen and typically occur within minutes to 2 hours of ingestion. Usual symptoms of these reactions can include urticaria, angioedema, cough/wheeze, and abdominal pain and/or vomiting.

ORAL IMMUNOTHERAPY

Oral immunotherapy (OIT) to foods is the process of eating increasing amounts of an allergen over a specified time at a goal dose. Protocols for OIT vary between published studies; however, the majority of protocols consist of three phases: (1) an initial dose escalation period over 1 to 2 days, (2) a build-up phase where the allergen dose is slowly escalated in observed visits over a specified period of time until a goal dose is achieved, and (3) a subsequent maintenance period where the goal dose is continued, usually daily. Trials of OIT for several foods have been undertaken including for milk, eggs, peanut products, and wheat. Published studies vary on the goal dose of allergen and the period over which the dose escalation occurs. Most data exist for peanut products and OIT. Systematic reviews for egg and milk OIT have been more inconsistent.^{5,6}

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There is little doubt that OIT appears to be efficacious in the majority of people who have participated in OIT.⁷ Ongoing exposure to the allergen on a daily basis at a given “dose” has resulted in desensitization to the food in most trials defined as elimination of clinical reactivity to the allergen at an increased threshold. Although desensitization appears transient and dependent on continued allergen exposure, fewer studies have undertaken re-evaluation of reactivity to the allergen after a period of cessation of ingestion. The phenomenon of clinical reactivity remaining eliminated after a period of cessation of OIT has been termed “sustained unresponsiveness” (SU) and has been documented as being successful in a proportion of people with allergies to eggs and peanuts.⁸⁻¹⁰

The safety of OIT has been of the utmost concern among researchers and practitioners. Reactions to doses are common throughout published studies; however, the majority are mild and limited to the gastrointestinal tract with mouth itching and abdominal pain being commonly reported.^{7,11} Severe, anaphylactic reactions requiring epinephrine do occur and may at times be unpredictable in their occurrence. In a Cochrane systematic review of 10 OIT studies for eggs, cumulatively 8.4% of the participants had serious adverse events requiring epinephrine use.⁵

Although no US Food and Drug Administration (FDA)-approved product for OIT was available at the time of this article, some clinical practices offer off-label OIT to families, which is growing in demand. A recent retrospective review of peanut OIT in a clinical practice real-world setting conducted over an 8-year period was reported in which 93% of the 2,700 children between ages 4 and 19 years reached a target of 3,000 mg of peanut protein in 1 year and 14 showed some evidence of SU.¹² Adverse events

during escalation were notable for 100 epinephrine-treated reactions in 63 participants (23%) including two people requiring three doses of epinephrine.¹² Twenty-eight people received epinephrine during their maintenance phase. Other adverse events were not formally studied.

AR101, an investigational drug for peanut OIT, aims to be the first FDA-approved product for OIT. The advantage of AR101 may lie in its potential ability to provide a standardized product for peanut OIT escalation to 300 mg of peanut protein. A phase 3 clinical trial randomized 551 people age 4 to 17 years with peanut allergy to AR101 or placebo. More than 67% of those receiving AR101 were able to ingest a substantially higher dose (600 mg) at an end-of-study double-blind placebo-controlled food challenge than those receiving placebo (4%).¹³ Adverse events were similar to those mentioned above with serious adverse reactions occurring in less than 6% of participants. Interestingly, the rate of withdrawals due to gastrointestinal side effects was lower than previously reported (6.5%).¹³ SU was not evaluated in this phase 3 trial.

In addition to safety concerns, psychosocial concerns and family dynamics are an important consideration. Undertaking OIT requires frequent visits to the allergist for up-dosing, limitation of activities such as exercise and hot baths that may raise body temperature within 2 hours of dosing, and dosing modifications with illness, surgical procedures, and travel. The unpredictability of adverse reactions with dosing and the need to keep the allergen in a previously allergy-free home can add additional stress to families who previously felt some comfort in strict avoidance. Despite these factors, studies of overall quality of life (QOL) in those who have undertaken OIT do tend to

show significant improvement in scores on a validated Food Allergy Quality of Life Questionnaire.^{14,15} In one study, a subset of patients experienced a significant worsening of QOL during the first months of OIT, which can be demanding with up dosing and a fear of reactions.¹⁶ In a subsequent study, the same author group looked at changes in QOL through the course of OIT and noted significant QOL improvement from OIT initiation to maintenance and significant improvement at 6-month follow-up after OIT completion.¹⁷

Despite the promising, growing evidence of efficacy in children to several foods and adoption of OIT in the practice of a limited number of private practice allergy offices, use of OIT outside of the research setting is controversial.¹⁸ A lack of consensus guidelines outside of clinical trial protocols highlights the need for further study to answer the outstanding questions of the allergy medical community.

SUBLINGUAL IMMUNOTHERAPY

Sublingual immunotherapy (SLIT) is the process of using allergen drops or tablets applied under the base of the tongue daily in escalating dosages over a period of time. Dosages in SLIT are much lower than those used in OIT and dosing is limited by available extract concentrations and volume. Like OIT, therapy consists typically of an escalation phase in which the dose is increased at varying intervals between studies and then moves to a maintenance phase once a pre-established goal dose is reached. Langerhan's cells in the oral mucosa are thought to take up the allergen and result in stimulation of regulatory T cells, an initial increase then a decrease in specific IgE, and an increase in specific IgG4.¹⁹

The first SLIT study to be performed with a double-blind placebo-controlled

study design for peanut allergy in children found a maintenance dose of 2,000 mcg of peanut resulted in the ability to ingest a median cumulative dose of 1,710 mg of peanut protein (compared to 85 mg in the placebo group) after 6 months of maintenance therapy.¹⁹ A multicenter randomized, placebo-controlled trial of SLIT for peanut allergy compared 20 people receiving SLIT to 20 people receiving placebo. Seventy percent of the SLIT participants were considered responders after 44 weeks of therapy as compared to 15% of the placebo participants.²⁰ In a follow-up study, patients continued SLIT for up to 3 years, repeating oral challenges to peanut yearly. If they passed a 10-g peanut oral food challenge (OFC) at year 3, they discontinued SLIT for 3 weeks and repeated the OFC to look for SU. All of the four people (11%) fully desensitized to 10 g of peanut protein showed SU after discontinuing dosing for the 3-week period.²¹

In SLIT, safety appears to be an advantage. Most reactions occur in the build-up phase of therapy and consist of oral itching and swelling. Rare systemic reactions have been reported. Yet, even though SLIT has shown a good safety profile, there continues to be a high rate of withdrawals from therapy not attributable to the possible side effects of treatment.²¹ In general SLIT does induce modest levels of desensitization.

A handful of studies have directly compared the efficacy and safety of SLIT to that of OIT. One open-label study of OIT versus SLIT in 28 people allergic to cow milk found SLIT followed by OIT was more effective in inducing desensitization than SLIT alone.¹⁰ The SLIT dose reached was 140-fold lower than the minimum cumulative OIT dose reached by partici-

pants who received OIT. Multisystem reactions were 11 times more likely in those receiving OIT, although the overall reaction rate was similar between those receiving SLIT versus OIT (29% and 23%, respectively).¹⁰ Two studies have directly compared SLIT and OIT in peanut allergy; both were performed in single center, small samples but both found OIT to be better overall at inducing desensitization.^{22,23} However OIT led to more symptoms with dosing and more treatment-related study withdrawals than did treatment with SLIT.^{22,23}

EPICUTANEOUS IMMUNOTHERAPY

Administration of allergens via a patch worn on the skin for immunotherapy is currently under investigation and is termed epicutaneous immunotherapy (EPIT). This therapy is transferred via a patch worn daily with a dry powder allergen sprayed on a membrane with an occlusive adhesive layer. After skin application, condensation is formed within the patch chamber, hydrating the skin and solubilizing the allergen for skin penetration. Initial studies in mice showed that allergens are taken up from the patch by dendritic cells in the epidermis, which then migrate to the lymph node for systemic effects while avoiding antigen presence in the blood.²⁴ As application continues, regulatory T cell and immunologic changes similar to those seen in OIT, SLIT, and in subcutaneous immunotherapy to aeroallergens occur.²⁴ Pilot studies in humans have been performed with a cow milk patch and subsequent phase 1, 2, and 3 studies have been undertaken with a peanut patch.

As expected, EPIT has shown good tolerability with fewer side effects than OIT making it a desirable option

for families. Local skin reactions such as itching, erythema, and mild swelling are the most common adverse effects noted; however, these have been mostly mild to moderate in severity and appear to decrease over time. In both phase 2 and 3 published studies for peanut allergy, adherence to the patch was 90% to 95% with minimal drop out, which was not due to treatment-emergent adverse events.²⁵⁻²⁷ Systemic reactions attributed to patch wear are rare, but have been reported with 10 systemic reactions occurring in 8 participants deemed to be related to the patch in the phase 3 study.^{26,27}

Efficacy data for use of the patch in peanut and milk allergy is limited thus far, but showed modest desensitization to peanut products in children age 4 to 11 years with little to no effect in adolescents and adults. Among children age 4 to 11 years, 50% in the phase II study and 66% in the phase IIb study achieved the primary endpoint defined as a 10-fold increase in the amount of peanut successfully consumed in the end-of-study challenge or an ability to ingest 5,044 mg of peanut protein with the use of a 250-mcg patch.^{25,26} Results of the phase 3 peanut patch study in children age 4 to 11 years was recently published showing a 35.3% favorable response in the amount of peanut tolerated at an end-of-study challenge to the 250-mcg patch, which was statistically significant when compared to placebo, although the results did not meet a predetermined lower bound confidence interval and did not technically meet criterion for a positive result.²⁷ The meaning of this result remains to be seen until follow-up study data are released.

Current trials of peanut allergens are focusing on children younger than age 4 years, looking at the safety and efficacy of the allergen patch, which

remains in an ongoing phase 1/2 efficacy and safety trial. No studies exist directly comparing EPIT to OIT and/or SLIT.

IMMUNOTHERAPY ADJUNCTS

Given that immunotherapy is a lengthy process and can lead to adverse reactions as noted above, the addition of adjunctive medications given in conjunction with escalating immunotherapy has been studied to see if higher doses can be reached more quickly with potentially fewer side effects. Omalizumab, a monoclonal antibody to IgE, is FDA approved for treatment of asthma and chronic urticaria. Multiple studies have added omalizumab prior to and/or during the initial steps of OIT desensitization with the allergens peanut, milk, and multi-allergen OIT.²⁸⁻³⁰ In the first published randomized, double-blind, placebo-controlled study of omalizumab with food OIT in participants with milk allergy, adverse reactions to OIT were significantly decreased; however, no difference was noted in overall efficacy of desensitization.²⁸ In the first double-blind, randomized, placebo-controlled multicenter study of omalizumab use in peanut OIT, pretreatment with omalizumab allowed 23 of 29 participants to escalate to 2,000 mg of peanut protein within an 8-week period (compared to 1 of the 8 participants treated with placebo).²⁹ Additional study would need to occur to refine its timing of use during OIT and to address the cost-benefit ratio in adding an expensive medication such as omalizumab to OIT. With the number of available biologic agents increasing rapidly, there is no doubt that other agents will be studied similarly. For instance, dupilumab, a monoclonal antibody targeting interleukin-4 receptor alpha approved for asthma and atopic dermatitis, is now in phase 2 trials with peanut OIT using AR101.

The use of probiotics as an adjunct to OIT has also undergone limited study. A double-blind randomized controlled trial looking at the combined effect of peanut OIT and probiotic use with *Lactobacillus rhamnosus* was published in 2015.³¹ Over 80% of the participants receiving peanut OIT and probiotic were desensitized compared to 7% of placebo.³¹ SU was also noted in the majority of participants receiving treatment.³¹ Study limitations include that the peanut OIT group without probiotic was not evaluated so it is difficult to know if probiotic use is an added benefit over peanut OIT alone for both desensitization and induction of SU. Further study of probiotic use would be necessary to determine if it is a successful adjunct.

CONCLUSION

The increasing prevalence of IgE-mediated food allergy and lack of a possible cure has made demand for treatment high. Finally, the prospect of an FDA-approved therapy is on the horizon with several others following closely behind. OIT, EPIT, and SLIT studies have documented varying degrees of desensitization to allergenic foods. Adjunct therapies such as biologics like omalizumab appear to hasten the process and may decrease adverse reactions. Although no therapy has provided a cure or true tolerance, these immunotherapy options appear to provide protection from accidental ingestion and, therefore, may improve the overall QOL of those suffering from IgE-mediated food allergy.

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