

Emerging Therapies for Peanut Allergy

Thomas S. Hong¹ , Amy Hu¹, Germin Fahim, PharmD¹, and Evelyn R. Hermes-DeSantis, PharmD¹

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Abstract

Peanut allergy (PA) is a food allergy that causes an IgE-mediated type I hypersensitivity reaction. PA has become an increasing public health burden, with 2% of American children reported to have this condition in 2010. Current guidelines recommend allergen avoidance, patient education, and administration of H₁ antihistamines, β_2 -agonists, or epinephrine based on the severity of reaction. In this review article, emerging therapies for PA are evaluated for their potential role in treating PA. Oral, epicutaneous, and sublingual immunotherapies have completed clinical trials with promising efficacy. In particular, Palforzia (AR101) is an oral immunotherapy that received Food and Drug Administration (FDA)-approval in January 2020 and Viaskin Peanut is an epicutaneous immunotherapy with an anticipated FDA decision date by August 5, 2020. Furthermore, adjuvant combinations with either probiotics or anti-IgE receptor antagonists have shown an improved efficacy and safety profile compared to oral immunotherapy alone. However, immunotherapy-induced adverse reaction rates are high due to the risks associated with intentional allergen exposure. These results suggest that peanut immunotherapy has a promising role in the treatment of PA, although further studies are needed before its incorporation into standard of care.

Keywords

peanut allergy, oral immunotherapy, epicutaneous immunotherapy, sublingual immunotherapy

Introduction

Peanut allergy (PA) is a public health burden with increasing prevalence. In 1999, 0.4% of American children were reported to have PA, but as of 2010, the prevalence increased to 2%. Most peanut allergies are a lifelong condition, beginning early in life and persisting to adulthood. In the United States, PA is the leading cause of death due to food-induced anaphylaxis.¹ A 2013 meta-analysis estimated that the incidence rate of fatal peanut anaphylaxis was 2.13 (95% CI: 1.09-4.16) per million person-years in people with PA, assuming a 1% PA prevalence. This incidence was reported to be lower than that of accidental death in the general population.² Even though mortality from peanut anaphylaxis is low overall, peanut allergies and the fear of anaphylactic reactions have a significant impact on the quality of life (QOL) of children and families and contribute to the psychosocial burden of the disease.¹ The annual economic cost of living with a food allergy is over \$4,000 per child and has been associated with increased risks of anxiety and depressive symptoms.³

PA is a type of food allergy that causes an IgE-mediated type I hypersensitivity reaction. This reaction is characterized by a phase of initial sensitization, during which peanut-specific IgE antibodies are produced and bind to mast cells and basophils. After sensitization, re-introduction of peanut allergen will cause binding to IgE receptors, causing cross-linking of IgE and allergen. Subsequent degranulation of preformed allergic mediators ultimately cascade into an IgE-mediated allergic

response.⁴ Despite their name, peanuts are classified as legumes and are not in the same family as tree nuts. Research has identified the 11 peanut proteins Ara h 1-11 as peanut allergens, with Ara h 1 through 3 being the most allergenic.⁵

The clinical manifestation of a PA ranges in severity and may involve 1 or multiple organ systems. Initial allergic reactions are usually seen between the ages of 14 to 24 months. According to a voluntary 2001 registry, 89% of PA patients manifested skin reactions (urticaria, erythema, angioedema); 42% had respiratory reactions (congestion, wheezing, dyspnea, cough, throat tightness); 26% had gastrointestinal (abdominal pain, vomiting diarrhea); and 4% had cardiovascular outcomes (hypotension, arrhythmia, cardiac arrest).⁵

Risk factors for food allergies include a family history of atopy as well as the presence of atopic dermatitis. Green et al. found that 82% of 138 patients with PA had atopic dermatitis.¹ Other studies have also suggested that children with severe eczema and egg allergy are at increased risk of developing PA.⁴ A landmark trial called Learning Early about Peanut

¹ Department of Pharmacy Practice and Administration, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ, USA

Corresponding Author:

Thomas S. Hong, Department of Pharmacy Practice and Administration, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA.

Email: tsh47@scarletmail.rutgers.edu

Table 1. NIAID Addendum Guideline Summary.

Addendum guideline	Infant risk category	Recommendations	Earliest age of peanut introduction
1	Severe eczema, egg allergy, or both	Strongly consider evaluation by sIgE measurement and/or SPT and, if necessary, an OFC. Based on test results, introduce peanut-containing foods.	4-6 months
2	Mild-to-moderate eczema	Introduce peanut-containing foods.	Around 6 months
3	No eczema or any food allergy	Introduce peanut-containing foods.	Age appropriate and in accordance with family preferences and cultural practices

Abbreviations: OFC, oral food challenge; sIgE, serum IgE; SPT, skin prick test.

Allergy (LEAP) indicated that the early consumption of peanuts in infants with high-risk atopic disease reduced the development of PA by an absolute risk difference of 11.8% in infants with a negative result on the initial skin-prick test ($p < 0.001$) and 24.7% in infants with a positive result on the initial skin-prick test ($p = 0.004$). These findings led to changes in recommendations about the approach to prevention of PA development.⁶ In 2017, the National Institute of Allergy and Infectious Disease (NIAID) published an addendum guideline recommending peanut consumption to prevent peanut allergies based on allergy risk category. These guidelines are summarized in Table 1.¹

Adapted from: Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. *Ann Allergy Asthma Immunol*. 2017; 118:166-173.

A clinician will diagnose PA using a history and physical examination. The majority of IgE-mediated reactions are known to occur within 60 minutes after ingestion but may be prolonged until 4 hours afterward. Minor allergic reactions often last less than an hour, while more severe reactions may last longer. Suspicions of allergy based on reported signs and symptoms are confirmed by the detection of peanut-specific IgE through a skin-prick test (SPT) or ImmunoCAP fluoroenzyme immunoassay (ImmunoCAP-FEIA). However, SPT results can be unclear, given a positive predictive value of approximately 50%. If the medical history does not corroborate a positive or negative test result, an oral food challenge may be suggested. Such food challenges can be performed as open, single-blind or double-blind, and are considered the “gold standard” for food allergy diagnosis.⁵

Current guidelines in the United States recommend allergen avoidance as the primary option for management of IgE-mediated food allergies. In cases of exposure resulting in a reaction, administration of H₁ antihistamines or β_2 -agonists for non-severe reactions and intramuscular epinephrine for anaphylaxis is recommended. Nonetheless, there has been no substantial evidence that strict food avoidance has contributed to natural remission to food allergen. On the contrary, this approach is unfavorable due to frequent cases of accidental reactions. Up to 75% of unintentional ingestion cases have led

to reactions. Contributory factors for high rates of accidental ingestion involve lack of family education and lack of recognition of different ingredient labels.⁴ Increasing research has been targeted at various modes of immunotherapy (oral, epicutaneous, and sublingual) and adjuvant combinations as a method to enhance the efficacy of the immunotherapy. These therapies have shown promise in reducing allergen sensitivity, which may subsequently reduce the psychological burden of disease and the frequency of adverse reactions due to accidental peanut allergen exposure. This review article seeks to discuss emerging therapies for PA and investigate their potential role in treating PA. The review will focus on the newly-approved product Palforzia (peanut allergen powder-dnfp), products most likely to be approved in the near future, as well as new research in adjuvant combinations designed to enhance response to immunotherapies.

Methods

An initial Medline search was conducted in February 2019 to investigate potential therapies for PA. The MeSH term “peanut hypersensitivity” was searched with the subheadings of “diet therapy,” “drug therapy,” and “therapy.” Search results were limited to “humans,” “English language,” and the last 6 years (2014 to current) in order to focus on recent research and avoid duplication with previous review articles. Relevant articles were chosen from the 138 results obtained through the search with a focus on clinical trials. Additional details on products to be approved, including economic value and drug pipeline information, was found on company and research organization websites. Results will cover oral, epicutaneous, and sublingual immunotherapy; adjuvant therapies; and cost implications of PA treatments. A summary of the important trials for PA based on therapy type are included in Table 2.

Results

Oral Immunotherapy

Oral immunotherapy (OIT) is one of the most promising immunotherapies in development to chronically manage PA. Most protocols for peanut OIT trials consist of 3 phases: a rush phase, a build-up phase, and a maintenance phase. The rush

Table 2. Summary of Important Trials for PA Based on Therapy Type.

Trial (therapy type)	Trial Design	Efficacy	Safety
Vickery et al. 2018 (OIT)	Ph 3, MC, DB, PC, Randomized (3:1) 4 to 17 years of age	250/372 (67.2%) ingested a single dose of at least 600 mg of protein	367/372 (98.7%) in OIT had AEs vs 118/124 (95.2%) in placebo.
Chinthrajah et al. 2019 (OIT)	Ph 2, SC, DB, PC, Randomized (2.4:1.4:1) 7 to 55 years of age	21/60 (35%) tolerated 4000 mg of peanut protein at week 104 and week 117.	Any AEs: Year 1: 57/60 (95%) in Peanut-0; 32/35 (91%) in Peanut-300; 16/25 (64%) in Placebo Year 2: 40/55 (73%) in Peanut-0; 20/31 (65%) in Peanut-300; 6/23 (26%) in Placebo Year 3: 1/51 (2%) in Peanut-0; 6/30 (20%) in Peanut-300; 1/20 (5%) in Placebo 95.4% in peanut-patch group had AEs vs 89% in placebo.
Fleischer et al. 2019 (EPIT)	Ph 3, MC, DB, PC Randomized (2:1) 4 to 11 years of age	84/238 (35.3%) were responders*	59.9% in peanut SLIT were symptom-free vs 99.4% in placebo
Fleischer et al. 2013 (SLIT)	MC, DB, PC Randomized (1:1) 12 to 37 years of age	14/20 (70%) were responders ^{&}	
Kim et al. 2019 (SLIT)	OL 1 to 11 years of age	32/48 (67%) tolerated 750 mg of peanut protein	3,599/75,366 (4.78%) doses were associated with symptoms
Tang et al. 2015 (PPOIT)	SC, DB, PC Randomized (1:1) 1 to 10 years of age	23/28 (82.1%) achieved sustained unresponsiveness [^]	14/31 (45.16%) in PPOIT had severe AEs vs 10/31 (32.26%) in placebo.
MacGinnitie et al. 2017 (anti-IgE + OIT)	Ph 2, MC, DB PC, Randomized (3.5:1) 7 to 25 years of age	23/29 (79%) were able to tolerate 2000 mg of peanut protein	4/28 (14.3%) in omalizumab had significant reactions vs 6/8 (75%) in placebo during the initial rapid desensitization state.

Abbreviations: AE, adverse event; DB, double-blinded; EPIT, epicutaneous immunotherapy; MC, multicenter; OIT, oral immunotherapy; OL, open label; PC, placebo-controlled; Ph, phase; PPOIT, probiotic and peanut oral immunotherapy; SC, single center; SLIT, sublingual immunotherapy.

* If pre-treatment eliciting dose $\leq$ 10 mg and post-treatment eliciting dose $\geq$ 300 mg.

OR if pre-treatment 10 mg $\leq$ eliciting dose $\leq$ 300 mg and post-treatment eliciting dose $\geq$ 1000 mg.

[&] Consumed 5 g of peanut powder or at least 10-fold more peanut powder than the baseline threshold.

[^] Participants have to pass double-blind, placebo-controlled food challenge (DBPCFC; cumulative dose of 4 g peanut protein) on the last day of study treatment (T1) and $\geq$ 2 weeks off the study treatment (T2).

phase involves rapidly increasing allergen doses every few hours during the initial part of the treatment. This phase is designed to shorten the next phase of treatment, the build-up phase. The build-up phase gradually increases the amount of allergen in 1 to 2-week intervals until the maximum dose is achieved. The maintenance phase begins once the target therapeutic dose is reached, and the dose is usually administered for a specified period of time.⁴

One OIT product that was approved in January 2020 is Palforzia [peanut (*arachis hypogaea*) allergen powder-dnfp], otherwise known as AR101. Palforzia [peanut (*arachis hypogaea*) allergen powder-dnfp] will be referred to as AR101 in this review. This product is by Aimmune Therapeutics and is the first Food and Drug Administration (FDA)-approved treatment for PA.⁷ AR101 gained Fast Track and Breakthrough Therapy designation by the FDA and was studied in 3 phase III trials (PALISADE, RAMSES, and ARTEMIS).^{8,9} PALISADE was the core trial studied in the United States, Canada and Europe, while RAMSES and ARTEMIS were supporting studies to gain further data in the real-world setting and Europe, respectively.⁹ The product is a formulation of oral peanut protein-capsules whose contents are intended to be emptied into age-appropriate, unheated foods, such as applesauce, for drug administration.^{8,10} AR101 is only available through a Risk Evaluation and Mitigation Strategy program due to the risk of anaphylaxis, with contraindications including uncontrolled asthma and a history of eosinophilic esophagitis or other eosinophilic gastrointestinal disease.¹⁰

The phase III double-blind, placebo-controlled, randomized trial of AR101 (PALISADE) was conducted in 499 children 4 to 17 years of age with PA. The study consisted of a rush phase, with an initial dose escalation from 0.5 mg to 6 mg depending on the individual's reactivity to an allergen; a build-up phase, during which the dose was increased gradually from 3 mg to 300 mg every 2 weeks; and a maintenance phase, in which the dose was 300 mg for 24 weeks. The primary efficacy endpoint was the proportion of participants who could ingest a single dose of at least 600 mg of peanut protein during the exit food challenge, without dose-limiting symptoms. At baseline, all participants displayed dose-limiting symptoms at the challenge dose of 100 mg or less (approximately one-third of a peanut kernel). At the end of the trial, a total of 67.2% of the active-drug group compared to 4.0% of placebo group passed an exit food challenge of at least 600 mg of peanut protein (approximately 2 whole peanut kernels). Fifty percent of these participants were able to tolerate the entire challenge of a 1000 mg single dose (approximately 3 or 4 peanut kernels). Excluding the events that occurred during the exit food challenge, 98.7% of the active-drug group compared to 95.2% of the placebo group had an adverse event during the intervention period. The most common adverse events were abdominal pain (52.2%, 24.2%), vomiting (41.4%, 24.2%), upper abdominal pain (40.9%, 21.0%), oral pruritus (40.6%, 16.1%), and nausea (39.2%, 23.4%) for active and placebo groups, respectively. Systemic allergic reactions, which included anaphylaxis as well as other clinically important systemic allergic reactions,

occurred in 53 of 372 participants (14.2%) in the active-drug group and 4 of 124 (3.2%) in the placebo group. Overall, AR101 increased the threshold dose for peanut exposure allergic symptoms compared to baseline, which translates into enhanced protection against accidental consumption of peanut and peanut-containing foods and a mitigation in the severity of allergic symptoms. However, these potential benefits must be weighed against the moderate risk for treatment-related adverse events.¹¹

Aimmune Therapeutics has an open-label, long-term safety extension study for participants who participated in a prior AR101 study (ARC008), with the study completion date in December 2024.¹² Furthermore, an independent single-site, double-blind, placebo-controlled, long-term phase II trial in Stanford (POISED) studied the safety and efficacy of peanut OIT for up to 156 weeks. In this study, 120 participants with PA aged 7 to 55 years (median: 11 years) were randomized into 3 groups (2.4:1.4:1), termed the peanut-0 (n = 60), peanut-300 (n = 35), and placebo groups (n = 25). The peanut-0 group received a 4000 mg dose of peanut build-up and maintenance through week 104, followed by avoidance for an additional 52 weeks. The peanut-300 group went through the same procedure up to week 104 as the peanut-0 group, but then continued 300 mg daily dosing for an additional 52 weeks (peanut-300 group). Lastly, the placebo group only received oat flour. The primary efficacy endpoint was the proportion of participants who passed the food challenge to a cumulative dose of 4000 mg at both 104 and 117 weeks, with results focused on comparing peanut-0 versus placebo groups. At week 104, 51 of 60 participants (85%) in the peanut-0 group, 29 of 35 participants (83%) in the peanut-300, and 1 of 25 (4%) in placebo group passed the peanut challenge. At week 117, 21 of 60 participants (35%) in the peanut-0 group versus 1 of 25 participants (4%) in the placebo group passed the 4000 mg peanut challenge (OR: 12.7, 95% CI: 1.8-554.8; p = 0.0024), reaching the primary efficacy endpoint. Even though there was a significant difference in a history of asthma between the peanut-0 and placebo groups (65% vs 88%; p = 0.013), the primary efficacy endpoint was still reached after the adjustment (OR: 13.4, 95% CI: 2.5-249.4; p = 0.015). Notably, even though there was no significant difference in success between the peanut-0 (35%) versus peanut-300 groups (54%) by week 117 (p = 0.086), all food challenges after week 117 showed that the peanut-0 group was significantly less likely to tolerate 4000 mg compared to the peanut-300 group. By week 156, 8 of 60 participants (13%) in the peanut-0 group were successful in tolerating the peanut challenge compared to 13 of 35 participants (37%) in the peanut-300 group (p = 0.010). The incidence rate of adverse events decreased by study year in all 3 groups, with adverse events primarily affecting gastrointestinal, skin, and respiratory systems. This study demonstrated that although OIT was able to desensitize people with PA to 4000 mg of peanut protein, discontinuation of peanut OIT, or even reducing the dose to 300 mg daily, decreased the tolerance to peanut protein over time.¹³

There are some additional considerations which limit the use of peanut OIT. A systemic review by Chu et al reported

that current peanut OIT approaches increase the likelihood of allergic reactions compared with allergen avoidance. Even though current peanut OIT regimens can achieve the immunological goal of desensitization, those outcomes may not necessarily translate into achieving clinical and patient-desired goals.¹⁴ Therefore, further studies focused on minimizing adverse effects, enhancing long-term efficacy, and selecting clinically-relevant endpoints may help establish OIT as a recommended treatment for PA.

Epicutaneous Immunotherapy

Epicutaneous immunotherapy (EPIT) is another form of immunotherapy which delivers peanut proteins on the skin to attenuate the PA reaction. A patch is applied to the skin daily to allow passive absorption of peanut allergen through skin pores to local dendritic cells. This formulation of immunotherapy is appealing due to its ease of administration and safety profile.¹⁵ The only EPIT product that is in clinical development for treatment of PA is Viaskin Peanut by DBV Technologies. It uses an allergen-adsorbed patch to deliver peanut protein through the epidermal layer and is being studied in ages 1 to 3, 4 to 11 and adolescents and adults.^{16,17} The company has Fast Track Breakthrough Therapy Designation from the FDA for the ages 4-11 group and has completed its phase III trials, PEPITES and REALISE, in this age category, with ongoing open-label extension studies (PEOPLE).¹⁷

In the pivotal phase III double-blind, placebo-controlled, randomized trial (PEPITES), 356 children (4-11 years) were randomized to either a 250 mcg peanut-patch or placebo patch. The primary endpoint was the percentage difference in responders between placebo and peanut patch after 12 months of treatment. A prespecified minimum of 15% as the lower bound of the 95% confidence interval (CI) in responder rate was necessary for a positive trial result. Responders were classified according to the subject's eliciting dose (ED) to food challenges at baseline and post-treatment: Post-treatment ED ≥ 300 mg for participants with a baseline ED ≤ 10 mg or post-treatment ED ≥ 1000 mg for participants with baseline ED > 10 mg. After 12 months of therapy, 84 of 238 participants (35.3%) in peanut-patch group compared to 16 of 118 participants (13.6%) were considered responders, difference 21.7% (95% CI: 12.4%-29.8%; $P < .001$). The incidence of treatment-emergent adverse events was 95.4% and 89% in peanut-patch and placebo patch groups, respectively. However, the adverse events that were specifically reported to be related to the patch were 59.7% and 34.7% in peanut-patch and placebo patch groups, respectively. Despite showing a 21.7% difference in treatment efficacy between peanut patch and placebo the Viaskin Peanut did not meet the lower bound of the CI threshold required for a positive trial result. Nevertheless, the product demonstrated a promising efficacy profile and additional research needs to be conducted to determine the clinical significance of not meeting the 15% minimum CI.¹⁸

Viaskin Peanut announced in October 2019 that the FDA accepted its resubmitted biological license application (BLA)

with a target action date by August 5, 2020. The initial BLA was withdrawn in December 2018 following comments from the FDA for more information on manufacturing processes and data controls.^{19,20} However, as of March 16, 2020, the FDA notified the company that due to questions regarding the product's efficacy and patch-site adhesion, the previously scheduled Allergenic Products Advisory Committee will no longer take place.²¹ There are no further updates from the FDA or DBV Technologies on how this may impact approval.

Sublingual Immunotherapy

Peanut sublingual immunotherapy (SLIT) has been investigated as another form of immunotherapy for PA due to its safety profile and simple route of administration, which involves holding a peanut protein solution under the tongue for 2 minutes before swallowing the solution.¹⁵ In a pilot study comparing peanut OIT with peanut SLIT, 21 participants ages 7 to 13 years were randomized 1:1 to either active SLIT/placebo OIT (3.7 mg/d) or active OIT/placebo SLIT (2000 mg/d) group. Even though the increased reaction threshold to peanut protein was significantly greater in the active OIT group (141- vs. 22-fold, $P = .01$) after 12 months of therapy, adverse reactions were more common with OIT (42.8% vs 9%, $P < .001$).²²

In the first multicenter, randomized, double-blind, placebo-controlled trial for peanut SLIT, 40 participants, ages 12 to 37 years (median: 15 years) were initially randomized 1:1 to either peanut or placebo SLIT therapy. At 44 weeks of SLIT therapy, 17 of 20 participants (70%) in the peanut SLIT group compared to 3 of 20 participants (15%) in the placebo group were able to successfully consume 5 g of peanut powder (approximately 2.5 g of peanut protein) or at least 10-fold more peanut powder than the baseline threshold, as measured through oral food challenge.^{23,24} After the original placebo-controlled study was complete, an open-label, long-term follow-up was conducted where participants from the placebo group crossed over to receive high-dose active peanut SLIT up to 3696 mcg/day and the original peanut SLIT group maintained the previous maximum dose of up to 1386 mcg/day and continued for up to 164 weeks. In the second year, 4 of 17 participants (23.5%) in the high-dose crossover group compared to 11 of 20 participants (55%) in the original peanut SLIT group were able to consume either 5 g of peanut powder or at least 10-fold more peanut powder than the baseline. In the third year, 2 of 17 participants (11.8%) in the high-dose crossover group and 2 of 20 participants (10%) in the original peanut SLIT group were able to consume 10 g of peanut powder after discontinuing peanut SLIT therapy for 8 weeks. In this long-term treatment with peanut SLIT, there was no significant difference in outcome between the 1386 and 3696 mcg/day treated groups. However, due to a high dropout rate, the final oral food challenge was only conducted on 5 and 9 participants in the high-dose crossover group and original peanut SLIT group, respectively. The most common reason for dropout in both the high-dose crossover group (6 participants) and the original peanut SLIT group (4 participants) was due to participant decision. Even though

the study had a high dropout rate, peanut SLIT induced a moderate level of desensitization with sustained unresponsiveness and a low rate of dose-related adverse reactions (18.3% in high-dose crossover group vs 18.1% in original peanut SLIT), with oropharyngeal symptoms being the vast majority.²⁴

In another open-label extension study to evaluate the long-term safety and efficacy of SLIT, 48 participants from 2 studies with PA aged 1 to 11 years underwent extended maintenance SLIT with 2 mg/d peanut protein for up to 3 to 5 years. Thirty-seven participants completed the protocol, with 32 subjects (67%) successfully consuming 750 mg or more of peanut protein during the food challenge. SLIT was overall well-tolerated, as only 3,599 of 75,366 (4.78%) total doses were associated with symptoms. The majority of symptoms in this study were self-resolved, with only 158 (0.21%) symptoms requiring antihistamines and none requiring epinephrine. However, 45 of 48 participants experienced at least 1 symptom.²⁵ These studies demonstrate that SLIT may also be a viable alternative for the treatment of PA with its comparable efficacy and safety.

Adjuvant Therapy

There have been studies to improve the efficacy and safety of OIT by administering bacterial adjuvant with OIT. In a trial that administered extensively hydrolyzed casein formula with the probiotic *Lactobacillus rhamnosus* GG (LGG), children with cow's milk allergy (CMA) had reduced incidence of other allergic manifestations and increased tolerance for CMA. It has been theorized that probiotics may have positive effects on the gut microbiota and modulate epigenetic changes on T_H1/T_H2 gene expression.²⁶ Therefore, a combined immunotherapy approach that integrates probiotic bacterial adjuvant with OIT may provide more sustained efficacy for OIT. This hypothesis was investigated for PA in a double-blind, placebo-controlled, randomized trial where 62 children were given PA probiotic *Lactobacillus rhamnosus* and peanut OIT for 18 months. After the treatment, participants underwent 2 stages of oral food challenge to assess sustained unresponsiveness, which was defined by ability to ingest 4 g of peanut protein after 2 or more weeks off the treatment. A total of 82.1% of the probiotic and peanut oral immunotherapy (PPOIT) group compared to 3.6% of the placebo group ($P < 0.001$) achieved sustained unresponsiveness.²⁷

Another adjuvant in peanut OIT to ensure efficacy and safety is the use of anti-IgE, which decreases the reactions during oral desensitization. Approved by the FDA in 2003, omalizumab is a subcutaneously administered anti-IgE that blocks the binding site for IgE receptors, decreasing free IgE concentration within a short period of time.^{28,29} Omalizumab decreases the incidence of asthma exacerbations as an add-on to existing treatments in patients 6 years of age and older with moderate to severe persistent, IgE-mediated asthma. Omalizumab is also indicated in adults and adolescents 12 years of age and older with chronic idiopathic urticaria who remain symptomatic despite H₁ antihistamine treatment. The dose and dosing frequency is based on the level of IgE in the blood and body

weight, with the indicated dose range between 75 and 375 mg every 2 or 4 weeks and 150 or 300 mg every 4 weeks for asthma and chronic idiopathic urticaria, respectively.^{29,30} Given omalizumab's place in therapy as an add-on treatment for IgE-mediated reactions, research is being conducted on its potential use in peanut immunotherapy as well.

In a small trial of 23 adolescents with PA in Sweden, individualized omalizumab treatment had effectively reduced sensitivity to peanuts. Fourteen out of 21 patients who completed the 2 peanut challenges had a 50-fold increase in the median ingested peanut dose.³¹ These results suggest that integrating omalizumab with OIT may enhance the efficacy and reduce the risk of side effects than OIT alone. This hypothesis was further tested in a phase II double-blind, placebo-controlled study consisting of 37 subjects with PA who received omalizumab in conjunction with peanut OIT. After 12 weeks of omalizumab treatment, participants were initiated with a rush phase, where subjects underwent a rapid desensitization up to 250 mg; a build-up phase, during which the dose was increased weekly up to 2000 mg; and a maintenance phase, during which the dose was 2000 mg. Omalizumab-treated subjects tolerated a median peanut dose of 250 mg during initial desensitization versus 22.5 mg for placebo-treated subjects ($p = 0.00027$). After discontinuing omalizumab for 6 weeks but remaining on peanut OIT, 79.3% of the omalizumab treated group was able to tolerate 2000 mg of peanut protein versus 12.5% of placebo-treated group (OR: 26.8, 95% CI: 2.7-262.3). These studies suggest that omalizumab allows rapid desensitization through OIT with sustained efficacy after omalizumab is discontinued.³²

More recent studies have investigated the efficacy and safety of dupilumab as an adjunct therapy to AR101. Dupilumab was approved by the FDA on 2017 as a subcutaneously administered interleukin-4 receptor alpha antagonist (IL-4RA) for the treatment of moderate-to-severe atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyposis.³³ Since blocking the interleukin-4 receptor inhibits interleukin-4 and interleukin-13, which are critical drivers of allergic inflammation, utilizing dupilumab may help with peanut OIT's desensitization approaches.^{33,34} There are currently ongoing studies for dupilumab as both adjunct for OIT and monotherapy in pediatric patients with PA, with results expected in 2021.^{35,36}

Cost Implications

With the approval and growing research on PA immunotherapies, a great deal of attention has now centered on whether these therapies are worth the safety risks, treatment burden, and cost. The Institute for Clinical and Economic Review (ICER) published a report in July 2019 investigating the cost-effectiveness of PA treatments AR101 oral immunotherapy and Viaskin Peanut. The report included evidence from randomized controlled trials in patients ages 4 to 17 for AR101, Viaskin Peanut, and other OIT. Comparing the trial designs of PALISADE (AR101) and PEPTIES (Viaskin Peanut), the report suggested that AR101 is likely to have higher treatment effects

than Viaskin Peanut but must be balanced with the disadvantages of greater treatment burden and potentially higher rates of adverse events. Limitations of this comparison were differences in inclusion criteria, adverse event categorizations, and desensitization protocols between the 2 treatments.³⁷

ICER also constructed a Markov model using PALISADE and PEPITES data to determine the long-term cost effectiveness of AR101 plus avoidance versus avoidance alone and Viaskin Peanut plus avoidance versus avoidance alone. The model used placeholder costs of \$350 per month for AR101 and \$6,500 per year for Viaskin Peanut.³⁷ [Note: The wholesale acquisition costs for Palforzia as of April 2020 are \$30 for the initial dose escalation pack, \$445 for each 2-week up-dosing level (\$4896 total for the 11 levels within 6 months), and \$890 for a monthly maintenance supply.³⁸] Base case results illustrated that AR101 produced 0.75 incremental quality-adjusted life years (QALY) compared with peanut avoidance alone and was calculated to have an incremental cost-effectiveness ratio of \$88,000. Viaskin Peanut resulted in 0.26 incremental QALYs and an incremental cost-effectiveness ratio of \$216,000 when compared to avoidance alone. In analyzing AR101's and Viaskin Peanut's potential budget impact, ICER issued an access and affordability alert for both products to warn key stakeholders that the added costs of the PA treatments may be difficult for the healthcare system to cover, as only 41% of AR101 and 71% of Viaskin Peanut eligible patients could be treated in a given year without crossing the ICER budget impact threshold of \$991 million. Likewise, a California Technology Assessment Forum panel voted unanimously that there was inadequate evidence to justify the net health benefit of AR101 and Viaskin Peanut.³⁷ Aimmune Therapeutics responded by arguing that ICER failed to incorporate data on long-term outcomes and QOL, and the panel failed to give adequate consideration of patient perspectives on the physical, social, and psychological burdens of PA.³⁹ The Asthma and Allergy Foundation of America agreed that the ICER review was premature and that appropriate treatment should be the decision of the patient and health care provider.⁴⁰ Other reviews have pointed out that ICER may have also biased the negative side effects of OIT by focusing on the Chu et al safety meta-analysis and by failing to distinguish treatment-associated versus accidental exposure-associated reactions, and induction/initial adverse effects versus long-term treatment from therapy.^{41,42} Additionally, one small systematic review argued that, contrary to ICER's report, existing studies have demonstrated improvements in QOL from OIT.⁴¹ Nonetheless, with more research on real-world long-term safety and effectiveness expected in the next few years, future data will likely elucidate peanut immunotherapy's place in therapy for clinicians, patients, and payers.

Another Markov cost analysis by Shaker et al showed that PPOIT had an incremental cost-effectiveness ratio of \$2,142 per QALY compared to a complete avoidance strategy. The simulation was conducted using PPOIT data from Tang et al. Nonetheless, the rate of allergic reactions was higher in PPOIT (mean: 12.3, 95% CI: 12.0-12.5) than placebo (mean 2.0, 95%

CI: 1.9-2.1). Sensitivity analysis indicated that lower rates of anaphylaxis with PPOIT are possible if the probability of sustained unresponsiveness after 4 years of PPOIT is $\geq 68\%$ or the rate of accidental reactions in the peanut avoidance group $\geq 25\%$ each year.⁴³ Both ICER and the Shaker et al analysis indicate that the cost-effectiveness of immunotherapy options are strongly dependent on their impact on QOL, reduction of anaphylaxis, and probability of sustained responsiveness.

Discussion

Given the increased prevalence of peanut allergies and its impact on QOL, there is a well-recognized need for novel therapies. However, there are several limitations to the role of current immunotherapies in PA treatment. Most of the trials were studied in the small pediatric population and did not show efficacy in groups that were older than 18 years, which suggests that the applicability of immunotherapy to adults is still unclear. Furthermore, even though current OIT may be effective in achieving immunological desensitization, the external validity of these outcomes remains unestablished. Utilizing in-clinic oral food challenges to assess the treatment efficacy may not accurately predict a patient's future risk and frequency of allergic reactions to peanuts in the real world.¹⁴ Additionally, both OIT and EPIT had a high rate of adverse reactions due to the inherent risk of intentional allergen exposure. While SLIT showed a relatively lower rate of adverse reactions, the treatment size was small compared to OIT and EPIT studies. Such significant adverse events associated with use can limit immunotherapy use in the real-world. Combination therapies with either probiotics or anti-IgE medications have shown an improved safety profile as well as sustained efficacy, but their role as immunotherapy adjuncts must be balanced with cost considerations for patients and payers.

Conclusion

As Palforzia was approved as the first immunotherapy for PA, other therapeutic options that are in different investigational stages may also be approved in the near future. Since each immunotherapy method offers a unique risk and benefit profile, it is important to evaluate each method before incorporating it into the standard of care. Overall, these therapies can address the unmet need for PA and the associated psychological burden of peanut avoidance on children and families. Nonetheless, the challenge for the future involves more research on the effect of immunotherapy on long-term desensitization, cost considerations, and the relative safety and efficacy for adult patients. Clinical considerations for engagement in these emerging therapies will depend on the age of the patient, the severity of the allergy, and the ability of the families to manage the condition or undergo treatment.

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ORCID iD

Thomas S. Hong  <https://orcid.org/0000-0002-4988-3209>

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