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FOOD ALLERGY (E KIM, SECTION EDITOR)

Could This Be IT? Epicutaneous, Sublingual, and Subcutaneous Immunotherapy for the Treatment of Food Allergies

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Abstract

Purpose of Review Over the last decade, there has been a spark in innovation in the development of therapies for food allergy. Herein, we describe the background and recent advances for food-specific immunotherapies including epicutaneous (EPIT), sublingual (SLIT), and subcutaneous (SCIT).

Recent Findings Studies have progressed most quickly for the treatment of peanut allergy. Data from the phase 3 EPIT trial add to the accumulating evidence that this will be a viable therapy for peanut allergy. Studies for SLIT and SCIT remain in earlier phases with promising results.

Summary This is an exciting era for the treatment of food allergy. Multiple therapies are under investigation, each with their own potential advantages. Specific strengths and limitations of each of these therapies may provide an opportunity to personalize the choice of therapy for individual patients.

Keywords Food allergy · Food hypersensitivity · Anaphylaxis · Peanut hypersensitivity · Nut and Peanut hypersensitivity

Abbreviations

APC	Antigen-presenting cell
DBPCFC	Double-blind, placebo-controlled food challenge
ED	Eliciting dose
EPIT	Epicutaneous immunotherapy
EVP	Epicutaneous Viaskin® Patch
IgE	Immunoglobulin E
IgG_4	Immunoglobulin G_4
IT	Immunotherapy
OIT	Oral immunotherapy
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
T_H1	T helper cell type 1
T_H2	T helper cell type 2
Treg	T regulatory cell

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Introduction

Food allergy is common, and studies suggest that the prevalence has increased over the past few decades [1]. It is now estimated that 15 million Americans are affected by food allergy, with children experiencing the highest burden [2]. This trend has emerged abroad as well, with a recent Australian study finding that greater than 10% of infants evaluated at age 1 year had food challenge-proven IgE-mediated food allergy [3].

The true impact of food allergy is far greater than this epidemiologic data. A 2009 UK study revealed that children with peanut allergy rated their physical health-related quality of life, quality of life within school, and general quality of life poorer compared to their siblings [4]. A 2010 study of adolescents and adults with food allergy in the Netherlands similarly revealed that these patients reported poorer health, more social limitations, and less vitality in comparison to the general population [5]. Additionally, children with food allergies and their families report significant anxiety about casual allergen exposure [6–8]. These fears can be exploited by bullies, and children with food allergy have reported experiencing malicious behavior including others waving the allergen in their face, having the allergen thrown at them, or having others intentionally contaminate food with an allergen [8, 9]. It is for these

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Table 1 Landmark Studies in the Development of EPIT, SLIT, and SCIT for Peanut Allergy. Key studies for each form of immunotherapy (IT)

Mode of IT	Study	Protocol	Findings
EPIT	Phase 1 *Jones* et al. [12]	Subjects were randomized 4:1 to apply EVP at doses of 20, 100, 250, and 500 μg or placebo for either 24- or 48-h intervals for 2 weeks ($n = 100$)	• The 24-h placement schedule demonstrated fewer local adverse effects
EPIT	Phase 2b *Jones et al. for* CoFAR [13•]	Participants were randomized to placebo, 100 μg patch, or 250 μg patch for 52 weeks ($n = 74$). Response was defined as (a) passing a 5044-mg peanut protein DBPCFC or (b) a 10-fold or more increase in successfully consumed dose.	• More EVP-treated participants achieved treatment success; this effect was more pronounced in younger children • EVP treatment was associated with increased peanut-specific IgG_4 and IgG_4/IgE ratios • Adverse reactions were more common in the active treatment group; majority were mild and confined to the patch site
EPIT	Phase 2b *Sampson et al.* [14•]	Participants were randomly assigned 1:1:1:1 to a 50 μg, 100 μg, 250 μg, or placebo patch with daily application for 12 months followed by open-label extension ($n = 221$). Treatment response was defined as ≥ 10-times increase in ED and/or successful ingestion of ≥ 1000 mg peanut protein.	• Treatment response was higher for subjects treated with the 250 μg peanut patch compared to placebo (50% vs 25%) • Treatment response was significant only in children in the age 6–11 year stratum • The response rate continued to increase during the 2 year open-label extension ($n = 171$; 59.7% after 12 months, 64.5% after 24 months) • Local patch reactions were more common in the active treatment group but diminished within 3 months for some
EPIT	PEPITES: Phase 3 *Fleischer et al.* [15••]	Subjects age 4–11 years were randomized 2:1 to daily application of a 250 μg patch or placebo ($n = 356$). Response was defined according to baseline ED: ≤ 10 mg: Increase to 300 mg or more. > 10–300 mg: Increase to 1000 mg or more.	• The response rate was 35.3% for the active group and 13.6% for the placebo group ($p < 0.001$) • Systemic reactions occurred infrequently (26 episodes of anaphylaxis in 23 patients) • Despite the difference in response, the statistical criteria for a positive trial were not met
SLIT	*Kim et al.* [16]	Children underwent 6 months of build-up starting with 0.25 μg of peanut protein followed by 6 months of maintenance with 2000 μg peanut protein with repeat DBPCFC at 12 months ($n = 18$)	• The actively treated participants successfully consumed 20 times more peanut protein than the placebo group (median 1710 vs 85 mg) • Immunologic changes included a decrease in skin prick test wheal size, an initial increase then decrease in peanut-specific IgE, an increase in peanut-specific IgG_4, and decreased basophil activation • Reactions were generally confined to the oropharynx and rarely required treatment with an antihistamine
SLIT	*Fleischer* et al. *for* CoFAR [17]	Participants were randomized 1:1 to daily peanut (started at 0.000165 μg peanut protein, maintenance 165–1386 μg) or placebo SLIT ($n = 40$). A repeat DBPCFC was performed at 44 weeks. An unblinded second phase of the study entailed an additional 120 weeks of SLIT for the active treatment group, and the placebo subjects crossed over to high-dose peanut SLIT (maximum maintenance dose 3696 μg) for 164 weeks. Response was defined as consuming the cumulative 5 g peanut powder dose or demonstrating a 10-fold increase in the amount consumed.	• At week 44, 14/20 (70%) actively treated subjects vs 3/20 (15%) placebo participants responded ($p < 0.001$) • For the peanut SLIT subjects, the median successfully consumed dose increased from 3.5 to 496 mg at week 44; this increased to 996 mg at week 68 • No subject who failed to respond at week 44 demonstrated response at week 68 • For placebo participants who crossed over to high-dose SLIT, 7/16 (44%) responded after 44 weeks; the median successfully consumed dose increased from 71 to 603 mg • Dose-related symptoms were generally mild and restricted to the oropharynx; one use of epinephrine was reported
SLIT	*Chin et al.* [18]	Retrospective study of subjects treated with SLIT ($n = 27$) or OIT ($n = 23$). The SLIT protocol involved 2 mg peanut protein daily doses for 12 months. The OIT protocol had a 4000 mg daily maintenance dose.	• SLIT subjects: 17/27 subjects (63%) tolerated 1000 mg peanut protein or more • OIT subjects: 17/18 (94%) tolerated 1000 mg or more (1 tolerated 3000 mg, 16 tolerated 5000 mg) • Subjects who passed the DBPCFC had lower baseline peanut IgE levels, a larger-fold increase in peanut IgG4, and less basophil activation • SLIT treatment was associated with increased peanut-specific IgG_4 and reduced basophil activation, but to a lesser degree than with OIT • No SLIT participants reported using epinephrine for dose-related reactions
SLIT	*Narisety et al.* [19]	Children were randomized to receive active SLIT/placebo OIT (maintenance 3.7 mg daily, $n = 9$)	• Active SLIT: The median cumulative dose threshold increased from 21 to 496 mg (at both 6 and 12 month DBPCFC)

Table 1 (continued)

Mode of IT	Study	Protocol	Findings
		or active OIT/placebo SLIT (maintenance 2000 mg daily, $n = 7$) for 12 months. After 12 months, there was an extension period when SLIT subjects were given the option to add-on OIT.	• Active OIT: The median cumulative dose threshold increased from 21 to 7246 mg (at both 6 and 12 month DBPCFC) • After the extension period, one SLIT subject with add-on OIT and 3 OIT subjects achieved sustained unresponsiveness • Adverse reactions were more common in the OIT group; 5 doses of epinephrine were administered to 4 OIT subjects
SCIT	Phase 1 Study of HAL-MPE1 *Bindslev-Jensen et al.* [20•] (Abstract)	15–20 weekly incremental subcutaneous doses of HAL-MPE1 ($n = 11$) vs placebo ($n = 6$)	• Subjects treated with HAL-MPE1 experienced more local reactions, but these were generally mild • Early systemic reactions and Grade I late systemic reactions were also reported • Participants showed increased IgG and IgG_4 levels for peanut, Ara h 1, Ara h 2, Ara h 3, and Ara h 6
SCIT	Murine Studies of Ara h1,2,3-LAMP--Vax *Li* et al. [21]	Mice were treated with intradermal Ara h1,2,3-LAMP-Vax or control vector for 4 weeks	• After treatment, mice had lower peanut-specific IgE and increased peanut-specific IgG2a • During challenge, mice had lower symptom scores, higher core body temperature, and lower plasma histamine level

psychosocial reasons, in addition to the medical benefits, that there is such keen interest in developing therapeutic options for patients with food allergies.

Immunotherapy involves the delivery of small amounts of allergen at regular intervals over months to years with the goal of achieving desensitization. It is hoped that with prolonged treatment, tolerance, or sustained unresponsiveness, can be attained. Even if tolerance cannot be achieved, it is thought that immunotherapy's effect to increase an individual's reaction threshold is clinically relevant for patients with food allergy. In a study by Baumert et al. using a model of US food consumption data and estimated peanut contamination, increasing the peanut threshold from a baseline of ≤ 100 mg peanut protein to 300 mg post-immunotherapy reduces the risk of experiencing an allergic reaction by 95% for most packaged foods that may contain traces of peanut [10•]. Further risk reduction was predicted for children who could achieve a threshold of 1000 mg or higher. A similar model using European consumption and peanut contamination data by Remington et al. suggested that the increase in peanut threshold achieved with immunotherapy was predicted to result in > 99% risk reduction for most potential sources of peanut cross-contact [11].

In recent years, there has been remarkable innovation in the development of immunotherapies for food allergy. The latest advances in oral immunotherapy (OIT) are discussed elsewhere in this issue. Herein, we review recent progress in the development of alternative modes of food-specific immunotherapy including epicutaneous (EPIT), sublingual (SLIT), and subcutaneous (SCIT). Key studies are highlighted for peanut allergy (Table 1) and cow's milk allergy (Table 2).

Epicutaneous Immunotherapy

Background

The first use of EPIT was reported in 1921 for the treatment of allergic asthma [26, 27]. This was followed by other scattered reports, but these efforts were largely abandoned as SCIT gained momentum. It was not until the early twenty-first century that interest in EPIT was revived, with the primary application of interest being food allergy.

Mechanism

Early epicutaneous approaches disrupted the outer layer of skin by scarification, adhesive tape stripping, or other methods of abrasion prior to allergen application to circumvent the low natural permeability of the stratum corneum [27]. While this enhanced allergen passage through the skin, it also induced a pro-inflammatory response concordant with current theories about the role of skin barrier function and cutaneous inflammation in the pathogenesis of food allergy [1, 2, 28–31]. Therefore, recent investigations of EPIT have sought to enhance allergen absorption by other means.

The primary EPIT product under investigation is the Epicutaneous Viaskin® Patch (EVP) (DBV Technologies, Paris, France). EVP is applied to intact skin, where the moisture created by natural transepidermal water loss dissolves lyophilized allergen protein on the patch surface [27, 31]. Additionally, the moist conditions increase the permeability of the stratum corneum and facilitate antigenic protein concentration near antigen-presenting cells (APCs). The epidermis is rich in Langerhans cells and other dendritic

cells, which actively capture allergen in the 24 h after patch placement [32–34]. APCs then deliver allergen to the draining lymph nodes and activate the immune response. With repeated application, T regulatory cells (Tregs) are induced; the T helper cell type 2 (T_H2) response is down-regulated; allergen-specific IgE decreases; and eosinophil recruitment to the skin after allergen exposure decreases [32, 34]. Induced Tregs include effector/memory and naïve (long-lived cells), and both Foxp3+ and LAP+/Foxp3− populations have been identified [35, 36]. EPIT-induced Tregs bear homing receptors for the skin (CLA), lung (CCR4), esophagus (CCR3), and gut (CCR9). It is thought that multi-organ protection from food allergy-induced anaphylaxis conferred by EPIT is due to this large repertoire of homing receptors and LAP+ Treg-mediated mast cell suppression via a TGF-β-dependent mechanism. The latter process may be critical for promoting tolerance. Because the epidermis is not vascularized, there is minimal systemic absorption and therefore reduced risk of systemic reactions [27].

Studies

Peanut

Investigation of EVP for the treatment of food allergy has progressed the furthest for peanut allergy. Initial studies in a murine model demonstrated similar efficacy to SCIT [32, 37]. In 2016, the results were published from a phase 1 study of 100 subjects with peanut allergy randomized 4:1 to apply EVP at doses of 20, 100, 250, and 500 μg or placebo for either 24- or 48-h intervals [12]. Subjects applied the patches to the upper arm or interscapular space of the back for 2 weeks and were monitored for one week of follow-up. The 24-h placement schedule demonstrated fewer local adverse effects.

Two phase 2b studies of EVP for peanut allergy have been published. In a multicenter, double-blind, placebo-controlled study, 74 peanut-allergic participants (age 4–25 years) were randomized to placebo, 100 μg patch (EVP100), or 250 μg patch (EVP250) [13•]. The primary outcome was treatment success at the end of the 52-week study period, defined as (1) passing a 5044 mg peanut protein double-blind placebo-controlled food challenge (DBPCFC) or (2) a 10-fold or greater increase in successfully consumed dose from baseline to week 52. Compared to placebo, more EVP-treated participants achieved treatment success (EVP100: $p = 0.005$, EVP250: $p = 0.003$); there was no difference between the EVP100 and EVP250 groups. Actively treated subjects were noted to demonstrate increased peanut-specific IgG_4 and IgG_4/IgE ratios, although no change in peanut-specific IgE was detected. There was a trend toward reduced basophil activation and peanut-specific T_H2 cytokines. Adverse reactions were reported in 14% of placebo- vs 79.8% of actively treated subjects ($p = 0.003$). Most reactions were confined to the patch site and mild in nature. One subject in the EVP100 group experienced systemic hives treated with an antihistamine. No epinephrine use was reported.

Results from a larger phase 2b study cohort were published in 2017 [14•]. In this double-blind, placebo-controlled trial, 221 peanut-allergic subjects age 6–55 years were enrolled in a 12-month study with 2-year open-label extension at 22 centers. Participants were randomly assigned 1:1:1:1 to a 50 μg, 100 μg, 250 μg, or placebo Viaskin® patch with daily application for 12 months. The primary endpoint was percentage of treatment responders; treatment response was defined as ≥ 10-times increase in eliciting dose (ED) and/or successful ingestion of ≥ 1000 mg peanut protein after 12 months of participation. Treatment response was higher for subjects treated with the 250 μg peanut patch compared to placebo (50% vs 25%, $p = 0.01$). No difference was observed for the 100 μg patch, and the 50 μg patch was not compared due to statistical testing hierarchical rules. A statistically significant response was identified only in children in the 6–11 year stratum (53.6% response vs 19.5% for placebo), with the caveat that the study was not designed to detect age-related differences. Following trial completion, 168 subjects participated in the 2-year open-label extension, and all were transitioned to the 250 μg patch. Participants underwent repeat DBPCFCs, with response rates of 59.7% after 12 months of extended therapy and 64.5% after 24 months of extended therapy. The response rates were slightly higher for children at both time points, at 63.3% and 68.4% respectively. These data suggested prolonged treatment might improve treatment response. Local patch reactions were more common in the active treatment group, but these diminished in the first 3 months of therapy for some. Generalized allergic reactions occurred in 25% of subjects, the majority of which were cutaneous reactions extending beyond the patch border. There was one case of moderate anaphylaxis possibly related to treatment.

The results from a phase 3, randomized, double-blind, placebo-controlled trial of EVP (PEPITES) were published in early 2019 [15••]. In this study conducted across 31 sites in 5 countries, 356 peanut-allergic subjects age 4–11 years were randomized 2:1 to daily application of a 250 μg Viaskin® patch or placebo. The primary outcome was the percentage difference in response between the active and placebo groups. Response was defined according to baseline ED. For participants with a baseline ED of ≤ 10 mg, an increase in the ED to 300 mg or more post-treatment was considered a response. For participants with a baseline ED of greater than 10 to 300 mg, response was defined as a post-treatment ED of 1000 mg or more. The response rate was 35.3% for the active group and 13.6% for the placebo group ($p < 0.001$). It was pre-specified that the trial would be considered positive if a threshold of 15% or more on the lower bound of a 95% confidence interval around the difference in response rate between active

Table 2 Summary of Key Studies in the Development of EPIT and SLIT for Milk Allergy

Mode of IT	Study	Protocol	Findings
EPIT	*Dupont et al.* [22]	Children age 3 months to 15 years were randomized 1:1 to a patch containing 1 mg skimmed cow's milk powder or placebo for a 3 month study period ($n = 18$)	• There was a trend toward improvement in the cumulative tolerated dose in the active treatment group, but this did not reach significance • It was suspected that 3 months was an insufficient treatment duration • Local reactions were more common in the active treatment group but were generally mild and did not impact adherence
EPIT	MILES: Phase 1/2 (Abstract) *Rutault et al.* [23]	Children age 2–17 years with cow's milk allergy were enrolled and randomized 2:1 to active patch (150 μg, 300 μg, or 500 μg cow's milk protein) vs placebo in 3 successive cohorts ($n = 18$)	• Local skin reactions were common • No epinephrine use was reported for dose-related adverse events • No efficacy data were published; study is ongoing
SLIT	*de Boissieu et al.* [24]	Children age 6–17 years were openly enrolled to start a SLIT protocol (starting dose 0.1 ml, maximum 1 ml (30 mg) daily dose) for 6 months ($n = 8$)	• Six subjects completed the trial • The mean ED increased to 143 ml (44–> 200 ml) • Three children went on to add milk to the diet without restriction at the end of the study; another did the same shortly thereafter • Half of subjects experienced side effects and one withdrew due to intolerable oral symptoms
SLIT	*Keet et al.* [25]	Children age 6–17 years were enrolled for SLIT ± add-on OIT. All initiated SLIT dose escalation to 3.7 mg milk protein. The SLIT-only group ($n = 10$) continued build-up to a goal dose of 7 mg daily. The participants who crossed over to OIT were further subdivided into SLIT/OIT-A ($n = 10$, goal dose 2000 mg daily) and SLIT/OIT-B ($n = 10$, goal dose 1000 mg daily) for a treatment period of 60 weeks.	• At week 60, 1/10 SLIT-only (10%), 8/10 SLIT/OIT-A (80%), and 6/10 SLIT/OIT-B (60%) subjects passed the 8 g challenge • The median increase in challenge threshold was 40-fold for SLIT-only, 54-fold for SLIT/OIT-A, and 159-fold for SLIT/OIT-B • A 10-times increase in challenge threshold was achieved for 60% of SLIT-only subjects compared to 90% of subjects in each SLIT/OIT group • To evaluate for sustained unresponsiveness, all 15 children who passed the 8 g challenge eliminated cow's milk; 6 subjects (all SLIT/OIT) regained reactivity, including 2 after just one week • Systemic reactions were more common with OIT than SLIT; epinephrine was used in 2 subjects who aspirated the SLIT dose and 4 times during OIT

patch and placebo was achieved. This threshold was not met, but the clinical relevance of this statistical metric is uncertain. The incidence of adverse reactions was similar between the two groups; these were mostly application site reactions and generally improved after the first month. Systemic reactions occurred infrequently (26 episodes of anaphylaxis in 23 patients) and were not severe in nature. No subject required greater than one dose of epinephrine. There were no adverse gastrointestinal effects noted. Separately, it was reported that subjects treated with the 250 μg peanut patch were calculated to have a 74.7–96.6% relative risk reduction for allergic reactions due to cross-contact exposures [38]. This was in contrast to the 2.5% risk reduction predicted for the placebo group.

Milk

The first study of EVP published in 2010 was for milk allergy [22]. In this double-blind, placebo-controlled study, 18 milk-allergic children age 3 months to 15 years with a baseline cumulative tolerated dose below 10 ml were randomized 1:1 to a patch containing 1 mg skimmed cow's milk powder or placebo. Patches were applied to the interscapular area for 48 h three times weekly during a 3 month study period. There was a trend toward improvement in the cumulative tolerated dose in the active treatment group, but this did not reach significance. This was attributed to insufficient treatment duration. Local reactions were more common in the active treatment group but were generally mild and did not impact adherence.

In 2016, preliminary safety results from a dose-finding phase 1/2 clinical trial were published [23]. Eighteen children age 2–17 years with cow's milk allergy were enrolled. In 3 successive cohorts, subjects were randomized 2:1 to active patch (150 μg, 300 μg, or 500 μg cow's milk protein) vs placebo. Local skin reactions were common; no epinephrine use was reported for dose-related adverse events. No efficacy

data were published. Phase 1/2 investigation of this product is ongoing (MILES, NCT02223182).

Pros/Cons

EPIT is a form of immunotherapy that obviates the need for ingestion of allergen, which some patients may find difficult. Home application and decreased frequency of medical follow-up may be more convenient for some families. The rate of systemic reactions is low, and there have been no reported cases of eosinophilic esophagitis (EoE). The favorable safety profile appears to come at the cost of a reduced magnitude of change in threshold.

Future Directions

With evidence that immunomodulation may be more effective in younger children, the EPITOPE study is currently evaluating EVP for peanut-allergic children age 1–3 years (NCT03211247). The effect of longer treatment duration is being explored as well. There is also interest in identifying biomarkers to bypass the need for oral food challenge to determine efficacy.

Additionally, animal models have provided evidence that EPIT may be effective for eosinophilic gastrointestinal diseases [39, 40]. A phase 2A pilot study evaluating EPIT for milk-induced EoE in 20 children age 4–17 years recently concluded (SMILEE, NCT02579876) [41]. Although no difference was observed in the intent-to-treat population, per-protocol analysis did reveal a lower mean eosinophil count in the active treatment group ($p = 0.038$). As such, the role of EPIT for the treatment of EoE remains unclear.

Sublingual Immunotherapy

Background

Sublingual immunotherapy (SLIT) involves application of a small amount of allergen in liquid or tablet form under the tongue [42]. The dose is held in position for a set period of time before being spit or swallowed. Dosing is started low and escalated until maintenance is achieved. Maintenance is generally continued for several years. Although SLIT is widely used for the treatment of allergic rhinitis in Europe, sublingual therapies have been FDA-approved for dust mite, grass, and ragweed allergies in just the last decade [43]. With the success in this realm, interest in the role of SLIT for the treatment of food allergy has been renewed.

Mechanism

Crucial to SLIT's efficacy is the administration of allergen at the site of the tolerogenic oral mucosa [44]. The oral mucosa contains a paucity of immune cells and is highly permeable to sublingual application of allergen [45, 46]. During SLIT, the allergen is captured by Langerhans-like dendritic cells [47]. These cells mature and migrate to nearby lymph nodes for antigen presentation to T cells, inducing a number of downstream immunologic changes [44]. These include an increase in FOXP3+ Tregs with a related increase in IL-10, a shift from a T_H2 to T helper cell type 1 (T_H1) inflammatory response, and an increase in the synthesis of allergen-specific IgG and IgA blocking antibodies.

Studies

Peanut

Kim et al. published the first trial of SLIT for peanut allergy [16]. In this double-blind, placebo-controlled study, 18 children age 1–11 years ($n = 11$ active, $n = 7$ placebo) underwent 6 months of build-up starting with 0.25 μg of peanut protein followed by 6 months of maintenance with 2000 μg peanut protein. Upon repeat DBPCFC at 12 months, the actively treated participants successfully consumed 20 times more peanut protein than the placebo group (median 1710 mg vs 85 mg, $p = 0.011$). Immunologic changes included a decrease in skin prick test wheal size ($p = 0.02$), an initial increase then decrease in peanut-specific IgE ($p = 0.003$), an increase in peanut-specific IgG_4 ($p = 0.014$), and decreased basophil activation ($p = 0.009$). Reactions in the active group were generally confined to the oropharynx, with 11/4182 (0.26%) peanut doses requiring treatment with an antihistamine. No epinephrine use was reported for dose-related reactions.

The NIH-sponsored Consortium of Food Allergy Research (CoFAR) led a multicenter study of SLIT for peanut allergy [17]. In this randomized, double-blind, placebo-controlled trial, 40 participants age 12–37 years underwent a baseline DBPCFC with objective allergic symptoms upon ingestion of ≤ 2 g peanut powder followed by 1:1 randomization to daily peanut or placebo SLIT. For subjects on active SLIT, dosing was started at 0.000165 μg peanut protein and escalated to a maintenance dose of 165–1386 μg. A repeat DBPCFC with 5 g peanut powder (~ 2.5 g peanut protein) was performed at 44 weeks. Afterward, an unblinded second phase of the study entailed an additional 120 weeks of SLIT for the initial active treatment group, and the placebo subjects crossed over to high-dose peanut SLIT (maximum maintenance dose 3696 μg) for 164 weeks. Responders were defined as those who could consume the cumulative 5 g peanut powder dose or demonstrated a 10-fold increase in the amount of peanut powder consumed

compared to the baseline DBPCFC without dose-limiting symptoms. At the week 44 DBPCFC, 14/20 (70%) actively treated subjects vs 3/20 (15%) placebo participants were responders ($p < 0.001$). For responders in the active group, the median successfully consumed dose increased from 3.5 to 496 mg. At a week 68 DBPCFC, the median successfully consumed dose increased further to 996 mg, which achieved statistical significance compared to week 44 ($p = 0.05$) and baseline ($p = 0.009$). No subject who failed to respond at week 44 demonstrated response at week 68. For the participants who crossed over from placebo to high-dose SLIT, a week 88 DBPCFC (after 44 weeks of active treatment) was performed, and 7/16 subjects (44%) responded. The median successfully consumed dose increased from a baseline of 71 to 603 mg ($p = 0.02$). Most dose-related symptoms were mild and restricted to the oropharynx. One subject used epinephrine for a suspected dose-related reaction involving urticaria and coughing.

In 2013, Chin et al. published the results of a retrospective study of the outcomes of subjects treated with SLIT ($n = 27$) and then compared them to OIT ($n = 23$) [18]. The SLIT protocol involved daily 2 mg peanut protein doses. After 12 months of SLIT, 17/27 subjects (63%) tolerated 1000 mg peanut protein or more. Among OIT subjects (4000 mg daily maintenance), 17/18 (94%) tolerated 1000 mg or more (one tolerated 3000 mg and 16 tolerated 5000 mg). It was calculated that OIT-treated subjects were 3 times more likely to pass the 12 month DBPCFC than SLIT-treated participants. Subjects who passed the DBPCFC had lower baseline peanut IgE levels, a larger-fold increase in peanut IgG4, and less basophil activation at 12 months. SLIT treatment was associated with increased peanut-specific IgG4 and reduced basophil activation, but more substantial changes were seen with OIT. No SLIT participants reported using epinephrine for dose-related reactions, but 2 OIT subjects (one active, one placebo) required a total of 4 doses of epinephrine. Although this was not a randomized study, these results suggested that clinical outcomes and immunologic changes induced by OIT treatment are greater than for SLIT.

In a double-blind study by Narisety et al., 21 peanut-allergic children age 7–13 years were randomized to receive active SLIT/placebo OIT or active OIT/placebo SLIT [19]. The SLIT maintenance dose was 3.7 mg daily, and the OIT maintenance dose was 2000 mg daily. Five subjects withdrew (one SLIT, four OIT), with 16 subjects (9 active SLIT, 7 active OIT) undergoing 12 month DBPCFC. The increase in median cumulative challenge threshold was higher for the active OIT subjects compared to the active SLIT participants at both 6 ($p = 0.009$) and 12 months ($p = 0.01$). For the active SLIT subjects, the median cumulative dose increased from a baseline of 21 to 496 mg at 6 and 12 months. For the active OIT subjects, there was an increase from baseline 21 to 7246 mg at 6 and 12 months. Following this challenge, the active SLIT subjects were given the option to add-on OIT. At the conclusion of the extension period, one SLIT subject with add-on OIT and 3 OIT subjects achieved sustained unresponsiveness ($p = 0.59$). Adverse reactions were more common in the OIT group ($p < 0.001$). Antihistamine use for dose-related symptoms was reported for 40.9% of OIT doses and 23.1% of SLIT doses ($p < 0.001$). Five doses of epinephrine were administered to 4 subjects in the OIT group (one during build-up, 4 during maintenance). These results suggested that when comparing SLIT and OIT, OIT showed greater efficacy in increasing the reaction threshold but higher rates of adverse reactions.

Milk

The first study of SLIT for food allergy was conducted by de Boissieu et al. for milk allergy [24]. In this open-label study, 8 children age 6–17 years were enrolled and underwent an initial milk oral food challenge to determine the ED. Participants then began the SLIT protocol, which entailed placing a dose of cow's milk in the mouth for 2 min daily. The starting dose was 0.1 ml for the first two weeks, and this was increased by 0.1 ml every 15 days until reaching a maximum 1 ml (30 mg) daily dose. The total duration of therapy was 6 months. Six subjects completed the trial; one discontinued due to local oral symptoms and one had poor compliance. The mean ED increased to 143 ml (range 44 to > 200 ml, $p < 0.01$). Three of the children went on to add milk to the diet without restriction at the end of the study, with another child noted to do so shortly thereafter. No significant adverse events were noted, but half of subjects experienced side effects and one withdrew due to intolerable oral symptoms.

In 2012, Keet et al. compared SLIT alone vs sequential treatment with SLIT then OIT for cow's milk allergy [25]. Thirty children age 6–17 years were enrolled, and all underwent a screening DBPCFC before initiating SLIT dose escalation to 3.7 mg milk protein. The SLIT-only group continued build-up to a goal dose of 7 mg daily. The participants who crossed over to OIT were further subdivided into SLIT/OIT-A (goal dose 2000 mg daily) and SLIT/OIT-B (goal dose 1000 mg daily). After 60 weeks, 1/10 SLIT-only (10%), 8/10 SLIT/OIT-A (80%), and 6/10 SLIT/OIT-B (60%) subjects passed the 8 g challenge ($p = 0.002$). The median increase in challenge threshold was 40-fold for SLIT-only, 54-fold for SLIT/OIT-A, and 159-fold for SLIT/OIT-B. A 10 times increase in challenge threshold compared to baseline was achieved for 60% of SLIT-only subjects compared to 90% of subjects in each SLIT/OIT group ($p = 0.53$). To evaluate for sustained unresponsiveness, all 15 children again eliminated cow's milk with a plan to re-challenge at 1 and 6 weeks. Six subjects (3 SLIT/OIT-A, 3 SLIT/OIT-B) regained reactivity, including 2 after just one week of avoidance. Systemic reactions were more common with OIT than SLIT ($p < 0.001$). Epinephrine was used in 2 subjects who

aspirated the SLIT dose and 4 times during OIT (one during build-up, one during maintenance, twice for possible accidental ingestions). These data were felt to show that OIT was more efficacious than SLIT for desensitization to cow's milk but was associated with more systemic side effects. Desensitization was not well sustained in this study.

Hazelnut

In the only trial published for hazelnut, Enrique et al. performed a randomized, double-blind, placebo-controlled study of SLIT vs placebo for 23 subjects (age 18–60 years) [48]. Twenty-two subjects achieved maintenance after a 4 day rush SLIT protocol. DBPCFCs were performed after 8–12 weeks of treatment. For the active treatment group, the mean ED increased from 2.29 to 11.56 g ($p = 0.02$), and almost half of subjects reached the maximum 20 g dose. This effect was not seen in the placebo group. The active group exhibited increases in mean IgG_4 (but not hazelnut-specific IgG_4) and IL-10. Systemic reactions were noted for 0.2% of doses, all during build-up. No epinephrine use was reported. Notably, this study included patients with both true hazelnut allergy and pollen-food allergy syndrome, limiting the generalizability of the findings.

Pros/Cons

SLIT has several potential advantages. The route of administration capitalizes on the tolerogenic oral environment. Additionally, the administration of whole antigen with all epitopes intact (no degradation by digestion) could facilitate a more complete immune response. Systemic reactions are rare, and no cases of EoE associated with SLIT for the treatment of food allergy have been reported [49].

A disadvantage of SLIT is that the dosing is limited by the volume that can be held under the tongue. This limitation may contribute to the reduced magnitude of clinical and laboratory changes observed with SLIT compared to OIT.

Future Directions

The reported studies of SLIT are early phase with small numbers of patients. Although the data remain limited, studies comparing SLIT and OIT suggest that SLIT may have a role not only as a stand-alone therapy, but as an initial desensitizing therapy to mitigate side effects, followed by OIT for maximum desensitization effect. Additional reports on experiences with a larger number of patients will be critical for elucidating the role of SLIT for the treatment of food allergies. There is an ongoing phase 2 study of SLIT for peanut allergy (NCT02304991).

Subcutaneous Immunotherapy

Background

Subcutaneous immunotherapy (SCIT) was first used over 100 years ago [50]. It is now widely implemented for the treatment of venom and environmental allergies [51]. Because of SCIT's efficacy for these conditions, there was great hope that SCIT could benefit patients with food allergies, specifically peanut allergy. Unfortunately, due to the potent allergenicity of peanut, early attempts at SCIT using aqueous peanut extract were met with a high rate of systemic reactions, and one study terminated early due to a fatality [52–54]. In the last decade, there has been renewed interest in SCIT for food allergy, employing innovative approaches to improve safety.

Mechanism

After injection, antigen is taken up by immature subcutaneous dendritic cells [55, 56]. These dendritic cells migrate to local lymph nodes, where tolerogenic dendritic cells induce development of Tregs. This ultimately leads to Treg-mediated suppression of T_H2 immune responses.

The use of SCIT for food allergy has been focused on patients with peanut allergy. To attenuate the potent allergenicity of peanut, the two types of peanut vaccines under investigation include: (1) a recombinant aluminum hydroxide-adsorbed vaccine (HAL-MPE1), (2) a DNA vaccine (ASP0892).

HAL-MPE1 is a chemically modified, aluminum hydroxide-adsorbed peanut extract for subcutaneous administration [57]. Integral to the development was the realization that Ara h 2 and Ara h 6 are potently allergenic and associated with systemic allergic reactions [58–61]. To improve the safety profile of HAL-MPE1, the three-dimensional structure of Ara h 2 and Ara h 6 proteins in peanut extract was altered by chemical modification; Ara h 1 and Ara h 3 were less affected [57]. Although incompletely understood, aluminum hydroxide is thought to act as an adjuvant by functioning as a depot, permitting the slow release of antigen and therefore continuous antigen presentation [62]. It has also been shown to down-regulate the T_H2 response and promote a T_H1 response and may block IgE-binding peanut epitopes [55, 57].

A DNA vaccine is a bacterial plasmid vector expressing the gene for an antigenic protein of interest. First developed in the 1990s, DNA vaccines have been found to be a relatively simple and efficient method of inducing humoral and cellular immunity [63–65]. Lysosomal-associated membrane protein-1 (LAMP-1) is a resident lysosomal protein, and inclusion of the sequence for LAMP-1 in DNA plasmids has been demonstrated to enhance the immunogenicity of the desired antigen and elicit a T_H1 response [66, 67]. Following administration, APCs take up the vector, which

translates DNA into allergen associated with LAMP-1. The first DNA-LAMP vaccine reported for the treatment of patients with allergies was targeted to the Japanese Red Cedar. ASP0892 is a multivalent peanut (Ara h 1, Ara h 2, Ara h 3) LAMP-DNA plasmid vaccine intended for intradermal or subcutaneous administration.

Studies

HAL-MPE1

Preliminary findings from the first human study of HAL-MPE1 were published in 2017 [20•]. In this randomized, double-blind, placebo-controlled phase 1 study, 17 peanut-allergic subjects were randomized to receive 15–20 weekly incremental subcutaneous doses of HAL-MPE1 ($n = 11$) vs placebo ($n = 6$). Subjects treated with HAL-MPE1 were more likely to experience early and late local reactions, but these were generally mild, involving local erythema with no wheal sizes > 5 cm. Early systemic reactions and Grade I late systemic reactions were reported in the active treatment group. The HAL-MPE1-treated participants showed increased IgG and IgG_4 levels for peanut, Ara h 1, Ara h 2, Ara h 3, and Ara h 6. There was also a trend toward reduced basophil histamine release. These results demonstrated tolerability and possible efficacy of HAL-MPE1. Enrollment in a larger phase 1 study has completed (NCT02991885), and follow-up is ongoing.

ASP0892

In 2015, Li et al. published the results of a murine study on the effects of an Ara h1,2,3-LAMP-Vax [21]. C3H/HeJ mice were sensitized to peanut and then treated with intradermal Ara h1,2,3-LAMP-Vax or control vector for 4 weeks. They then underwent peanut challenge 3 weeks later. The vaccine-treated mice were noted to have 70% lower peanut-specific IgE ($p < 0.05$) and increased peanut-specific IgG2a ($p < 0.02$). The vaccine-treated mice also had lower symptom scores, higher core body temperature, and lower plasma histamine level after challenge. These data suggested that Ara h1,2,3-LAMP-Vax provided protection against anaphylaxis in peanut-allergic mice. A phase 1, randomized placebo-controlled trial of ASP0892 for intradermal or intramuscular administration in adults recently completed enrollment (NCT02851277). There is an ongoing trial evaluating intradermal administration in adolescents (NCT03755713).

Pros/Cons

SCIT is a safe and effective therapy for venom allergy and allergic conditions driven by environmental allergens. For this reason, it is recognized to have great potential for the treatment of food allergy. Although initial studies yielded discouraging results with a high rate of systemic reactions, recent innovations in the field have improved the safety profile of SCIT for peanut allergy.

If effective, SCIT has many potential advantages. In-office administration may improve the comfort of patients and their families who are apprehensive about the emergency management of dose-related reactions with home dosing for other forms of immunotherapy. Additionally, some may prefer administration every 1–2 weeks (rather than daily as for other modes of immunotherapy).

A potential disadvantage of SCIT is that systemic reactions are not uncommon in patients undergoing treatment for venom and environmental allergies [51, 68]. It is not known if the rate of systemic reactions will be similar when used for food allergy or how this compares to other forms of immunotherapy. Additionally, with regard to HAL-MPE1, some hesitation about the use of aluminum salts has been reported [69]. Specifically, it is feared this may initially enhance allergen-specific IgE antibodies with the effect of exaggerating adverse effects of SCIT until allergen-specific IgG antibodies increase [70, 71]. Prolonged exposure to aluminum salts as would occur with a traditional multi-year SCIT schedule is another concern to be addressed.

Future Directions

Investigational studies of HAL-MPE1 and ASP0892 remain in the early stages. Further safety and efficacy data are required to evaluate whether SCIT employing recombinant or DNA vaccines will prove a viable therapy for food allergy. Pepsin-digested and peptide vaccines are also being investigated for peanut and cashew allergy [72–75]. These remain in the nascent stages of development. A cashew DNA-LAMP vaccine is being studied in mice [76].

Conclusions

Patients with food allergy and their loved ones have great reason to be optimistic. With many families desiring proactive options to prevent reactions to trace amounts of allergen, the recent advances in the development of EPIT, SLIT, and SCIT hold great promise for the future [77]. Each of these modes of immunotherapy possesses unique strengths and limitations, and it appears likely that the efficacy and safety profile of each method of immunotherapy will provide an opportunity to personalize the choice of treatment for the individual patient.

Compliance with Ethical Standards

Conflict of Interest Dr. Wang received research support from NIAID, Aimmune, DBV Therapeutics, Regeneron; consultancy fees from ALK Abello and DBV Technologies; and royalties from UpToDate.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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