

Oral Immunotherapy, Sublingual Immunotherapy, or Epicutaneous Immunotherapy: Which Is the Right Solution?

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Opinion statement

The current standard of care treatment for food allergy relies on avoidance. However, as outlined in this review, over the past decade, the literature has grown significantly showing promising results for interventional therapies for IgE-mediated food allergies utilizing oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT). Within the near future, we expect to have multiple FDA-approved products on the market for treatment of life-threatening food allergies and will have options to present to our patients. As we move into this next phase of our practice, we will need to consider meaningful endpoints for our patients (e.g., likelihood of inducing desensitization versus sustained unresponsiveness, the relevance of various threshold changes induced by therapy, effects on quality of life, etc.). This review provides a comprehensive overview of the currently published literature and will prepare the practicing allergist for a thoughtful discussion with their patients and colleagues on the most recent developments in the field.

Introduction

Food allergy is a common condition with an increasing prevalence in the USA, particularly over the past two decades [1]. Approximately 8% of children and 5% of adults in the USA have a food allergy [2]. Food allergy is typically outgrown, though allergies to foods like peanut, tree nuts, fish, and shellfish tend to be lifelong for the majority of affected individuals [3, 4]. The current consensus guidelines recommend strict allergen avoidance and use of emergency medications with accidental exposure [4]. With no cure, food-allergic individuals face the constant risk of a life-threatening reaction. Food-allergic children and their parents experience significant anxiety leading to restriction of daily activities and decreased quality of life [5, 6]. Furthermore, food allergen avoidance can compromise vital nutrition in growing children [7]. Over the past decade, food immunotherapy has emerged as an investigational therapy for the treatment of food allergy. The first reported use of food as an immunotherapy in 1905 utilized oral desensitization to treat milk allergy and then reports of oral desensitization for egg allergy in 1908 and 1912 [8–10]. Later, in the 1920s, subcutaneous immunotherapy was introduced to treat egg allergy [11].

Subcutaneous immunotherapy was further described for fish allergy in the 1930s [12]. Oral, sublingual, and epicutaneous immunotherapies have shown the most promise as potential vehicles for desensitizing allergic individuals for a variety of food allergies.

This review focuses on the recent developments in oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT). OIT is the most well studied, and the majority of research has focused on its utility in treating peanut, egg, and milk allergies along with recent reports in treating multifood allergic individuals. Literature supporting SLIT is less substantial than that with OIT, and EPIT for treatment of food allergy is currently in the very early stages of investigation. The primary endpoint of treatment regardless of the modality used is variable, but most studies have focused on the outcome of desensitization with few measuring sustained unresponsiveness (SU). Desensitization is defined as an absence of symptoms while the patient continues to consume an allergenic food at regular intervals. SU is achieved when the formerly allergic individual does not develop symptoms of an allergic reaction when consuming an allergenic food despite cessation of ingestion at regular intervals [13].

Treatment options

Oral immunotherapy (OIT)

OIT is an immunomodulatory treatment that involves repeatedly consuming an allergen mixed into a vehicle food beginning with a dose that is unlikely to trigger a reaction and gradually increasing the amount ingested over a period of weeks to months. The majority of OIT protocols consist of an initial escalation phase, followed by a dose-buildup phase, followed by a maintenance phase. During the dose-buildup phase, doses are gradually increased to reach a target dose or the maximum dose tolerated by the subject. These increases typically occur on a weekly or biweekly basis. The target maintenance dose varies by protocol. The variability amongst published OIT protocols impairs head-to-head comparison between studies; however, studies investigating peanut, egg, and milk OIT have shown between 50 and 90% of allergic individuals are able to achieve the primary study outcome, typically desensitization, regardless of the food administered (see Table 1).

Peanut OIT

Peanut allergy affects 1.5–3% of all children and has been studied in numerous OIT trials [26]. The first open-label, uncontrolled peanut OIT trial enrolled 39

Table 1. Oral immunotherapy trials

Study	Type	Sample size	Maintenance dose (protein)	Duration	OFC dose (protein)	Outcomes
<i>Peanut</i>						
Jones et al. [14]	Open label	39	1800 mg	36 months	3.9 g	93% (27/29) desensitized
Vickery et al. [15•]	Follow-up to Jones et al.	24			5 g	50% (12/24) achieved 4-week SU
Varshney et al. [16••]	Randomized DBPC	28	4000 mg	12 months	5 g	100% (16/16) desensitized
Anagnostou et al. [17]	Prospective cohort	22	800 mg	8 months	6.6 g	64% (14/22) desensitized
Anagnostou et al. [18]	Randomized controlled crossover	85	800 mg	6 months	1.4 g	62% (24/39) initial OIT group and 54% (25/46) crossover OIT group desensitized
Blumchen et al. [19]	Open label	22	500 mg	2 months	≥0.5 g	79% (11/14) passed OFC after 2 weeks off therapy; 77% (17/22) did not reach goal dose on 7-day rush protocol
<i>Egg</i>						
Burks et al. [20]	Randomized DBPC	55	2000 mg	10/22 months	4 g/8 g ^a	55% (22/40) desensitized at 10 months, 75% (30/40) desensitized at 22 months, 28% (11/40) achieved 8-week SU
Jones et al. [21]	Follow-up to Burks et al.	40		24–48 months	8 g ^a + 1 whole cooked egg	50% (20/40) achieved 4-week SU by year 4
<i>Milk</i>						
Meglio et al. [22]	Open label	21	6600 mg ^b	6 months	6.6 g ^b	71% (15/21) desensitized
Longo et al. [23]	Open label	60	5000 mg ^b	12 months	5 g ^b	36% (11/30) desensitized, 54% (16/30) partially desensitized to ≥160 mg
Skripak et al. [24]	Randomized DBPC	19	500 mg	5–6 months	2.5 g	Median tolerated dose 5140 mg in active group (12 subjects)
Narisety et al. [25]	Follow-up to Skripak et al.	15	500–4000 mg	3–19 months	16 g	40% (6/15) desensitized; 46% (7/15) desensitized to ≥3 g

^a10 g egg-white powder = 8 g egg-white protein

^b200 mL cow's milk = 6.6 g cow's milk protein; 150 mL cow's milk = 5 g cow's milk protein

young children (median age 57.5 months) [14]. In this study published by Jones et al., 27 of 29 subjects were able to ingest 3.9 g peanut protein (1 peanut = ~260 mg peanut protein) during an exit oral food challenge (OFC) after 36 months of therapy building up to an 1800-mg maintenance dose. This sentinel study demonstrated successful desensitization as well as significant immunomodulation. After only 3 months of treatment, significant increases were noted in peanut-specific IgE, peanut-specific IgG, and peanut-specific IgG₄. Basophil activation was significantly reduced after 4 months of therapy. Skin prick test (SPT) wheal diameters decreased significantly by 6 months, and FoxP3 regulatory T cells increased 1.5-fold at 6 and 12 months. Importantly, the authors also reported that though more than 90% of the participants experienced a treatment-related side effect, the large majority were mild and few (3.5%) and occurred with home dosing [14, 27].

The same subjects reported by Jones et al. were followed up to 5 years and the results of SU were reported by Vickery et al. [14, 15•]. Twenty-four of the original subjects completed the protocol. SU was measured 4 weeks after discontinuation of OIT by passing a 5000-mg double-blind placebo-controlled food challenge (DBPCFC) and then an open OFC of 8000–10,000 mg peanut protein on the same day [15•]. Twelve of the original 24 subjects achieved 4-week SU. These responders exhibited smaller SPT wheal diameters at baseline (9 vs 14 mm). Mean SPT wheal diameters decreased after OIT and endured after stopping OIT. Treatment-success subjects also had lower median peanut-specific IgE, Ara h 1, and Ara h 2. All subjects demonstrated a significant reduction in peanut-specific IgE to total IgE ratio after OIT, though more pronounced in the subjects who achieved 4-week SU. This landmark study demonstrated that peanut OIT could achieve 4-week SU with 50% efficacy, particularly in those with a milder phenotype of peanut allergy.

Varshney et al. demonstrated desensitization and immunomodulation in the first randomized, double-blind, placebo-controlled trial, in which 16 subjects were able to ingest 5000 mg peanut protein after building up to a 4000-mg maintenance dose of OIT in comparison to the placebo group whose median cumulative dose at exit DBPCFC was 280 mg peanut protein [16••]. The OIT group showed significant decreases in SPT wheal diameter (from 7 to 1.75 mm), IL-5, and IL-13 and increases in peanut-specific IgG and IgG₄. OIT subjects also demonstrated an increased ratio of FoxP3^{hi}:FoxP3^{intermediate} CD4 + CD25+ T cells at the time of OFC.

Anagnostou et al. have reported similar outcomes to those mentioned above, though utilizing a lower maintenance dose [17, 18]. Their initial study reported increased peanut tolerance in a prospective cohort of 22 subjects receiving a daily maintenance dose of 800 mg peanut protein [17]. In 14 of 22 subjects, 6.6 g peanut protein was tolerated after 32 weeks of OIT. This work was followed by the STOP II trial, a randomized controlled crossover trial also utilizing an 800-mg maintenance dose, and this trial included a comparison group who did not receive treatment [18]. In phase 1 of this large trial, 24 of 39 underwent successful desensitization defined by negative peanut challenge of 1400 mg protein at 6 months in comparison to 0 of 46 of the control group. In phase 2, 46 control subjects subsequently received OIT and 25 of 46 achieved desensitization with 42 of 46 able to tolerate daily ingestion of 800 mg peanut protein. After 24 weeks of OIT, there was a significant reduction in median SPT wheal diameter and an increase in peanut-specific IgE. Basophil stimulation test

data showed no differences within individual patients, but there was an overall reduction in mean fluorescent intensity and proportion of CD63-positive cells at low peanut concentrations after OIT. There was also a significant improvement in quality-of-life scores after OIT.

Most trials have followed similar buildup protocols; however, in 2010, Blumchen et al. reported results from a 7-day rush escalation protocol to achieve a maintenance dose of 500-mg whole crushed peanuts (~125 mg peanut protein) in 22 children [19]. However, 17 of 22 patients did not reach 500 mg after the rush protocol. Ultimately, 14 of 22 patients reached the goal maintenance dose. At the final DBPCFC after an 8-week maintenance phase and 2 weeks off OIT, 3 of 14 patients tolerated the same amount of peanuts as during maintenance. Additionally, 8 of 14 patients tolerated a higher dose than their previous maintenance, and only three patients tolerated less than their maintenance dose indicating a breakthrough in their maintained desensitization once off therapy.

Egg OIT

Egg allergy affects 0.5–2.5% of children and tolerance often develops with age in the majority of patients [28]. However, egg is a ubiquitous ingredient that is particularly difficult to avoid. Burks et al. published a randomized, multicenter, DBPC egg OIT study with 55 children ages 5–11 years using a 2-g daily maintenance dose, similar to the median dose previously reported by Vickery et al. [20, 29]. In the OIT group, 22 of 40 were desensitized at 10 months (cumulative 5-g dose) versus 0 of 15 in the placebo group. At 22 months, 30 of 40 of the OIT group were desensitized, passing a 10-g egg-white powder OFC. Furthermore, 11 of 40 OIT subjects achieved SU and continued consuming egg up to 12 months after completing OIT.

A long-term follow-up of the same subjects was published recently [21]. By the fourth year of egg OIT, 20 of 40 patients achieved 4-week SU. OIT dosing extended into years 3 and 4 for 22 subjects. Of the 18 subjects who achieved 4-week SU and responded to the questionnaires, all 18 reported consumption of baked and unbaked eggs at study conclusion and 1 year later. Subjects achieving SU had significantly lower egg SPT and endpoint titration SPT measurements and greater egg IgG₄ levels over time. Longer duration of egg OIT increased the rate of 4-week SU to 50%, comparable to that of peanut OIT; however, more prominently, it increased the number of subjects incorporating egg in their diet.

Milk OIT

Cow's milk allergy is the most common food allergy in children. The majority of children develop tolerance naturally; however, for some affected individuals, cow's milk allergy may persist, and the likelihood of developing tolerance diminishes with persistent symptomatic sensitization [30, 31]. In 2004, a pilot study with 21 children achieved desensitization in 71% of participants with a daily intake of 200 mL cow's milk over 6 months [22]. Desensitization rates were further elucidated in a large, randomized open-label trial by Longo et al. [23]. While this study found a lower desensitization rate of 36% in OIT subjects and lower tolerated doses of 5–150 mL, it still demonstrated considerable efficacy of OIT when compared to that in the placebo group, who had 0 of 30

subjects pass the OFC. Notably, this study included children with a history of severe cow's milk allergy and high cow's milk-specific IgE levels, which likely affected the results.

A 2007 trial of children with either cow's milk or hen's egg allergy randomly assigned subjects into an OIT group or an elimination diet group [32]. At the follow-up OFC, there was no significant difference in rates of 8-week SU in the treatment group compared to those in the control avoidance group; however, with inclusion of those children classified as partial responders (who maintained a desensitized state with ongoing ingestion), desensitization did differ significantly from that of the control group (64 vs 35%).

Another randomized, placebo-controlled study demonstrated marked improvement in desensitization with milk OIT [24]. Desensitization was induced with a daily maintenance dose of 500 mg milk protein. The active treatment group reacted to a median cumulative dose of 5140 mg at OFC whereas the placebo group (adhering to milk avoidance) reacted at 40 mg, same as at baseline. The success of desensitization in this study emphasized the importance of continued milk exposure. The benefits of milk OIT were countered by the significantly increased rate of reactions in the intervention group (45%) compared to that in the placebo group (11%), though reactions were most commonly mild local symptoms.

An open-label follow-up study examined the safety of continued milk intake after OIT and only enrolled subjects who could tolerate >2540 mg cow's milk protein at OFC after completion of initial OIT [25]. Subjects were given higher doses of 500–4000 mg daily milk protein, which resulted in higher tolerated doses of 1000–16,000 mg milk daily (median 7000 mg). Ultimately, 33% tolerated at least 16,000 mg milk protein. While threshold doses appeared to improve over time, it was unclear in this study if tolerance would persist without regular cow's milk intake.

Multiple food OIT

Studies to concurrently treat multiple food allergies are underway. One preliminary multifoed allergen study included 40 subjects ages 4–46 years [33]. Subjects were eligible for inclusion if they had proven sensitivity to the food allergen documented by both a skin prick test greater than 7 mm (wheal) and specific IgE greater than 2 kU/L to peanut as well as positive allergic reaction in a DBPCFC up to a cumulative dose of 182 mg peanut protein. Further, DBPCFCs were also performed following the same protocol to tree nuts, sesame seed, milk, or egg to document additional food allergies. OIT was administered with a food flour vehicle (e.g., peanut flour, egg powder, et al.). Fifteen received peanut-only OIT, and 25 received up to five foods based on initial peanut DBPCFC followed by other food DBPCFCs. The primary outcome was to achieve a tenfold increase from initial DBPCFC threshold. The goal of daily maintenance dose of each allergen was 4000 mg. There were no significant differences in the groups or in their rates of reaction per dose (3.3–3.7%). No differences were reported in dropout rates. Most reactions were mild with abdominal pain the most common symptom. There were two severe reactions requiring epinephrine in each group. Subjects on multiple food OIT took significantly longer to reach equivalent doses per food due to protocol design. After 1 year, peanut-specific IgE remained unchanged in both groups, and peanut-specific IgG₄ increased significantly in

both groups. This study demonstrated a similar safety profile in multifoed OIT compared to that of peanut OIT.

OIT combined with anti-IgE therapy

Safety concerns are one of the major limitations to administering OIT outside of a research setting. Anti-IgE monoclonal antibody has been studied as an adjunct to OIT. Nadeau et al. investigated the addition of omalizumab to minimize the side effects encountered with using a cow's milk rush OIT protocol [34]. The authors enrolled 11 children with cow's milk allergy who received omalizumab for 9 weeks then underwent rush oral desensitization. Nine of 11 subjects reached the 1000-mg dose on the first day of desensitization with one subject requiring epinephrine while another subject voluntarily withdrew from the study. After discontinuation of omalizumab, all nine patients who reached a daily maintenance dose of 2000 mg passed the DBPCFC of five doses with a maximum of 3000 mg (cumulative dose 7250 mg or 220 mL milk) and an open challenge. Overall reaction rate was 1.6% of all doses causing a reaction, with all subjects experiencing some adverse events (AEs), though the majority (63%) of the symptoms were classified as mild not requiring treatment. This study did not evaluate subjects with a baseline OFC.

Similarly, Schneider et al. utilized omalizumab to facilitate rapid oral desensitization in 13 peanut-allergic children [35]. After pre-treatment with omalizumab dosed by weight and serum total IgE for 12 weeks, all children who previously failed initial DBPCFC of 100-mg peanut flour entered rush desensitization. All 13 tolerated the maximum dose of 500 mg peanut flour (cumulative dose, 992 mg). Once 12 of 13 subjects reached the maximum maintenance dose of 4000 mg peanut flour per day (median time of 8 weeks), omalizumab was discontinued. All 12 patients subsequently passed an OFC of 8000 mg peanut flour. Notably, 8 of 13 subjects had grade 2 or grade 3 reactions that responded to treatment.

To address the frequency of AEs and waning long-term efficacy of milk OIT once treatment is discontinued, Wood et al. investigated omalizumab in addition to milk OIT to improve desensitization outcomes [36•]. In this DBPC trial, omalizumab or placebo was given over 4 months then open-label milk OIT was escalated over 22–40 weeks and maintained daily through month 28, at which time, omalizumab was stopped. Subjects who passed an OFC at that time continued OIT for an additional 8 weeks then discontinued daily therapy for 8 weeks and underwent another OFC. Twenty-four (89%) of omalizumab-treated subjects versus 20 (71%) of placebo-treated subjects passed a 10-g OFC to demonstrate desensitization ($p = 0.18$). In the omalizumab group, 48% demonstrated SU versus 36% of the placebo group. There was a significant decrease in AEs during escalation and maintenance doses in the omalizumab-treated group. Safety was improved by the addition of omalizumab to milk OIT, but rates of desensitization and SU were unchanged.

A phase 1 study has shown that omalizumab treatment over 16 weeks allowed for subsequent successful rush OIT to multiple foods [37]. The trial enrolled 25 subjects (median age 7 years). After 9 weeks with omalizumab, 19 subjects (76%) underwent an initial escalation day with a starting dose of 5 mg total food allergen protein (or 1 mg each of five different food proteins) and reached the full-dose goal of 1250 mg total in 2.5 h. The remaining six subjects

were started on their highest tolerated dose from OFC. Reactions occurred at a rate of 5.3% of doses triggering a reaction, and 94% of the reactions were mild. One severe reaction requiring epinephrine was reported. Subjects reached the goal maintenance dose of 4000 mg protein per allergen at a median time of 18 weeks. All subjects were able to reach a dose equivalent to a tenfold increase of all allergens by 2 months. Theoretically, multifoed OIT poses a challenge as the risk of AEs may increase while attempting to achieve sufficient doses of each food; however, preliminary studies display an acceptable safety profile, and additional clinical trials should be performed.

Future of OIT

Oral immunotherapy shows much promise in treating common food allergies in children. However, questions remain including the best age at which to administer therapy, identification of subjects at greatest risk of having an AE, and approaches to minimize AEs. Furthermore, assessment of quality of life before, during, and after OIT is of paramount importance. Currently, enrollment has completed for a phase 3 clinical trial with breakthrough designation status as the first OIT study pursuing FDA approval of a new desensitization treatment for peanut allergy. The study is titled PALISADE (Aimmune Therapeutics, clinical [trials.gov](https://clinicaltrials.gov) identifier NCT02635776) and it is expected to end on November 2017.

Sublingual immunotherapy (SLIT)

SLIT for treatment of food allergy consists of sublingual administration of solubilized food protein held orally for 1–2 min, then swallowed or discharged. As compared to OIT, SLIT uses significantly smaller amounts of protein (milligrams of protein in SLIT vs gram quantities with OIT) and exposes the protein to antigen-presenting cells in the oral mucosa.

Peanut SLIT

SLIT for peanut allergy was first studied in a DBPC trial including 18 children [38]. The treatment group tolerated approximately 20 times more peanut protein than the placebo group (median tolerated dose 1710 vs 85 mg). Side effects were mild not requiring treatment and typically oropharyngeal in nature. Treatment subjects demonstrated a decrease in SPT wheal diameter and basophil responsiveness. Peanut-specific IgE decreased over the latter 8 months of the 12-month treatment period. Peanut-specific IgG4 increased over 12 months, and IL-5 levels decreased after treatment. This small study demonstrated the acceptable safety profile of peanut SLIT, its ability to improve immunologic responses, and its efficacy in achieving clinical desensitization in the majority of patients aged 1–11 years.

A large, multicenter, randomized, DBPC crossover study of SLIT in adolescents and young adults demonstrated desensitization in the majority of the initial treatment group as well as the crossover treatment group [39]. Fleischer et al. showed that 70% (14 of 20) of treatment subjects responded in comparison to a response rate of 15% (3 of 20) in the placebo group. Subjects successfully consuming 5 g or at least tenfold more peanut powder than the baseline OFC threshold were considered responders. This study was unable to

show differences in immunomodulation measured by peanut-specific IgE, peanut-specific IgG₄, basophil activation, or SPT. This study further elucidated the safety profile of peanut SLIT, though in an older population than that in the aforementioned study.

Peanut SLIT with placebo OIT was compared to OIT with placebo SLIT in a double-blind study with 21 children aged 7–13 years [40]. The SLIT-dosing goal was 3.7 mg/day and OIT-dosing goal was 2000 mg/day. Sixteen subjects underwent OFC after 6 and 12 months of maintenance therapy. After unblinding at 12 months, therapy was continued for another 6 months with repeat OFC at 18 months. Subjects who passed challenges at 12 or 18 months discontinued treatment for 4 weeks and were re-challenged. All subjects had at minimum a tenfold increase in threshold dose. The active OIT group had a significantly greater increase in threshold dose than the active SLIT group (141-fold vs 22-fold, respectively). Both groups demonstrated within-group significant changes in endpoint SPT results with a decrease in wheal diameter, and peanut-specific IgE levels decreased in both groups, though the OIT group had a greater decrease. Peanut-specific IgG₄ increased in both groups with the OIT group again having a significantly greater change. AEs were more frequent in the OIT group, with the OIT group also having increased numbers of moderate reactions and reactions requiring medication. OIT achieved higher rates of desensitization and immunomodulation than SLIT but treatment was associated with significantly greater AEs and early study withdrawal.

Milk SLIT

Keet et al. compared SLIT and OIT for cow's milk allergy and found OIT to be more efficacious than SLIT alone [41]. However, OIT patients experienced a higher rate of systemic AEs. Both groups underwent SLIT escalation then divided into exclusive SLIT escalation to 7 mg daily or began OIT to either 1000 or 2000 mg milk protein. All subjects were challenged with 7 g milk protein after 12 and 60 weeks of maintenance. SU was tested in those who passed the 60-week challenge when OFC was repeated after 1 and 6 weeks off therapy. At final OFC at completion of maintenance therapy, one of ten patients in the SLIT group passed, whereas six of ten subjects in the SLIT with higher OIT dose group and eight of ten subjects in the SLIT with lower OIT dose group passed and demonstrated desensitization. Nine of 30 subjects demonstrated SU off therapy. Symptoms with dosing occurred at similar rates in both SLIT (29%) and OIT (23%). OIT recipients had a significantly higher rate of systemic symptoms with need for beta-agonists and antihistamines. Epinephrine was required twice in SLIT patients who aspirated the dose and four times in OIT patients in all phases including home up-dosing, maintenance, and office up-dosing. While both SLIT and OIT groups had moderate immunologic responses with decreased SPT, CD63, and CD203c expressions and increased cow's milk-specific IgG₄ levels, OIT continued to demonstrate a greater immunomodulatory effect with decreased cow's milk-specific IgE levels and spontaneous histamine release values.

Epicutaneous immunotherapy (EPIT)

Delivery of a food allergen through an epicutaneous patch is still under early investigation. Dupont et al. published a DBPC pilot study on cow's milk EPIT including 18 children randomized to active EPIT or placebo [42]. Ten subjects

received three 48-h applications of a skin patch containing 1 mg skimmed cow's milk powder weekly for 3 months. The active group had mostly increased threshold doses at final oral milk challenge from a mean of 1.8–23.6 mL while the placebo group had no change. One patient in the active group had a slightly decreased cumulative tolerated dose. Cow's milk-specific IgE levels did not change. Side effects included local erythema, pruritus, and eczema in both groups, though at a higher rate in the active group. No subjects stopped treatment due to AEs. This pilot study shows the potentially superior safety profile of EPIT in comparison to that of OIT, though further study with larger trials of greater duration with measures of immunologic effects is needed.

Peanut EPIT safety was recently investigated in a multicenter, randomized, DBPC phase 1b study including 100 subjects aged 6–50 years with severe and non-severe peanut allergy [43]. Non-severe allergy was defined as any age of individual with a positive SPT response (≥ 8 mm), peanut-specific IgE level of >0.7 kU_A/L, and a history of clinical peanut allergy with Sampson grade 3 anaphylaxis or less [44]. Severe allergy included subjects with the same inclusion parameters of positive-SPT response and peanut-specific IgE levels with a history of clinical peanut allergy with Sampson grade 4 or 5 anaphylaxis [44]. Active group subjects were divided into cohorts at doses of 20, 100, 250, and 500 μ g applied for either 24- or 48-h intervals during a 2-week dosing period with a 1-week follow-up. Systemic reactions occurred at similar rates in both treatment and placebo groups, 52.5 versus 45%, respectively. Local reactions were frequent and mild occurring in 84% of the treatment group versus 60% in the placebo group. All site reactions resolved to low-grade ratings within 1 week of patch discontinuation. A compliance rate of 96% measured by diary records was comparable in both groups. IgE and SPT responses did not change in either treatment groups. This study confirms EPIT is a relatively safe and well-tolerated treatment, but efficacy in inducing desensitization and SU for various food allergens needs further study.

Future directions

The next steps for the field of food allergy immunotherapy should focus on investigating diagnostic markers of food allergy to eliminate the need for food challenges used to conclusively confirm the presence of disease or efficacy of treatment and duration of and compliance to treatment, safety, and efficacy. Identification of more accurate diagnostic criteria will better identify which patients are most qualified to undergo immunotherapy. The duration of immunotherapy will likely vary depending on the food allergy, type of treatment, and patient's response to treatment discontinuation. However, it remains difficult to determine when to discontinue immunotherapy as many factors play a role. Patients' preferences may decide immunotherapy duration as many children or parents may tire of ingesting or administering OIT or maintaining SLIT. Compliance with EPIT has been high though clinical outcomes have yet to be reported. Several ongoing studies continue to explore the safety profile and efficacy of food allergy immunotherapy. Patient safety is of paramount importance, especially considering the optional nature of immunotherapy. Lastly, measures of quality of life prior to, during, and after immunotherapy should be examined, as the goals of immunotherapy may vary for each patient and allergist. As food allergy immunotherapy advances and FDA-approved methods

arise, consideration of the patient's and family's goals balanced by the allergist's knowledge and comfort with treatment must be prioritized.

Conclusions

Food allergy immunotherapy has advanced considerably in the last 15 years and we are currently on the precipice of potentially having FDA-approved therapeutic options for our food-allergic patients. OIT, SLIT, and EPIT each offers advantages in terms of level of efficacy, safety profile, and effects on quality of life. Within the next 10 years, food allergy research is likely to focus on improving the safety profile of existing products and expanding capabilities for treating multifood allergic individuals.

Compliance with Ethical Standards

Conflict of interest

Tiffany J. Lieu declares no conflict of interest.

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Human and animal rights and informed consent

With regard to the authors' research cited in this paper, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. In addition, all applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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