

Sublingual and Patch Immunotherapy for Food Allergy



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KEYWORDS

- Peanut allergy • Sublingual immunotherapy • Epicutaneous immunotherapy
- Desensitization • Sustained unresponsiveness • Food allergy treatments

KEY POINTS

- Sublingual immunotherapy studies have demonstrated modest desensitization and excellent safety profile with longer studies indicating potential for sustained unresponsiveness.
- Epicutaneous immunotherapy studies have demonstrated modest desensitization in children younger than 11 years with excellent safety profile and adherence rates.
- Sublingual and epicutaneous immunotherapy methods could serve as alternative treatment options for peanut-allergic patients who are unable to tolerate oral immunotherapy.

INTRODUCTION

Food allergy is a significant public health problem in industrialized nations, but has also become an increasing problem globally.^{1,2} An estimated 10.8% of adults³ and 8.0% of children⁴ in the United States have food allergies, and census data have indicated a tripling of prevalence over the past 10 to 15 years.⁵ Although numerous foods are implicated in allergic disease, peanut allergy has been extensively studied, as it remains the most common food allergy, exhibits higher severity reaction on exposure, and only a fraction of people outgrow this allergy.⁵

Management of peanut allergy primarily focuses on avoidance measures with self-injectable epinephrine for treatment of accidental ingestions; there are no current Food and Drug Administration (FDA)-approved treatment options. Peanut allergy is also associated with poor quality of life for individuals diagnosed with peanut allergy and their caregivers, both of whom have expressed desire for treatment options for improvement in quality of life.^{6,7} To meet this growing need, research has focused on multiple immunotherapy modalities for peanut food allergy, including oral (OIT), sublingual (SLIT), and epicutaneous (EPIT) immunotherapy.

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Immunol Allergy Clin N Am 40 (2020) 135–148

<https://doi.org/10.1016/j.iac.2019.09.008>

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Immunotherapy involves exposure to increasing doses of an allergen over time with the primary goal of providing clinical desensitization and possibly long-term tolerance. Desensitization is an increase in the threshold amount of food required to cause an allergic reaction that is dependent on regular exposure to the allergen, whereas tolerance is the nonresponsive state to an allergenic food that persists and is independent of routine exposure.³ As specific clinical and immunologic indicators for tolerance have remained undefined, studies have primarily focused on the term sustained unresponsiveness (SU), defined as the phenomenon of persistence of desensitization for a defined time after discontinuation of immunotherapy (most studies have defined this as 4–8 weeks, although a specific time frame for SU remains undefined).^{8,9} Clinical trials assessing food allergy immunotherapy have relied on double-blind, placebo-controlled food challenges (DBPCFC) to confirm reactivity at baseline and to assess treatment response while on therapy (desensitization) as well as after a prescribed amount of time off of therapy (SU). Food immunotherapy studies share common dosing phases of initial dose escalation, buildup dosing, and maintenance dosing; however, there remains significant variability in study protocol with regard to dosing, rate of dose escalation, and duration of therapy as food allergen immunotherapy methods remain under active investigation.

OIT has been extensively studied with current phase III trials being conducted in anticipation of FDA approval in the near future. OIT has shown promise for desensitization and potential for SU in a subset of patients, but is also associated with significant adverse side effects that may limit its use. Therefore, it is important to continue to pursue alternative therapeutic options for individuals that may not tolerate OIT or who wish to undergo therapy with a more acceptable side-effect profile. In this article, the authors have focused on advancements regarding investigational studies on SLIT and EPIT in peanut food allergy ([Table 1](#)).

SUBLINGUAL IMMUNOTHERAPY

SLIT was pursued as an alternative to OIT due to ease of administration, which involves holding a peanut protein solution sublingually for 2 minutes followed by swallowing of the solution. SLIT for food allergy includes phases that are similar to other forms of immunotherapy, including dose escalation and a maintenance phase. Maintenance doses have been determined by both the maximum amount of peanut protein in solution and the largest volume of liquid expected to be comfortably held in the sublingual space by a young child.¹ Investigations on SLIT also have been motivated by its safety profile, which is considered an advantage compared with alternative immunotherapy options. SLIT is thought to mediate its immune effects via oral Langerhans cells that take up antigen within the mouth and induce downstream immune modulation that results in antigen tolerance.¹⁰ In addition, as SLIT is administered via a mucosal surface, it is possible that immunoglobulin IgA and secretory IgA involvement may help mitigate inflammatory response and play a role in downstream immune modulation.¹¹

Early studies investigating immunotherapy for food allergies focused on cow's milk (CM) allergy. Keet and colleagues¹² were the first study to compare OIT and SLIT for food allergy in 2011. Thirty children (median age of 8 years) with CM allergy were randomized to SLIT or OIT; CM allergy was defined as documented CM allergy, CM-specific IgE (CM-sIgE) of greater than 0.35 kU/L, positive skin prick test (SPT) to CM, and positive baseline DBPCFC at study entry. All participants underwent initial dosing with SLIT with daily maintenance dose (DMD) of 3.7 mg for 8 weeks. Participants were then randomized in equal numbers into 1 of 3 groups: 2 OIT crossover

Table 1
Summary of key studies in peanut sublingual and epicutaneous immunotherapy

Food Immunotherapy Modality and Study	No. Subjects	Blinding	Maintenance Dosing	Treatment Duration	Comments
SLIT					
Kim et al, ¹ 2011	18	Yes	2 mg	12 mo	First double-blind study of peanut SLIT
Fleischer et al, ¹³ 2013	40	Yes	1.4 vs 3.7 mg	12 mo	First multicenter study of peanut SLIT
Burks et al, ¹⁴ 2015	40	Yes	1.4 vs 3.7 mg	36 mo	First multicenter study of extended therapy peanut SLIT
Burk et al, ¹⁵ 2016	33	No	2 mg	12 mo	Immune markers to predict peanut SLIT response
Kim et al, ² 2019	48	No	2 mg	36–60 mo	Efficacy of extended therapy peanut SLIT
OIT vs SLIT					
Narisety et al, ¹⁶ 2015	21	Yes	2000 mg (OIT) vs 3.7 mg (SLIT)	12–18 mo	First study comparing peanut OIT and SLIT
EPIT					
Jones et al, ²¹ 2016	96	Yes	20 vs 100 vs 250 vs 500 µg		Phase I multicenter study on safety of peanut EPIT
Jones et al, ⁸ 2016	74	Yes	100 vs 250 µg	12 mo	NIH-sponsored double-blind phase II study of peanut EPIT
Sampson et al, ²² 2017	221	Yes	50 vs 100 vs 250 µg	12 mo	Industry-sponsored double-blind phase IIb study of peanut EPIT
Fleischer et al, ⁶ 2019	356	Yes	250 µg	12 mo	Industry-sponsored double-blind phase III study of peanut EPIT

Abbreviations: EPIT, epicutaneous immunotherapy; NIH, National Institutes of Health; OIT, oral immunotherapy; SLIT, sublingual immunotherapy.

groups (DMD of 2000 mg in “OITA” vs 1000 mg in “OITB”), and continued SLIT, but at increased dose of 7 mg compared with entry SLIT dosing. Primary outcomes were safety, efficacy, and immunologic changes (CM-sIgE, IgG4, and basophil function) following 60 weeks of therapy. Efficacy was defined as proportion of subjects who would tolerate 10-fold or greater increase in milk protein during DBPCFC compared

with baseline DBPCFC. Secondary end points included SU after 1 and 6 weeks after therapy cessation and adverse effects (AEs). Twenty-eight subjects completed 60 weeks of maintenance therapy; 2 subjects withdrew during dose escalation due to AEs (both participants were assigned to OIT, citing worsening eczema and concerns for eosinophilic esophagitis, respectively). DBPCFCs were performed at 12 and 60 weeks of maintenance therapy, with all participants having observed increase in median successfully consumed dose (SCD) compared with baseline; however, there was a significant increase in SCD with OIT therapy (79-fold and 64-fold for OITA and OITB, respectively) at 12 weeks and at 60 weeks (54-fold and 159-fold for OITA and OITB, respectively) when compared with SLIT treatment arm (7-fold and 40-fold at 12 and 60 weeks, respectively). For participants who successfully passed the 8000 mg DBPCFC at 60 weeks without rate-limiting symptoms, the assigned therapy was discontinued and the patient underwent 1-week DBPCFC and, if tolerated, underwent a second DBPCFC at 6 weeks after therapy was discontinued. One participant (10%) in SLIT, 8 (80%) of 10 in OITA, and 6 (60%) of 10 in OITB tolerated the 8000 mg and were eligible for DBPCFC off therapy; after 1 week, 2 subjects from OITB arm failed repeat DBPCFC. At 6 weeks after therapy, 4 subjects failed repeat DBPCFC (3 from OITA and 1 from OITB); 1 (10%) SLIT subject, 5 (50%) of 10 OITA subjects, and 3 (30%) of 10 OITB subjects had observed tolerance or SU at 6 weeks. Overall, CM-sIgE levels increased initially but decreased by study completion in OIT arms (there were no significant changes in CM-sIgEs in SLIT treatment arm), CM-sIgG₄ levels increased in all groups, SPT reactivity to CM decreased in all groups (no statistically significant difference among treatment arms), and basophil activity decreased in OIT arms (no significant change was observed in SLIT arm). With regard to safety, 29% of SLIT doses and 23% of OIT doses had associated symptoms; there were no significant differences in the rate of symptoms between treatment arms; however, there were more respiratory, gastrointestinal, and multisystem symptoms reported with OIT dosing compared with SLIT dosing. Two SLIT doses (due to aspiration of dosing) and 4 OIT doses (2 accidental ingestions, 1 maintenance, and 1 up dosing) required epinephrine.

The first double-blind, placebo-controlled SLIT trial for peanut allergy was published by Kim and colleagues¹ in 2011. This study included 18 children aged 1 to 11 years old who were randomized to placebo (median age 4.7 years) versus active SLIT (median age 5.8 years); subjects in the active SLIT arm received a DMD of 2 mg for a total of 12 months. At the end of treatment, patients exhibited a 20-fold greater median SCD compared with those receiving placebo SLIT (1710 mg after peanut SLIT vs 85 mg after placebo); notably, this study did not include an entry DBPCFC and results reflect the direct comparison of end study DBPCFC between study arms. The investigators reported an initial increase followed by decrease to baseline levels in peanut-specific IgE (PN-sIgE) laboratory values, decreased basophil responsiveness to peanut, and increased PN-sIgG₄, indicating diminished allergic response and potential for long-term immunologic change and tolerance. Regarding safety, the treatment group tolerated SLIT with few AEs; the primary AE was transient oropharyngeal symptoms reported in 9.3% doses in the treatment arm with 0.26% doses requiring antihistamines for symptomatic improvement; no epinephrine was required, supporting an overall favorable safety profile.

The first multicenter, randomized placebo-controlled trial for peanut SLIT was published by Fleischer and colleagues¹³ in 2013. This study, conducted by the National Institutes of Health (NIH)-sponsored Consortium for Food Allergy Research (CoFAR), included an entry DBPCFC of up to 2000 mg peanut protein and then randomized 40 subjects (aged 12–37 years) to daily peanut SLIT (DMD of 1.386 mg) versus placebo,

followed by a 5000 mg DBPCFC after 44 weeks. The primary measured outcome was percentage of responders, defined as a 10-fold increase in median SCD compared with baseline DBPCFC or consumption of a cumulative dose of 5000 mg peanut protein without dose-limiting symptoms. Seventy percent of subjects in the treatment arm were responders, that is, all met criteria of a 10-fold increase in median SCD compared with baseline oral food challenge (OFC). However, no participants were able to tolerate 5000 mg during the OFC. Participants were then unblinded and the placebo arm was crossed over to a “high-dose” active treatment group (DMD of 3.696 mg) for an additional 44 weeks, whereas the original treatment arm extended treatment on the same DMD (1.386 mg) for a total of 68 weeks for the second phase of this study. Seven (44%) high-dose crossover participants had observed a 10-fold increased SCD compared with baseline OFC. All initial responders remained responders at week 68. However, none of the week 44 nonresponders converted to responders with extended SLIT therapy. This suggests that SLIT therapy may benefit a limited subgroup of peanut-allergic subjects. In addition, no subject in the original treatment arm or crossover arm was able to tolerate a 5000 mg OFC, indicating a modest level of desensitization of unclear clinical significance. This study did uphold the safety profile of SLIT, with only 127 (1.1%) of 11,854 doses requiring treatment in phase I (125 doses required antihistamines, whereas 1 dose required albuterol, and 1 dose required both antihistamines and epinephrine) and 147 (2.9%) of 5030 doses requiring treatment in phase II (146 doses required antihistamine alone, whereas 1 dose required antihistamine and albuterol). Immunologic endpoints included a significant decrease in basophil reactivity after active SLIT compared with placebo, although there were no significant differences in PN-sIgE levels between treatment arms, suggesting that PN-sIgE at 12 months of therapy has poor predictive value for clinical outcomes with SLIT.

Building on the initial study by Fleischer and colleagues,¹³ which suggested statistically significant but moderate desensitization after 44 weeks, Burks and colleagues¹⁴ aimed to determine the potential for long-term desensitization with 3-year extended maintenance data from the original study. The previously enrolled 40 subjects were continued on “standard” peanut DMD SLIT (20 participants from the original “active” treatment arm with DMD of 1386 µg) and “high-dose” DMD SLIT (20 participants from the original “crossover” arm with DMD of 3696 µg). Participants underwent 5000 mg peanut protein DBPCFCs following 2 and 3 years of daily peanut SLIT, and an additional DBPCFC following an 8-week discontinuation of SLIT at study exit. By the study end, 4 (10%) of 37 SLIT-treated subjects (2 of 17 or 23.5% subjects from “high-dose” crossover SLIT arm and 2 of 20 or 10% subjects from “standard-dose” SLIT arm) were considered responders (by meeting criteria of 10-fold increase in median SCD compared with baseline DBPCFC) and all 4 achieved SU. This study continued to support the safety of SLIT with 98% of doses tolerated without adverse reaction when oropharyngeal symptoms were excluded; no symptoms were defined as severe or required epinephrine. Limitations of this study include an observed high dropout rate (>50%) despite overall perceived SLIT tolerance, thus making conclusions of long-term SLIT efficacy difficult to interpret due to small sample size. A slightly older population (median age of 14 years) was postulated as a potential reason for the high dropout rate, with 11 participants citing personal decision for study withdrawal, compared with previous studies, such as Kim and colleagues,¹ with younger participants (median age of 5.8 years) and no study withdrawals.

As previous publications indicated potential for response in a subgroup of peanut-allergic participants, a study by Burk and colleagues¹⁵ in 2016 aimed to identify immune markers that could serve as predictors for clinical response to SLIT therapy.

Thirty-three subjects who were actively enrolled in SLIT trials had blood collected at study entry and exit; the study concluded with a 2500 mg DBPCFC of peanut protein after 12 months of SLIT therapy. Ten (30%) subjects passed the DBPCFC without symptoms and were considered desensitized; those who passed had significantly lower baseline levels of PN-sIgE, Ara h 2, and Ara h 3 subcomponent testing compared with subjects who did not pass exit OFC. The investigators suggested that PN-sIgE of greater than 81.3 kU/L and Ara h 2 sIgE of greater than 48.55 kU/L at baseline were able to discriminate and accurately predict a higher likelihood of failing the exit OFC, and thus were predictive of poor clinical response to SLIT therapy. However, this study was limited by small sample size and being a single-center trial.

Although various studies have been performed comparing specific immunotherapy methods with placebo, few studies have directly compared immunotherapy methods. Narisety and colleagues¹⁶ published a randomized, double-blind, placebo-controlled study of SLIT versus OIT in 2015 to compare safety, efficacy, and mechanistic correlates of these 2 immunotherapy methods. This study consisted of an initial blinded monotherapy phase, followed by an unblinded combination therapy phase. The blinded phase consisted of 21 subjects (median age 11.1 years) with baseline OFCs who were randomized to active SLIT/placebo OIT ($n = 10$ at 3.7 mg SLIT DMD) or active OIT/placebo SLIT ($n = 11$ at 2000 mg OIT DMD) for 12 months of therapy; peanut desensitization was defined as 10-fold increase in SCD with 10,000 mg OFC compared with baseline OFC. During this blinding phase, 1 active SLIT (due to persistent gastrointestinal symptoms with dosing) and 4 active OIT subjects withdrew from study (1 due to diagnosis of eosinophilic esophagitis, 1 due to persistent gastrointestinal symptoms with dosing, 1 due to systemic reaction with dosing, and 1 due to noncompliance). Of those who completed the blinded phase to 12-month OFC, all participants achieved greater than 10-fold increase in SCD compared with baseline (9 of 9 participants in the SLIT arm and 7 of 7 participants in the OIT arm), although subjects in the OIT arm had significantly greater change in median SCD (21 mg at baseline vs 7246 mg after 12 months of therapy) compared with those in the SLIT arm (21 mg at baseline vs 496 mg after 12 months of therapy). One participant from the active OIT arm passed the 12-month OFC (as defined by tolerated cumulative ≥ 5000 mg OFC); he exhibited SU when rechallenged via OFC 4 weeks after discontinuing therapy. Participants in both treatment arms exhibited a decrease in SPT at 12 months, although the active OIT arm exhibited a greater change from baseline in SPT wheal diameter (12 mm vs 0 mm) compared with the active SLIT arm (9.3 mm vs 5.5 mm); PN-sIgE decreased in the active OIT arm at 12 months compared with baseline (169 kU/L vs 53 kU/L), whereas the active SLIT arm exhibited no significant difference compared with baseline (163 kU/L vs 273 kU/L) after 12 months of therapy. At 12 months, the study was unblinded and all participants who failed the 12-month OFC (as defined by development of dose-limiting symptoms during OFC preventing a cumulative ingestion of ≥ 5000 mg peanut protein) underwent an additional 6 months of active therapy combined with active alternative treatment to assess effect of dual therapy; 10,000 mg OFC was then performed at 18 months. Subjects who passed the 18-month OFC were then rechallenged via OFC 4 weeks after discontinuing all immunotherapy to assess SU. Five (71%) active SLIT/crossover OIT participants were able to pass exit OFC at 18 months, with only 1 demonstrating SU 4 weeks after discontinuing therapy (2 subjects withdrew during OIT buildup secondary to side effects). Four (67%) active OIT subjects passed exit OFC at 18 months with 3 exhibiting SU. Subjects achieving SU in either group were found to have lower PN-sIgE levels at baseline (median PN-sIgE of 79 kU/L) compared with those unable to achieve SU (median PN-sIgE of 257 kU/L), which is consistent with results from Burk and

colleagues.¹⁵ Another observation by the investigators included persistent safety profile for SLIT, as AEs were more commonly observed with OIT doses both during blinded monotherapy phase (43% OIT doses had AEs vs 9% of SLIT doses) and unblinded combined therapy (5.1% doses in active SLIT/crossover OIT vs 35.3% doses in active OIT/crossover SLIT). This study suggests that OIT appears to be more effective at achieving desensitization, but was also associated with significantly more adverse reactions and early study withdrawal.

More recently, Kim and colleagues² conducted a study on long-term SLIT with subjects receiving therapy up to 5 years. The investigators enrolled participants from a previous SLIT cohort and extended SLIT protocol (with DMD of 2 mg daily for up to 5 years); participants in the initial placebo cohort were crossed over into the active SLIT group. This study included 48 participants (median age 6.5 years) with history of clinical reaction to peanut and PN-sIgE of ≥ 7 kU/L at study entry. Subjects with SPT wheal less than 5 mm and PN-sIgE less than 15 kU/L who had completed at least 3 years of maintenance SLIT were allowed to complete therapy before 5 years (10 subjects met this criteria). Subjects completing maintenance SLIT (either after 5-year maintenance SLIT or by meeting criteria for early cessation) then underwent 5000 mg peanut protein DBPCFC. SU was also assessed by identical DBPCFC 2 to 4 weeks after cessation of SLIT therapy. Eleven (22.9%) subjects withdrew from the study before exit OFC, citing difficulty with compliance ($n = 8$), recurrent abdominal pain ($n = 2$), and other reasons ($n = 1$). Compliance in the 37 participants completing long-term SLIT was estimated at 95.5%. Thirty-two (87%) participants tolerated SCD of ≥ 750 mg during exit DBPCFC, whereas 12 (32%) of 37 tolerated the 5000 mg OFC with 10 of 12 demonstrating SU. Peanut SPT wheal, PN-sIgE, and basophil activation decreased significantly compared with baseline values. In addition, safety profile was upheld with 4.8% of doses having associated symptoms (most reported as transient oropharyngeal pruritus); antihistamine requirement was rare at 0.21% doses and no epinephrine was administered. This study suggests that extended peanut SLIT therapy provides clinically meaningful desensitization in most peanut-allergic children and can provide SUs in a subset of participants.

A significant advantage of SLIT has been its proven safety across studies. Study outcomes have shown modest desensitization, although there remains variability among therapeutic outcomes that warrant further investigation to support generalizability to peanut-allergic patients. In addition, many studies that report a modest desensitization response have also suggested that SLIT may have improved benefit in selected patient populations. Studies have used a wide range of dosing and treatment courses, although studies on longer maintenance courses have shown promise of improved clinical outcomes. Despite the safety and ease of administration, some trials had an unexpectedly high dropout rate, which is concerning for differences in overall treatment goals between investigators and participants. Further studies focused on clarifying treatment goals, dosing, and selection of appropriate patient population may aid in future applicability of SLIT for treatment of peanut food allergy.

EPICUTANEOUS IMMUNOTHERAPY

EPIT is another immunotherapy modality that has previously shown efficacy in other forms of allergic disease,^{17,18} and has since been applied to food allergy.⁸ This method is appealing due to its ease of administration. A patch with a peanut protein adsorbent film is applied to the skin for 24 hours during which there is passive absorption of peanut through skin pores where it is taken up by local dendritic cells. A new patch is applied in a few designated skin locations daily for maintenance dosing. Furthermore,

EPIT has the potential for a more robust safety profile compared with other immunotherapy methods, as murine studies have demonstrated a lack of systemic antigen absorption.¹⁹ Prolonged epicutaneous delivery of antigen is thought to downregulate TH₂ immune response via enhanced T regulatory and TH₁ response²⁰; antigen-driven activation of dermal dendritic cells that are trafficked to lymph nodes is thought to drive this immune modulation, mitigating systemic response to antigen exposure in murine models.¹⁹

Early phase I studies indicated safety and tolerability of EPIT by using Viaskin peanut product (DBV Technologies, Montrouge, France). Jones and colleagues²¹ conducted the first phase I study, which was a randomized, double-blind, placebo-controlled multicenter study in which 100 subjects (median age 22 years) with peanut allergy were randomized to active EPIT ($n = 80$) versus placebo ($n = 20$). Subjects assigned to active EPIT were further randomized to 1 of 4 doses (0.02, 0.1, 0.25, and 0.5 mg). The primary outcomes were safety and tolerability of peanut EPIT as measured by presence and severity of treatment-emergent adverse events (TEAEs), treatment required, and adherence to therapy. Active treatment arms had no observed difference between rates of TEAEs, with 42 (52.5%) of 80 active EPIT subjects reporting TEAEs, 41.3% were mild severity and 11.3% were moderate severity; in comparison, 9 (45%) of 20 in the placebo group reported at least 1 TEAE with 30% mild severity and 15% moderate severity with no statistically significant difference in reported TEAEs in placebo and active EPIT groups. Most TEAEs were local reactions, including reports of patch-site erythema, pruritus, and edema. The study reported no severe adverse events or use of epinephrine and there was a high treatment adherence with 4 (4%) of 100 participants withdrawing from the study. OFC were not conducted in this study with peanut sensitization measured by PN-sIgE and SPT; there was no significant change in PN-sIgE or SPT in treatment groups during the study (specific levels were not reported).

Jones and colleagues in 2016⁸ addressed the efficacy of EPIT in a phase II NIH-sponsored CoFAR, multicentered, double-blind, randomized, placebo-controlled study. Seventy-four participants (median age 8.2 years) with peanut food allergy (as defined by the following criteria: physician-diagnosed allergy or convincing clinical history with positive SPT or PN-sIgE >0.35 kU/L, and positive baseline OFC to cumulative dose of ≤ 1044 mg peanut protein) were randomized to receive 52 weeks of 1 of 3 treatments: placebo ($n = 25$), Viaskin 0.1 mg (VP100, $n = 24$), or Viaskin 0.25 mg (VP250, $n = 25$). The primary outcome was the percentage of responders at the end of study period, which was defined as passing a 5044-mg peanut protein DBPCFC or achieving a 10-fold or greater increase in median SCD from baseline. After 52 weeks, 3 (12%) of 25 placebo-treated participants, 11 (46%) of 24 VP100 participants, and 12 (48%) of 25 VP250 participants were considered responders (by achieving a 10-fold or greater increase in median SCD from baseline). However, only 1 participant (from the placebo group) passed the exit OFC (cumulative 5044 mg peanut protein). These findings indicate a modest but statistically significant treatment effect. Treatment success was higher among younger children (4–11 years) compared with older participants (>11 years), as older participants exhibited no statistically significant treatment effect. Significant immunologic differences were observed between treatment groups for peanut IgG4 levels and peanut IgG4/PN-sIgE ratios with participants in active treatment arms exhibiting increases in both when compared with those receiving placebo. No differences were observed for PN-sIgE levels or total IgE levels; a significant decrease in SPT wheal diameter compared with baseline was observed in the VP250 treatment arm only. Significant differences were observed with a decrease of basophil activation at a stimulant dose of 0.01 μ g in treatment

arms, but not at higher stimulant doses; this is consistent with a shift in threshold of reactivity to peanut rather than a loss of reactivity to peanut. There were 14.4% of placebo doses and 79.8% of VP100 and VP250 doses that resulted in reactions, predominantly mild local patch-site reactions. Although patch-site reactions were common and occurred with higher frequency in active treatment arms, most responded to oral antihistamines and/or topical corticosteroids (no reactions required epinephrine). The study had an overall high compliance at 97.1% for all groups, had high participant retention, indicating that EPIT was overall well tolerated.

Sampson and colleagues²² conducted a larger multicentered industry-sponsored phase II trial in 2017 to identify the most effective dose and establish adverse event profile, efficacy, and acceptability of peanut EPIT. Study criteria were determined by eliciting dose, defined as the highest dose at which objective symptoms of an immediate hypersensitivity reaction develop. A total of 221 peanut-allergic patients who failed entry DBPCFC (as defined by eliciting dose of ≤ 300 mg peanut protein) were enrolled and randomized to 1 of 4 arms: 0.05-mg, 0.1-mg, 0.25-mg, or placebo Viaskin patch for 12 months. The primary efficacy end point was percentage of treatment responders, defined as a 10-fold increase in median SCD and/or tolerance of ≥ 1000 mg of peanut protein. A significant difference in response rates was observed at 12 months between the 0.25-mg patch arm (50%) and placebo groups (25%). No difference was seen between the placebo patch versus 0.1-mg patch, therefore the 0.5-mg patch was not analyzed. When response rate was stratified by age group, younger subjects (6–11 years) in the 0.25-mg patch group had significant response (53.6%) compared with their age bracket in the placebo group (19.4%), whereas the older subjects (>11 years) showed no difference in response between the 0.25-mg patch (46.4%) and placebo (32%). The percentage of patients with 1 or more AE was similar across all groups, although the rate of TEAEs related to investigational product was higher in treatment arms (94.6%–96.4%) compared with placebo (48.2%); most reported AEs were local skin reactions with no dose-related serious AEs observed. Immunologic changes included increase in peanut sIgG4 levels, decrease in median peanut SPT wheal diameter, and no change in overall PN-sIgE across all treatment arms when compared with placebo group.

Participants from the initial study phase were then recruited for a 2-year open-label extension trial to assess 36-month EPIT outcomes; volunteers were initially randomized to the 3 previously defined treatment arms, but then all were switched to 0.25-mg patch at the 6-month extension time period, as this was found to be the more efficacious dose. Eighty-nine (59.7%) participants were responders at 12-month extended treatment (24-month total study period), whereas 80 (64.5%) of 124 were responders at the 24-month extended treatment (36-month total study period). Although outcome data were collected through the 2-year extension phase, giving a total of 36-month data, comparison analyses were unable to be performed given the lack of placebo control group during the extension phase, thus warranting long-term DBPC trials for EPIT.

As previous studies on EPIT suggested an increased treatment benefit in younger populations and with 0.25-mg patch dosing, follow-up phase III trials were aimed at targeting this specific age range and dose. Fleischer and colleagues⁶ published their phase III multicenter, randomized, double-blinded, placebo-controlled EPIT trial in 2019. A total of 356 peanut-allergic children aged 4 to 11 years (median age 7 years) who had objective reaction to an entry DBPCFC at dose of ≤ 300 mg peanut protein were recruited from 31 sites in 5 countries; subjects were randomized to receive daily 0.25-mg peanut patch (Viaskin) versus placebo patch for 12 months. The primary outcome was the percentage difference in responders between peanut patch and

placebo patch based on eliciting dose determined by DBPCFC at baseline and month 12. Participants were considered responders based on results of baseline DBPCFC (if baseline eliciting dose was ≤ 10 mg, response was defined as eliciting dose of ≥ 300 mg; if baseline eliciting dose was 10–300 mg, response was defined as eliciting dose of ≥ 1000 mg). There was a statistically significant difference ($P < .001$) in responder rate with 35.3% responders in peanut-patch treatment arm versus 13.6% in placebo arm. However, the prespecified threshold of 15% or more on the lower bound of a 95% confidence interval around responder rate difference to determine positive trial result was not met (the 15% cutoff value was the accepted value as determined by discussion between the FDA and the investigators in the absence of guiding historical data; however, the investigators note there is no consensus regarding what threshold of sensitivity may confer clinically meaningful protection). As such, further hierarchical analyses of secondary and exploratory outcomes were not analyzed or reported. Most TEAEs were patch application site reactions, which occurred in 34.5% peanut patch and 11.9% of placebo patch. Skin reactions were more prominent during month 1, and were mostly grade 1 or 2. However, there were 10 (4.2%) reported serious TEAEs from the peanut-patch group and 6 (5.1%) from the placebo group; 3 participants in the peanut arm experienced 4 serious TEAEs that met criteria for anaphylaxis and were responsive to standard treatment with epinephrine, corticosteroids, and antihistamines. The all-cause rate of discontinuation was 10.5% and 9.3% in peanut-patch and placebo groups, respectively. Adherence was 98.5%.

Similar to SLIT therapy, EPIT studies have suggested a moderate desensitization response. Although treatment-related AEs were more prevalent with EPIT compared with SLIT, reactions were overall mild and readily treated with topical therapies. Despite these reported AEs, compliance with EPIT was commonly reported among studies, indicating a clear advantage over other immunotherapy methods (Table 2).

FUTURE CONSIDERATIONS/SUMMARY

As the impact of food allergy continues to be felt worldwide, there has been a shared desire among providers and patients for therapeutic options. Food allergy carries significant risk to health and safety for the food-allergic individual, but also increases burden on quality of life and health care utilization.⁵ Food allergy not only impacts patients themselves, but entire family systems, and providers must recognize this to understand and address therapeutic goals. To help clarify these goals of therapy, Greenhawt and colleagues⁷ interviewed caregivers of peanut-allergic children seeking enrollment in OIT or EPIT trials; a common theme among families was a desire for a protective buffer from accidental exposures. As most families viewed food allergy immunotherapy as an adjuvant to ongoing allergen avoidance, families expressed willingness to accept minimal or limited protection in exchange for minimal therapeutic risk.

As phase III trials of OIT are nearing completion with anticipated FDA approval, we are seeing the first generation of therapeutic options for food allergy come to fruition. OIT has been extensively studied, and appears to provide a greater degree of desensitization and increased tolerance of allergen in comparison with SLIT and EPIT. However, OIT also has a higher rate of AEs compared with other immunotherapies.

SLIT studies have demonstrated modest desensitization outcomes when compared with OIT, but exhibit advantageous improved safety profile with rare serious AEs. Across all SLIT studies, few doses of SLIT were associated with adverse side effects with most AEs involving transient oropharyngeal symptoms; even fewer doses

Table 2
Comparison of peanut immunotherapy methods

Study	Dosing			Safety			Efficacy	
	Initial Dose, mg	DMD, mg	Buildup Period, wk	Doses Causing Symptoms, %	Doses Requiring Epinephrine	Withdrawal Due to Symptoms	Median SCD	Proposed Mechanism of Action
OIT ²³								
Vickery et al, ²³ 2018	3	300 mg	20	98.7% ^a	14%	11.6%	67.2% ^b	Activation of gut mucosal dendritic cells, which cause downstream immunomodulation with increased T regulatory response and suppression of Th ₂ response.
SLIT ^{1,12,14}								
Kim et al, ¹ 2011	0.00025	2 mg	26	11.5%	0%	0%	1710 mg	Antigen is taken up by oral Langerhans cells to induce downstream immune modulation, resulting in antigen tolerance. IgA and secretory IgA may help mitigate inflammatory response and play a role in downstream immune modulation.
Fleischer et al, ¹³ 2013; Burks et al, ¹⁴ 2015	0.000066	1.386 mg	26	40.1%	0.01%	5%	371 mg	
Narisety et al, ¹⁶ 2015	0.000066	3.696 mg	18	9%	0%	10%	496 mg	

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Table 2
(continued)

Study	Dosing			Safety			Efficacy	Proposed Mechanism of Action
	Initial Dose, mg	DMD, mg	Buildup Period, wk	Doses Causing Symptoms, %	Doses Requiring Epinephrine	Withdrawal Due to Symptoms	Median SCD	
EPIT ^{6,8,20}								
Sampson et al, ²² 2017	0.25 (3 h)	0.25 mg	3	96.4%	0.01%	0.6%	144 mg	Downregulation of TH ₂ immune response via enhanced T regulatory and TH ₁ response. Antigen-driven activation of dermal dendritic cells that are trafficked to lymph nodes is thought to drive immune modulation and mitigate systemic response to antigen exposure (as evidenced in murine models).
Jones et al, ⁸ 2016	0.25 (3 h)	0.25 mg	3	79.8%	0%	2%	144 mg	
Fleischer et al, ⁶ 2019	0.25 (3 h)	0.25 mg	2	59.7%	2.9%	1.7%	35.3% ^b	

Abbreviations: DBPCFC, double-blinded placebo-controlled food challenge; DMD, daily maintenance dose; EPIT, epicutaneous immunotherapy; Ig, immunoglobulin; OIT, oral immunotherapy; SCD, successfully consumed dose; SLIT, sublingual immunotherapy; SU, sustained unresponsiveness.

^a Reported as % of participants that experienced an adverse event during intervention (active treatment).

^b Responder rate or the percentage of participants that were considered responders.

required treatment and severe reactions requiring epinephrine were rare to absent. As current studies have used a variety of doses and duration of therapy, future studies would benefit from clarifying the optimal dose and duration of SLIT.

EPIT has also demonstrated modest desensitization in children, but proves advantageous with regard to high therapeutic adherence rates and excellent safety profile. Compared with SLIT, EPIT studies involved seemingly higher rate of AEs, although most of those reported were mild local skin site reactions that responded to topical therapies; the rate of serious AEs were rare among EPIT studies, suggesting a robust safety profile. As many current EPIT studies have focused on short-term outcomes, future investigation would benefit from long-term therapeutic outcomes.

As food allergy affects a heterogeneous group of individuals, therapeutic utility of food allergen immunotherapy will vary and a common threshold for therapeutic risk or clinical protection cannot be assumed for individuals desiring treatment. Although each immunotherapy method remains at different investigational stages, each method seems to have established a unique risk and benefit profile that is complementary to alternative immunotherapy options. With a shared goal of empowering food-allergic patients to meet each individual's specific treatment goals, it is important that we continue to pursue alternative immunotherapies, such as SLIT and EPIT, as a single therapeutic option with OIT may not prove feasible for all.

DISCLOSURE

The authors declare that they have no conflicting interests to disclose.

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