

Safety and efficacy of epicutaneous immunotherapy for food allergy

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Abstract

Food allergy is increasingly common in children, affecting about 4%-8%. The mainstays of management remain allergen avoidance and emergency preparedness to treat allergic reactions with emergency medications. Unfortunately, these approaches are unsatisfactory for many patients and their families as the restrictions, constant vigilance, and unpredictable severity of allergic reactions negatively impact quality of life. In recent decades, there has been significant interest in developing treatments for food allergy that lead to desensitization to increase thresholds for triggering allergic reactions and decrease the risk of reacting to allergen-contaminated food products. Epicutaneous immunotherapy (EPIT) is a novel therapy that is currently under investigation, delivering allergen via repeated applications to the skin and targeting antigen-presenting cells in the superficial skin layers. Murine models have demonstrated that allergen uptake is an active process by skin dendritic cells with subsequent migration to draining lymph nodes. Allergen exposure to the non-vascularized epidermis limits systemic absorption, contributing to the high-safety profile. Results from murine experiments showed that EPIT has comparable efficacy as subcutaneous immunotherapy in terms of challenge outcomes, airway hyperresponsiveness, and immunologic parameters. Several clinical trials of EPIT have recently been completed or are ongoing. Results support the high safety and tolerability of this approach. Efficacy data suggest that the change in threshold eliciting dose following 1 year of therapy is less than that seen compared to high-dose (2-4 g peanut protein) oral immunotherapy, but more prolonged treatment with EPIT appears to lead to increasing desensitization. Additional data from larger-scale studies should provide a more robust assessment of safety and efficacy of EPIT.

KEYWORDS

allergic reaction, anaphylaxis, epicutaneous, food allergy, immunotherapy

1 | INTRODUCTION

Food allergy is a major health concern, affecting 4%-8% of children in the United States.¹ Allergen avoidance and preparation to treat allergic reactions are the main pillars of management.² Despite increased vigilance, accidental exposures and reactions of unpredictable severity still occur, which can lead to morbidity and significant

negative impacts on quality of life.²⁻⁴ Specific allergen immunotherapy has been used to treat allergic diseases for over a century. One form of such therapy, subcutaneous immunotherapy (SCIT), is widely used for environmental allergens. However, this approach has been limited by potentially severe systemic side effects requiring epinephrine and the lengthy treatment duration.⁵ This route of immunotherapy administration has also been attempted for food allergy,

but it has not been pursued for many years due to safety concerns, including the risk of fatality.⁶ Oral immunotherapy for food allergy was first published nearly a century ago⁷ and has been subject to more intensive investigation in the last 20 years.⁸ Epicutaneous immunotherapy is a novel alternative that has garnered much interest as a potentially safer approach for treating food allergies.

2 | EARLY INVESTIGATIONS IN EPICUTANEOUS IMMUNOTHERAPY

Early epicutaneous approaches entailed disrupting the outer layer of skin prior to allergen application. This layer, the stratum corneum, is comprised of cornified keratinocytes embedded in a lipid-rich matrix conferring low permeability to environmental microbes, antigens, and toxins. Different methods for disrupting the skin were employed, including scratching with a needle (scarification), adhesive tape stripping, or other methods of abrasion. In addition to increasing allergen passage across the skin, disruption of the epidermis in this way induced a pro-inflammatory response whereby keratinocytes are activated to secrete alarmins and various cytokines and chemokines with the potential to increase antigen uptake and maturation of dendritic cells.⁹

Scattered reports detailing the effects of allergen administration via the skin for the treatment of allergic disorders were published in the early 20th century.¹⁰ The first case report of epicutaneous immunotherapy to treat asthma triggered by horsehair was published in 1921.¹¹ Administration of pollen extract on scarified skin as a method of allergic rhinitis treatment was reported to be effective in 1936.¹² Additional studies from Europe in the 1950s-1960s can be found in the medical literature citing promising results of epicutaneous pollen administration in relieving allergy symptoms, with side effect profiles more favorable than conventional subcutaneous immunotherapy.¹²⁻¹⁷ However, epicutaneous approaches were not further pursued for several decades until a resurgence of interest occurred in recent years.

In 2009, a randomized trial of an epicutaneous patch containing 12 pollen extracts was published, showing that subjects receiving active treatment experienced significant symptom improvements compared to placebo.¹⁸ The same group also published a phase I/II randomized, double-blind, placebo-controlled study that included 132 adults with grass-induced allergic rhinitis.¹⁹ Subjects were allocated to receive 1 of 3 treatment doses or placebo. Skin tape stripping was performed prior to patch placement for 8 hours, and subjects were treated with a total of 6 patches: 1 patch pre-pollen season and 5 weekly patches during the pollen season. The primary end-point was a patient-reported outcome of symptom improvement using a visual analog scale. A dose response was seen, with the greatest efficacy observed in the high-dose treatment group. Local side effects were common, but decreased over time. Systemic reactions leading to study dropout occurred in 8% of study patients, but were all reported to be World Allergy Organization (WAO) grade 1-2 in severity. A pediatric study that included 15 children also

demonstrated efficacy and safety of once-a-week patch placement for 12 weeks during the grass pollen season, further supporting this approach as a novel treatment for pollen allergies.²⁰

3 | EPIDERMAL DELIVERY SYSTEM (EPICUTANEOUS VIASKIN® PATCH—EVP)

In recent years, epicutaneous immunotherapy in food allergy has been pursued using a novel product that employs occlusion to increase allergen delivery across intact skin, the Epicutaneous Viaskin® Patch (EVP) (DBV Technologies, Paris, France).²¹ This approach aims to take advantage of the high density of Langerhans cells in the non-vascularized epidermis. When applied to the skin, moisture from natural transepidermal water loss accumulates under the EVP and dissolves the lyophilized allergen protein electrostatically adhering to the inside of the patch surface (Figure 1). The moisture collected under the EVP increases the permeability of the stratum corneum, allowing native protein to concentrate near target antigen-presenting immune cells. The epidermis is not vascularized, and therefore, systemic absorption of allergen is largely eliminated.

4 | EPICUTANEOUS VIASKIN® PATCH (EVP) IN MURINE MODELS OF IGE-MEDIATED FOOD ALLERGY

Potential efficacy and mechanisms of effect of EPIT have been explored using animal models. Utilizing a murine model of peanut allergy, repeated application of the EVP for 8 weeks resulted in

Epicutaneous Viaskin® Patch Technology

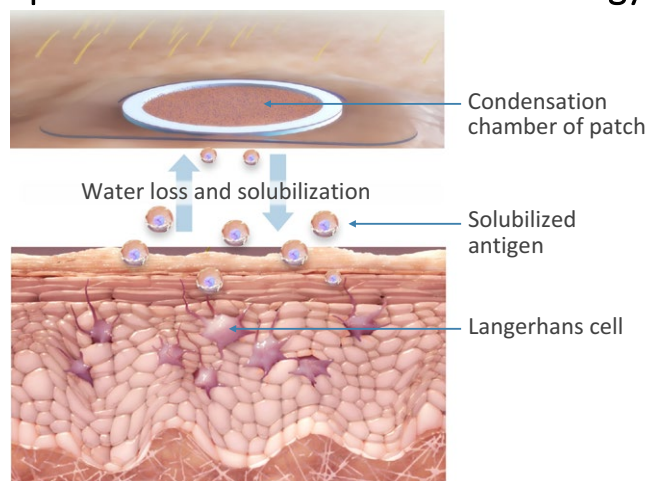


FIGURE 1 Epicutaneous Viaskin® Patch: The epicutaneous patch forms a condensation chamber that contains allergenic protein on its inner surface. When it is applied to intact skin, the skin's natural water loss solubilizes and releases allergen, which penetrates the stratum corneum and is then taken up by Langerhans cells that process and transport the allergen to regional lymph nodes where immune responses are initiated

comparable efficacy as SCIT in desensitization.²² No increase in histamine release was measured after oral challenge to peanut in EPIT-treated mice. Other immunologic changes included decreased levels of specific IgE, increased specific IgG2a, and decreased Th2 cytokine production by peanut-stimulated splenocytes, along with reduction in airway hyper-responsiveness and lung eosinophilia.^{22,23} EPIT was similarly effective for the treatment of other allergies, including ovalbumin (OVA), pollen, and house dust mite.²⁴

Application of EVP on intact skin targets antigen-presenting cells (APCs) in the superficial layers of skin. Using fluorochrome-conjugated OVA, allergen was shown to be primarily captured by Langerhans cells in the epidermis within the first 24 hours of EVP placement.²⁴ Allergen delivery using the EVP occurs via active allergen capture, and APCs deliver allergen to the draining lymph nodes (LNs).²⁵ Transfer of OVA to regional lymph nodes was seen in sensitized, but not naïve mice, indicating that the immunologic status of the mice influences the uptake of allergens. Additional findings included a lack of passive movement of allergen through the dermis as well as allergen-specific cytokine responses in the regional LNs, suggesting activation of lymphocytes. Experiments using a peanut-sensitized mouse model demonstrated that the immune responses to application of EVP on intact skin versus disrupted skin differ.²³ On intact skin, predominantly Th1/Treg responses are induced. In this model, allergen is captured by the epidermal Langerhans cells, which then migrate to the draining lymph nodes. In contrast, Th2-skewed responses were observed when the EVP was applied to disrupted (inflamed) skin. These findings

are consistent with clinical findings in humans that peanut allergen exposure to eczematous inflamed skin is an important risk factor for sensitization.²⁶

Repeated application of EVP also leads to reduced recruitment of eosinophils to the skin after allergen exposure, and these decreased systemic allergen-specific immune responses are likely due to induction of Tregs.²⁵ More recent studies have found that allergen exposure by the various immunotherapeutic routes (OIT, SLIT, EPIT) induces different Treg subsets. Among the different phenotypes of Tregs, EPIT induces a population of Tregs that are Foxp3+ and latency-associated peptide (LAP)+.²⁷ EPIT induces both effector/memory and naïve (long-lived) Tregs, whereas only effector/memory Tregs are induced by OIT and SLIT, suggesting different mechanisms of effect depending on the route of allergen delivery.²⁸ In addition, EPIT induced Tregs bearing homing receptors for the skin (CLA), lung (CCR4), esophagus (CCR3), and gut (CCR9), whereas OIT induced Tregs predominantly with homing receptors to the gut (CCR9) and SLIT induced a lesser but significant number of Tregs bearing homing receptors to the skin and gut (Figure 2).²⁸ Additional studies demonstrate that the epicutaneous route induces Foxp3+ and LAP+ Tregs that bear homing receptors to the gut, lung, and skin and that protection from food-induced anaphylaxis occurs via a TGF-beta-dependent mechanism.²⁷

Additional studies investigated the effect of early EPIT on prevention of sensitization to new allergens. Using a milk allergy model, sensitized mice underwent 8 weeks of EPIT containing milk protein. Tregs were isolated from the EPIT-treated mice and

Homing receptors allow EPIT-induced tregs to target sites of allergic reactivity

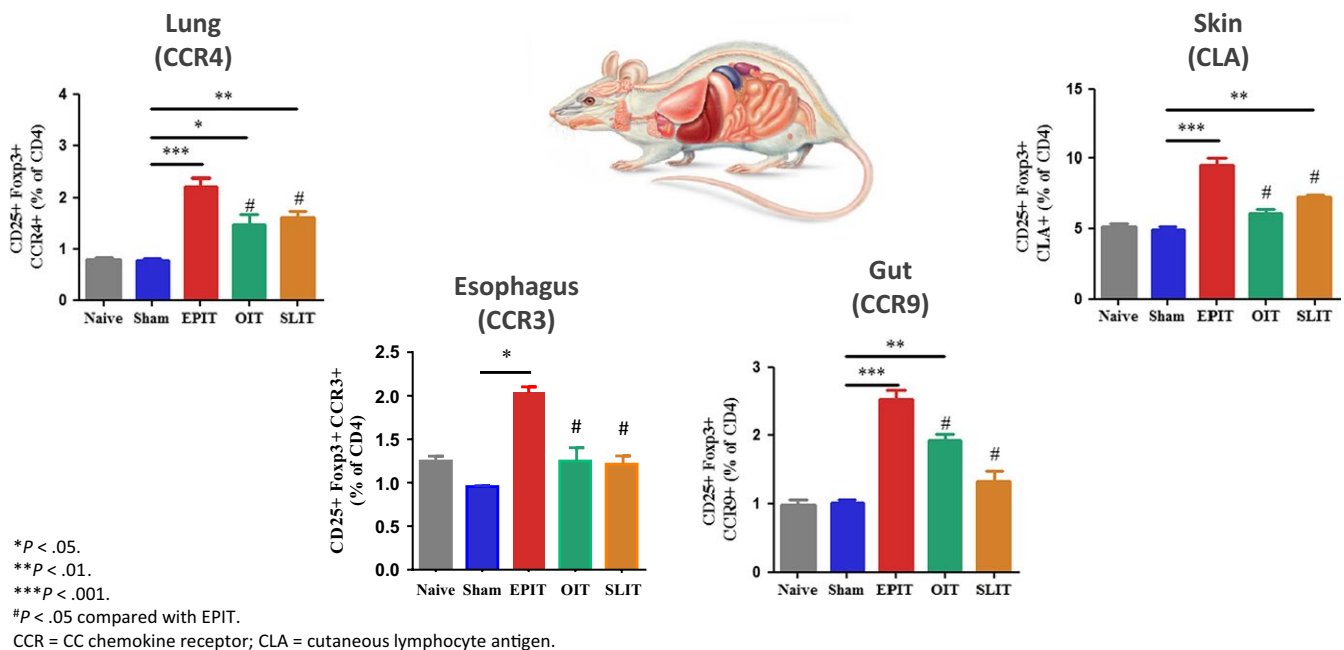


FIGURE 2 Epicutaneous immunotherapy has the unique property of inducing Tregs bearing homing receptors for other target organs, for example, the skin (CLA), lung (CCR4), esophagus (CCR3), and gut (CCR9)

injected into mice that then underwent a protocol to sensitize them to peanut and house dust mite. The mice were then challenged, and those mice receiving Tregs from the EPIT-treated mice did not develop new sensitizations whereas mice receiving Tregs from untreated mice developed sensitivity to peanut and house dust mite, demonstrating that this protective effect was Treg-dependent.²⁹ These results suggest that EPIT may be not only effective for the treatment of established allergic disease, but may also have a role in influencing future sensitization, for example, the atopic march.

5 | EPICUTANEOUS VIASKIN® PATCH IN CLINICAL TRIALS

To date, results from 4 clinical trials examining EVP for milk and peanut allergies have been published in peer-review form, 1 for milk and 3 for peanut. One of the peanut studies reports only safety data, whereas the other studies provide information on both safety and efficacy. There are several larger-scale studies that are ongoing which will provide a more robust assessment of safety and efficacy in the near future.

5.1 | Safety

The first EPIT study was performed in children 3 months to 15 years of age with a history of systemic allergic reactions to milk.²¹ Nineteen subjects were randomized 1:1 to receive active Viaskin patch (1 mg milk powder) or placebo (1 mg glucose). Patches were applied for 48 hours, 3 times per week for 3 months. Active treated subjects had higher rates of local, patch site symptoms, but there were no interruptions in treatment due to adverse events (AEs). No serious AEs and no epinephrine use were reported in this study.

Three studies examining EPIT for peanut allergy, with a total of 395 subjects, have been published. Results from these studies demonstrate a favorable safety profile, with no serious AEs and no non-anaphylactic gastrointestinal AEs. The first was a randomized, double-blind, placebo-controlled dose-ranging phase Ib study where 100 subjects aged 6-50 years with peanut allergy were enrolled.³⁰ Subjects were randomized 4:1 active:placebo to 20, 100, 250, or 500 mcg or placebo patch at 24- or 48-hour intervals for 2 weeks (500 mcg was not used in children). The second was a phase IIb, multinational, randomized, controlled dose-ranging trial where 221 subjects were randomized (1:1:1:1) to receive a daily epicutaneous patch containing 50, 100, or 250 mcg of peanut protein or placebo for 12 months.³¹ And the third was a NIH-sponsored phase II, multicenter, double-blind, randomized, placebo-controlled trial that enrolled 74 subjects aged 4-25 years who received a daily epicutaneous patch containing 100 or 250 mcg of peanut protein or placebo (1:1:1 randomization) for 52 weeks.³²

Adverse events primarily included mild symptoms localized to the patch sites. When treatment was needed, topical treatment with corticosteroids and/or oral antihistamines was sufficient to relieve symptoms. Local patch site reactions tended to be more frequent in the active vs placebo cohort (84% vs 60%, $P = .21$).³⁰ Fewer local

reactions were seen with the 24-hour patch placement compared to 48 hours,³⁰ and overall, more frequent symptoms were reported for the 250 mcg dose compared to 100 mcg.^{30,32} Local AEs often decreased over time and did not impede continuation of treatment.³¹ AEs outside of the patch site were uncommon, and no significant differences were reported between active doses as compared to the placebo.^{30,32} In addition, no differences in other safety parameters measured (including vital signs, physical examination, atopic dermatitis severity, peak expiratory flow/FEV1, and clinical laboratory results) were reported.³⁰

High adherence rates were reported in the peanut studies (all > 96%).³⁰⁻³² In addition, a low rate of dropouts occurred across the 3 peanut EPIT studies. In the phase Ib trial, 1 placebo and 3 active subjects withdrew early.³⁰ Three (1 placebo and 2 active) were withdrawn for treatment-related AEs. In the NIH-sponsored phase II trial, 3 placebo and 3 active patients withdrew early, with only 1 in the active group due to treatment-related AEs.³² In the large-scale phase IIb study, the dropout rate for treatment-related AEs was 0.9%.³¹

Results to date demonstrate a high-safety profile, with majority of AEs being mild and localized to the skin patch site (Table 1). Low rates of AEs outside the application site have been reported. This has been coupled with a high rate of adherence across the published trials. Unlike OIT and SLIT, no persistent GI symptoms or eosinophilic esophagitis has been reported with EPIT treatment.³³

5.2 | Efficacy

The first pilot study examined the efficacy of EPIT to treat milk allergy.²¹ Children aged 3 months-15 years who had a history of milk allergy underwent baseline food challenges (cumulative tolerated dose < 10 mL milk) prior to randomization (1:1 active Viaskin patch containing 1 mg milk powder or placebo containing 1 mg glucose). Twenty-one subjects were screened and 19 randomized (10 active, 9 placebo). Patches were applied for 48 hours 3 times per week for 3 months. In the per-protocol population, the active group had change in cumulative tolerated dose (CTD) from a mean $\pm$ SD of 1.77 ± 2.98 mL milk at baseline to 23.61 ± 28.61 mL post-treatment ($P = .18$). Mean CTD was unchanged in the placebo group (4.36 ± 5.87 mL at baseline to 5.44 ± 5.88 mL post-treatment). This short pilot study demonstrated a trend toward efficacy, prompting further study of this approach for treating food allergy.

To date, 2 double-blind, randomized, placebo-controlled studies have assessed efficacy of EPIT for peanut allergy. One phase IIb dose-ranging trial enrolled subjects with peanut allergy from 22 centers in the United States and Europe.³¹ Eligible subjects were 6-55 years of age who had an eliciting dose less than or equal to 300 mg peanut protein at the baseline double-blind, placebo-controlled food challenge (DBPCFC) using the PRACTALL-recommended dosing schedule, that is, 1, 3, 10, 30, 100, and 300 mg.³⁴ The primary endpoint was an eliciting dose at the 12-month DBPCFC of 1000 mg peanut protein or greater (~ 4 peanuts) or a 10-fold or greater increase over the eliciting dose at the baseline DBPCFC. A total of 221 subjects were randomized (1:1:1:1) to receive a daily epicutaneous

patch containing 50, 100, or 250 mcg of peanut protein or placebo. Subjects < 12 years of age had the patch applied to the upper central back area, and those 12 years of age and older applied the patch to the inside of the upper arm. The median age of subjects was 11 years, and 93.7% completed the trial. At the 12-month DBPCFC, a significant absolute difference in response rate was observed between the highest dose group and placebo (50% vs 25%, $P = .01$). An age interaction was seen in the highest dose group, with a significant response rate seen in the 6- to 11-year-old subgroup (53.6% active vs 19.4% placebo, $P = .008$). The median cumulative reactive dose in this group overall increased from 30 mg to 400 mg of peanut protein (one-tenth to one and one-third peanuts) in 1 year. No difference was seen in the adolescent/adult cohort.

The authors noted that the results may have been affected by a higher-than-expected placebo response rate, given that one of the primary end-point parameters of 10-fold or greater increase in eliciting dose may not have been stringent enough at the lower doses of the DBPCFC. In addition, this end-point may not be clinically meaningful as such a small incremental increase in reactive dose may not be sufficient to provide protection in case of true accidental

exposures, for example, change from 1 mg to 10 mg post-treatment dose. The authors also postulated that the age effect observed may be due to differing patch placement location for younger subjects (back) compared to older subjects (upper inner arms). Other possible limitations considered included suboptimal dosing effect for older subjects with higher weight or body surface area, differences in skin characteristics by age, and less immunoplasticity in older participants, which has also been suggested in OIT and SLIT studies.

Immunologic changes included increases in median peanut-specific IgE over the first 3-6 months in all 3 active treatment arms, followed by declines in levels to near baseline by month 12.³¹ A progressive 5-fold increase in peanut-specific IgG₄ was observed over the course of the 12-month treatment period. Diminished skin test median wheal diameters were also noted between months 6 and 12 for all 3 active groups.

A 2-year open-label extension trial followed, in which 82.6% (171) of those completing the initial blinded trial were enrolled.³¹ All were transitioned to the 250 mcg patch at month 6 of this extension study. Food challenges were performed at yearly intervals. The response rate was 59.7% at month 12 and 64.5% at month 24

TABLE 1 Clinical trials for EPIT assessing safety

Study	Subjects	Design	Safety
Pilot milk EPIT study ²¹	N = 19; 3 mo-15 y; history of systemic allergic reactions to milk	Double-blind, randomized, placebo-controlled study Application: 48 h, 3 times per week for 3 mo Doses: 1 mg milk powder or placebo	Local AEs: 4 subjects in the active group, 2 subjects in the placebo group Non-local AEs: 24 systemic AEs in the active group, 8 in the placebo group; no anaphylaxis Epinephrine: none
Phase Ib peanut study ³⁰	N = 100; 6-50 y	Double-blind, randomized, placebo-controlled study Application: 24 or 48 h for 2 wk Doses: 20, 100, 250 or 500 mcg or placebo	Treatment-emergent AEs (TEAEs): 52.5% subjects in the active group had at least 1 TEAE, 45% subjects in the placebo group No severe AEs Epinephrine: none
Phase IIb dose-ranging peanut study ³¹	N = 221; 6-55 y	Double-blind, randomized, placebo-controlled study Application: 24 h, daily for 12 mo Doses: 50 mcg, 100 mcg, or 250 mcg of peanut protein or placebo	All TEAEs: 50 mcg group—96.2% 100 mcg group—94.6% 250 mcg group—96.4% Placebo group—48.2% More generalized allergic TEAEs ~25% 20 serious AEs, none related to study drug (occurred during food challenges and accidental peanut ingestion)
Phase II peanut study ³²	N = 74; 4-25 y	Double-blind, randomized, placebo-controlled study Application: 24 h, daily for 52 wk Doses: 100 mcg or 250 mcg of peanut protein or placebo	All active treated subjects reported at least 1 symptom related to dosing Overall rate of AEs by dose: 100 mcg group—79.8% 250 mcg group—79.8% placebo group—14.4% Reactions extending outside the patch site: 100 mcg group—8.9% 250 mcg group—16.2% placebo group—1.5% 3 unrelated serious AEs reported: syncopal episodes, abdominal pain, and migraines

(6–11 years: 63.3% and 68.4%; adolescents/adults: 54.2% and 57.8% at months 12 and 24, respectively). In 21 children receiving the 250 mcg patch for all 3 years (phase IIb trial + 2-year extension trial), the response rate was 57.1%, 80.0%, and 83.3% at the end of years 1, 2, and 3, respectively. The median (mean) cumulative reactive dose (CRD) increased from 44 mg (84.5 mg) at baseline to 444 mg (1067.8 mg), 1440 mg (1883.5 mg), and 1440 mg (2453.9 mg) at years 1, 2, and 3 years, respectively. Overall, 61% of the children achieved a CRD $\geq$ 1000 mg and 39% achieved a CRD $\geq$ 5000 mg. Following 3 years of treatment, peanut-specific IgE levels decreased by 40% compared to baseline values, while peanut-specific IgG₄ levels remained about 4-fold greater than baseline. Given that there was no placebo arm in the 2-year extension study, conclusions regarding the potential benefits of longer duration of treatment must be interpreted with caution.

The NIH-sponsored phase IIb trial enrolled 74 subjects aged 4–25 years from 5 U.S. sites.³² Eligible subjects had a positive DBPCFC at a cumulative dose of less than or equal to 1044 mg peanut protein. Subjects were randomized (1:1:1) to receive a daily epicutaneous patch containing 100 mcg or 250 mcg of peanut protein or placebo for 52 weeks. The primary end-point was passing a challenge of 5044 mg or a 10-fold or greater increase in successfully consumed dose as compared to baseline. Treatment success was achieved by 45.8% and 48.0% of the 2 treatment groups (100 mcg and 250 mcg, $P = .005$ and $P = .003$, respectively) as compared to 12% in the placebo group. Post hoc analysis using a stricter definition of 10-fold increase and no dose-limiting symptoms at 1044 mg peanut protein revealed that less than 15% of treated subjects achieved this level of efficacy following 1 year of therapy. Those

who did improve were all younger than 11 years of age, suggesting an age effect similar to the larger phase IIb study results. No dose effect was seen when comparing the 100 mcg group vs the 250 mcg group. Associated immunologic changes included increases in peanut-specific IgG₄ and IgG₄/IgE ratios and reduction in T-cell and basophil responses.

Thus far, results demonstrate that EPIT shows significant efficacy after 1 year, although inducing less change in the threshold eliciting dose from baseline to 1 year compared to published reports of high-dose OIT (2–4 g daily maintenance dose) for 1 year. However, EPIT efficacy continues to increase with more prolonged treatment (Table 2). An age effect has been noted, with improvements seen primarily in children aged 11 years or younger. The clinical findings are associated with significant immunologic changes, including decreases in skin tests and allergen-specific IgE, increases in specific IgG₄, and reductions in T-cell and basophil responses, which are similar to changes seen in OIT and SLIT. Outcomes of longer duration treatment suggest increases in efficacy, but sustained effects of EPIT treatment after discontinuation have not yet been published.

5.3 | Ongoing studies

Ongoing trials should provide a better understanding of the safety and efficacy of EPIT using the EVP. MILES is a phase I/II study for children with milk allergy aged 2–17 years (ClinicalTrials.gov Identifier: NCT02223182). Phase I was a safety study of 150, 300, and 500 mcg doses versus placebo over 3 weeks in 18 subjects. This part of the study has been completed, and the phase II portion evaluating safety and efficacy of the 3 doses versus placebo for 12 months aims to

TABLE 2 Clinical trials of EPIT assessing efficacy

Study	Primary outcome	Results
Pilot milk EPIT study ²¹	Increase in CTD after 3 mo	No significant difference in mean CTD in the per-protocol analysis ($P = .13$): Active— 1.77 ± 2.98 mL to 23.61 ± 28.61 mL Placebo— 4.36 ± 5.87 mL to 5.44 ± 5.88 mL
Phase IIb dose-ranging peanut study ³¹	Eliciting dose at the 12-mo DBPCFC of (1). 1000 mg peanut protein or greater or (2). 10-fold or greater increase over the eliciting dose at the baseline DBPCFC	Response rate: significant difference comparing 250 mcg vs placebo (50% vs 25%, $P = .01$). Significant response rate seen in the 6- to 11-y-old subgroup (53.6% active vs 19.4% placebo, $P = .008$). No difference was seen for the adolescents/adults.
Open-label extension trial ³¹	All were transitioned to the 250 mcg patch at month 6 of this extension study; food challenges performed yearly	Overall response rate: 1 y—59.7% 2 y—64.5% 61% of the children achieved a CRD $\geq$ 1000 mg and 39% achieved a CRD $\geq$ 5000 mg
Phase II peanut study ³²	Passing a challenge of 5044 mg or a 10-fold or greater increase in successfully consumed dose as compared to baseline DBPCFC	Treatment success: 100 mcg—45.8% (compared to placebo, $P = .005$) 250 mcg—48.0% (compared to placebo, $P = .003$)

enroll up to 176 subjects in North America. All eligible subjects have an eliciting dose ≤ 300 mg milk protein at the baseline DBPCFC. The primary end-point will be assessed at 12 months by DBPCFC, with success defined as 10-fold or greater increase in cumulative reactive dose (CRD) compared to baseline and tolerance to at least 144 mg milk protein or CRD of ≥ 1444 mg milk protein.

Several large-scale trials of EPIT for peanut allergy have started. PEPITES (ClinicalTrials.gov Identifier: NCT02636699) is a multinational phase III trial using the 250 mcg peanut patch in 356 children 4-11 years of age. PEOPLE (NCT03013517) is the follow-up extension study, and 300 subjects (93%) completing PEPITES elected to enroll. Another phase III trial (REALISE—NCT02916446) enrolled subjects without baseline food challenges to more closely match real-life use if this therapy becomes available; 393 subjects, aged 4-11 years, have been enrolled in this multicenter, randomized double-blind, placebo-controlled trial. Given the greater effect in younger children and favorable safety profile, a phase III trial for peanut in younger children, aged 1-3 years, has also begun (EPITOPE—NCT03211247).

Epicutaneous immunotherapy is also being explored as a potential treatment for eosinophilic gastrointestinal diseases (EGIDs). In a murine model of allergic esophago-gastro-enteropathy induced by sustained oral peanut exposure, EPIT treatment prior to peanut exposure led to reduced esophageal eosinophilia and diminished Th2 immune responses.³⁵ Recently, a piglet model of EGID induced by peanut was developed.³⁶ Using this large animal model, 3 months of EPIT resulted in significant reductions in gastric mucosal lesions and gastric mucosa eosinophil counts, supporting the concept that EPIT may also have a role beyond the treatment of IgE-mediated food allergy, to EGIDs as well. Currently, there is an ongoing phase IIA study evaluating safety and efficacy of EPIT for milk-induced eosinophilic esophagitis in children 4-17 years of age (SMILEE—ClinicalTrials.gov Identifier: NCT02579876).

6 | NEXT STEPS/ADDITIONAL QUESTIONS

Further exploration of EPIT is needed to improve understanding of the potential role of this approach for food allergy treatment. Although comparison of published clinical trial data is limited by the heterogeneity in study designs, it appears that EPIT efficacy may be similar to that of SLIT,³⁷ but efficacy does not reach the levels seen in high-dose OIT.^{38,39} EPIT may be more comparable in efficacy to low-dose OIT, which has been examined in some studies. In a short-term phase II trial of low-dose peanut OIT (300 mg; AR101), which is also being evaluated for commercial distribution,⁴⁰ 55 subjects (29 AR101, 26 placebo) enrolled, and 79% and 62% of active subjects tolerated 443 mg and 1043 mg cumulative reactive dose at the exit DBPCFC, respectively (median therapy = 22 weeks; mean = 24 weeks). In contrast, 19% and 0% of placebo subjects achieved these parameters ($P < .0001$). Consistent with other OIT studies, 20% of active subjects dropped out of the study prior to the exit DBPCFC. Ongoing EPIT studies will continue to examine outcomes of longer treatment duration to determine whether efficacy

similar to that seen in low-dose OIT can be achieved in larger groups. In addition, studies will explore whether efficacy is sustained after treatment discontinuation. Identification of biomarkers that would allow for determination of efficacy and predict treatment outcome is essential.

Assuming multiple options will become available to food-allergic individuals, the decision for choosing which approach to use will likely depend on patient-specific factors such as age and allergy history as well as their preferences and values. The different routes of immunotherapies have shown differing levels of safety and efficacy, with higher efficacy approaches having the drawback of lower safety profiles. EPIT has the advantages of a high-safety profile and convenient home administration, which may appeal to certain patients and/or families. Currently, there are no comparisons of rates of adverse reactions in the real world between those receiving treatment and those continuing with the current standard of care of allergen avoidance. However, quantitative risk assessment suggests that raising the thresholds of reactivity by immunotherapy is clinically relevant.⁴¹ Increasing the threshold from 30 mg peanut protein pre-treatment to 300 mg post-treatment reduces the risk of allergic reaction by $>99\%$, and additional risk reduction would be seen with threshold increases to 1000 mg. Quality-of-life assessments are starting to be investigated, but no large-scale studies are yet published. Ultimately, a patient-centered approach that takes into account these various factors will have an important influence on treatment/management selection.

7 | CONCLUSION

Epicutaneous immunotherapy represents an important addition to the growing potential options for treating food allergies. Murine models have provided insights into possible mechanisms underlying this approach to immunotherapy, including the unique induction of naïve (long-lived) T-regulatory cells and T-regulatory cells bearing homing receptors to skin, gut, and respiratory tract. Several clinical trials of EPIT have been completed, showing favorable safety profiles and good tolerability leading to high adherence rates. There are no head-to-head studies, but results reported to date suggest that efficacy and immunologic changes may be comparable to SLIT, which also uses lower dose allergen exposures.^{37,42} EPIT safety is more favorable as compared to SLIT and OIT, and no persistent gastrointestinal symptoms have been reported for EPIT. If longer durations of immunotherapy can lead to greater efficacy, as suggested in a small subset of patients in the phase IIb extension trial,³¹ then the high rates of adherence and ease of use for EPIT would make this a desirable option for many.

The potential power of the cutaneous immune system in regulating systemic immune responses presents intriguing possibilities for further exploration. For example, in the clinical studies published to date, the daily exposure of peanut protein on the skin is 1/10th the daily oral exposure with SLIT and 1/1200th the daily oral exposure with low-dose (300 mg) OIT (ie, 3 years of EPIT exposes patients to

less peanut protein than a single administration of low-dose OIT). As suggested in preclinical studies and early clinical trials, the epicutaneous induction of Treg cells may be useful for treating non-IgE-mediated disorders as well, for example, Th2-mediated eosinophilic esophagitis and Th1-mediated autoimmune disorders such as relapsing multiple sclerosis.⁴³ Future studies should aim to explore this potential, elucidate mechanisms of effect in humans, and provide more robust data regarding safety, efficacy, and durability of effects.

CONFLICT OF INTEREST

J. Wang receives research support via grants to her institution (from NIAID, Aimmune, and DBV Technologies), has received consulting fees from Aimmune and DBV Technologies, and receives royalties from UpToDate. H.A. Sampson receives research support via grants to his institution from NIAID and is the Chief Scientific Officer at DBV Technologies (60%) and a consultant for Allertein Therapeutics, LLC.

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