Food allergy: Epicutaneous immunotherapy

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ABSTRACT

The goal of allergen-specific immunotherapy for treatment of immunoglobulin E (IgE) mediated food allergy is to safely and effectively modify the allergic response, providing protection against anaphylaxis via ongoing exposure to the triggering allergen. Targeted allergen exposure via *application of allergen to the epidermis has emerged as a potentially promising approach to desensitization. Epicutaneous immunotherapy (EPIT) uses allergen embedded on an adhesive patch secured to the skin. This allows for long-lasting allergen exposure, with subsequent antigen uptake and trafficking by skin antigen–presenting cells to regional lymph nodes, which produce immunomodulatory effects in a manner that is noninvasive and limits exposure of allergen to the systemic circulation when applied to intact skin. As such, EPIT is overall well tolerated; local application site reactions are common, but systemic adverse effects are infrequent compared with other forms of immunotherapy. For peanut allergy, EPIT may increase the dose-triggering threshold in some individuals with peanut-allergy, especially younger children, but induction of remission has not been closely studied, and reliable predictors of clinical response are lacking. With U.S. Food and Drug Administration approved treatment for peanut allergy now available, the precepts of shared decision-making will be crucial in discussions with patients and their families with regard to treatment options.*

(J Food Allergy 2:81–85, 2020; doi: 10.2500/jfa.2020.2.200016)

Food allergy is common, with evidence of shifting prevalence and differences across demographic groups as reviewed by Jiang et al.[1] It is associated with extensive burden, which manifests not only as a potentially life-threatening condition but which also produces significant adverse psychosocial effects.[2] Although the foundation of food allergy management has been anchored in allergen avoidance and preparation to manage accidental exposures, there has been a recent, rapid expansion of investigation into different forms of allergen-specific immunotherapy that target immunoglobulin E (IgE) mediated food allergies.[3] Allergen-specific immunotherapy seeks to achieve desensitization through exposure to an allergen at regular intervals and doses, with the goal of increasing the dose-eliciting threshold for systemic reactions to a given allergen.[4] The greater goal of achieving sustained tolerance maintained after cessation of immunotherapy remains elusive and understudied. This review highlights recent developments in the understanding of the mechanisms and clinical use of EPIT.

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J.A. Bird reports personal fees from Food Allergy Research and Education, personal fees and non-financial support from American College of Allergy, Asthma and Immunology, grants from Nestle Health Sciences, personal fees from Nutricia North America, personal fees from Pharm-Olam International Ltd, personal fees and other from Pfizer Pharmaceuticals, grants, personal fees and non-financial support from Aimmune Therapeutics, personal fees from Prota Therapeutics, personal fees from Allergy Therapeutics, Ltd, grants from the National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), grants from Novartis, personal fees from AllerGenis, personal fees from Abbott Nutrition International, grants and personal fees from DBV Technologies, outside the submitted work. C.P. Parrish reports personal fees from Aimmune Therapeutics, grants and non-financial support from DBV Technologies, grants from NIH-NIAID, grants form Novartis, grants from Regeneron, outside the submitted work. T. Chow has no conflicts of interest to declare pertaining to this article

Funded by Food Allergy Research & Education (FARE)

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MECHANISMS OF EPIT

The first reports of EPIT were in allergic asthma, in which an allergen was introduced onto scarified skin, facilitating rapid systemic absorption of the allergen.[5] Since then, the recognition of skin as an immune organ that plays a complex role in immunomodulatory responses to an allergen has led to advances in EPIT, which harness the skin's innate immune properties without producing a proinflammatory response. In its modern form, EPIT embeds the allergen on a patch that is secured to the skin by surrounding adhesive, allowing for long-lasting allergen exposure that is noninvasive and does not lead to distribution of the allergen through systemic circulation when applied to intact skin.[6] This diminished allergen exposure to vascular circulation is a distinguishing factor of EPIT compared with other forms of immunotherapy, which contributes to the improved clinical safety profile of EPIT.

Through the process of antigen uptake by cutaneous antigen-presenting cells and trafficking to regional

lymph nodes, EPIT subsequently produces a broad range of immunomodulatory cellular and humoral effects. Almost all of our current understanding of the immune mechanisms of EPIT comes from murine models. The induction of regulatory T cells (Treg) is a critical mechanism of EPIT, highlighted by observations that Treg ablation leads to abrogation of EPIT response in mice.[7] This cascade of events is initiated by allergen presentation to intact skin, leading to antigen uptake by antigen-presenting cells, such as epidermal Langerhans cells (LC).[8,9] Antigen-presenting LCs migrate to regional lymph nodes and induce differentiation of Tregs that target sites of allergic reactivity.[9] LC antigen presentation seems to be necessary for a robust Treg induction response; LC-depleted mouse models have significantly decreased Treg induction despite the presence of other antigen-presenting cells such as type-2 conventional dendritic cells.[10]

The mode of immunotherapy seems to have a significant impact on the unique populations of Tregs that are induced. Tregs induced by EPIT have been shown in a murine model to exhibit greater expression of target organ homing receptors as well as a longer duration of Treg suppressive action after immunotherapy discontinuation compared with oral immunotherapy (OIT) and sublingual immunotherapy.[11] One mechanism that contributes to the sustained suppressive activity may be epigenetic modifications produced by EPIT; Mondoulet *et al.*[12] demonstrated epigenetic modifications in response to EPIT that favor a Treg-mediated immune response through the upregulation of Treg transcription factors and downregulation of T-helper type 2 regulators, *e.g.,* GATA3. These Tregs then downregulate T-helper type 2 responses, with subsequent decreases in mediators such as interleukin 4, interleukin 13, and end-organ eosinophil recruitment.[6,11] Interestingly, there may be a protective effect from single antigen EPIT in reducing further sensitization to other antigens; in a murine model, milk EPIT was observed to prevent the development of subsequent peanut and human dust mite sensitization.[13] EPIT also has an impact on humoral responses. EPIT applied to intact skin decreases antigen-specific IgE production and increases IgG2a production in a murine model.[6] A humoral response has also been identified in humans undergoing EPIT; Koppelman *et al.*[14] demonstrated that children undergoing peanut EPIT responded with increases in IgG4 to major peanut allergens *in vivo.*

SAFETY AND EFFICACY OF EPIT

The primary EPIT product currently being investigated in clinical trials is the epicutaneous Viaskin Patch (DBV Technologies, Paris, France). Applied to intact skin, the Viaskin patch interacts with moisture, which results from basal transepidermal water loss, dissolving lyophilized allergen protein contained on the patch surface.[6] Other modalities under investigation include the use of microneedle arrays to deliver protein powder without significant physical disruption of skin, which has shown some initial promise as an effective delivery device in mice.[15] The first study that investigated Viaskin in cow's milk allergy was a pilot study to determine short-term safety and tolerability, and demonstrated that milk EPIT was well tolerated, with a nonsignificant trend toward improvement in the cumulative tolerated dose of milk.[16] This prompted further investigation with a phase I/II study that evaluated Viaskin milk at 150-, 300-, and 500-μg doses (Efficacy and Safety of Viaskin Milk in Children With IgE-Mediated Cow's Milk Allergy (MILES), NCT02223182),[17] which is ongoing.

Investigation of peanut EPIT has been the primary focus of subsequent clinical trials. After safety and tolerability were demonstrated in a phase I study, two phase II studies were completed.[18–20] The first was a double-blind placebo controlled (DBPC) study Consortium of Food Allergy Research (CoFAR)6 that randomized 74 patients, ages 4 to 25 years, with peanut allergy to Viaskin peanut 100 μg, 250 μg, or placebo for 12 months of treatment.[18] The primary outcome was defined as passing a 5044 mg of peanut protein (one peanut is equal to ~250–300 mg of peanut protein) oral DBPCFC or tolerating a ≥10-fold increase in peanut protein from baseline. The 10-fold increase in successfully consumed dose end point was achieved by 45% and 48% of subjects at the 100-μg and 250-μg doses of Viaskin peanut respectively, significant compared with 12% of subjects taking placebo. Preplanned analysis revealed the greatest effect in the 4–11-year-old group.[19]

The second study was a larger phase IIb DBPC study (Efficacy and Safety of Several Doses of Viaskin Peanut in Adults and Children With Peanut Allergy (VIPES)) that randomized 221 patients, ages 6–55 years, with peanut allergy to Viaskin peanut 50 μg, 100 μg, 250 μg, or placebo for 12 months of treatment. The primary outcome was defined as the percentage of the treatment responders, defined as a ≥10-fold increase in symptom eliciting dose (ED) and/or an ED of ≥1000 mg of peanut protein at the end of 12 months. Treatment response was achieved in 50% of the subjects at the 250-μg dose compared with 25% of placebo ($p = 0.01$); no difference was demonstrated at the 100-μg dose, and the 50-μg dose was not compared secondary to statistical testing hierarchical rules.

In a secondary analysis of age-related differences in treatment effect, only the 6–11-year-old group showed significant change in primary outcome versus placebo (53.6 versus 19.5%; $p = 0.008$).[20] On completion of this trial, 168 subjects were enrolled in a 2-year open-label

extension Follow-up of the VIPES Study to Evaluate Efficacy and Safety of Viaskin Peanut in Adults and Children (OLFUS-VIPES) and transitioned to the 250-μg dose.[20] Repeated DBPC food challenges during this extension were performed after 12 months and 24 months. The treatment response was achieved in 59.7% and 64.5% at 12 months and 24 months of extended treatment, respectively.[20] These studies demonstrated common local skin reactions but no serious dose-related adverse events and excellent adherence.[19,20]

Given that the greatest treatment effect was observed in younger children, subsequent phase III studies have focused on this age group. The first published results were from a DBPC study Efficacy and Safety of Viaskin Peanut in Children With Immunoglobulin E (IgE)-Mediated Peanut Allergy (PEPITES), which randomized 356 subjects, ages 4–11 years, with peanut allergy to Viaskin peanut 250 μg or placebo in a 2:1 fashion.[21] The primary outcome was the percentage difference in response between treatment and placebo groups; treatment response was defined based on baseline ED. For subjects with a baseline ED $\leq$ 10 mg of peanut protein, a positive response was defined as an increase in ED to $\geq$300 mg. For subjects with ED between 10 and 300 mg, a positive response was defined as an increase in ED to $\geq$1000 mg. The primary outcome was achieved in 35.3% of the treatment group compared with 13.6% in the placebo group ($p < 0.001$). However, the study did not meet the prespecified definition of a positive trial because the lower bound of 95% confidence interval for the difference in response rate between treatment and placebo groups crossed a prespecified threshold of 15%.

The clinical relevance of this statistical measure is not clear in the setting of food immunotherapy in which there currently are no established treatments. Similar to previous studies, the most common adverse event was local skin reactions.[21] There were 26 episodes of anaphylaxis; 10 of these were possibly drug related, and none were severe or required more than one dose of epinephrine. On further review of the 10 episodes of possible treatment-related anaphylaxis, one was considered definitively related, three were probably related, and the rest were possibly related to treatment.[21] Additional ongoing studies include a follow-up phase III study to the PEPITES study[21] that evaluated the long-term efficacy and safety of Viaskin peanut 250 μg in children ages 4–11 years (Follow-up of the PEPITES Study to Evaluate Long-term Efficacy and Safety of Viaskin Peanut in Children (PEOPLE), NCT03013517).[22] In addition, a phase III study that evaluated the safety and efficacy of Viaskin peanut 250 μg in children, ages 1–3 years, with peanut allergy is currently recruiting patients (Safety and Efficacy Study of Viaskin Peanut in Peanut-allergic Young Children 1–3 Years of Age (EPITOPE), NCT03211247),[23] with an open-label extension planned to follow (Follow-up of the EPITOPE Study to Evaluate Long-term Efficacy and Safety of DBV712 in Young Children (EPOPEX), NCT03859700).[24]

Whether EPIT achieves "field efficacy," which reduces reactions from accidental exposures to peanut, has not yet been demonstrated, but efforts have been made to estimate the clinical benefits that result from achieving increased ED thresholds noted in interventional clinical trials.[25] In a separate statistical analysis with Monte Carlo simulations, treatment with Viaskin 250 μg was modeled to have a 73.2–78.4% relative risk reduction for allergic reactions secondary to unintended exposure to peanut in packaged food products compared with a 2.5% risk reduction predicted in the placebo group.[26]

Furthermore, there is an investigation into the role of EPIT in managing non–IgE-mediated disease, such as eosinophilic esophagitis. A phase II study that evaluated Viaskin milk 500 μg in pediatric patients with milk-induced eosinophilic esophagitis demonstrated tolerability with no drug-related serious adverse reactions as well as a significant decrease in esophageal eosinophils per high-power field in the milk EPIT group compared with control in the per-protocol analysis.[27] Intriguingly, after an 11-month open-label extension, 47% of evaluable subjects had mean values of <15 eosinophils per high-power field.[27]

EPIT Implementation in Clinical Practice: Next Steps

The investigations of EPIT described above have contributed to the growing understanding of the possible role that EPIT may play in the management of food allergy, with its advantages and limitations compared with other immunotherapy modalities as well as questions that require further investigation (Table 1). As multiple studies that evaluated Viaskin EPIT have demonstrated, EPIT is overall well tolerated, with excellent adherence to therapy observed throughout the duration of the studies. Local application-site reactions are common, but systemic symptoms are rare in comparison with other forms of immunotherapy. The risk of anaphylaxis due to therapy is low.

EPIT's favorable tolerability characteristics are balanced by the unpredictable and variable therapeutic benefit observed. EPIT may increase the dose-triggering threshold in some individuals, particularly younger children, but induction of remission has not been closely studied and reliable predictors of clinical response are lacking. Furthermore, there is no regular confirmation of efficacy as seen with daily ingestion of peanut in OIT.[28] At the present time, there are no surrogate biomarkers to gauge efficacy,

Table 1 **Advantages and limitations of epicutaneous immunotherapy**

	Advantage	Limitation	Unknown or More Study Needed
Adherence	High in studies to date Ingestion not required (avoids issue of allergen aversion)	Daily application Patch removal by child	Adherence outside of trials
Efficacy	Significant peanut desensitization effect ages 4–11 years for treatment responders	Surrogate biomarkers do not predict which patients will respond to treatment Approximately two-thirds of the patients in the phase III trial did not meet the primary end point Oral food challenge required to measure efficacy Phase II trials did not show significant treatment response in individuals with peanut-allergy ≥ 12 years	Translation of benefit with "real-life" accidental exposure to allergen Durability of treatment response Identification of likely treatment responders Treatment response in ages 1–3 years Efficacy for foods other than peanut Efficacy for eosinophilic esophagitis
Safety	Lack of detectable allergen in systemic circulation Rare systemic reactions Lack of gastrointestinal adverse effects	Frequent, mild local cutaneous reactions	Use in conjunction with other therapies

which makes observed oral food challenges necessary to measure the benefit from therapy.

With additional FDA-approved treatments for peanut allergy likely available in the next 1–2 years, the precepts of shared decision-making will be crucial in discussions with patients and their families regarding treatment options.[29] Further investigations will continue to guide these discussions. Key questions include further definition of populations that would most benefit from EPIT, evaluation of EPIT in food allergy apart from milk and peanut, and the identification of surrogate biomarkers to replace oral food challenges as the measure of efficacy. Also, although adjuvants have been explored with other forms of immunotherapy, recently reviewed by Nicolaides *et al.*,[30] this has not been investigated in EPIT.

CLINICAL PEARLS

- Additional FDA-approved treatment options for peanut allergy are likely within the next 1 to 2 years.
- Peanut allergy has been the focus of most EPIT investigations thus far, with evidence that peanut EPIT may elevate dose-triggering threshold, particularly in younger children.
- Further studies are needed to investigate EPIT in IgE-mediated food allergies apart from peanut as well as non–IgE-mediated processes, *e.g.*, eosinophilic esophagitis.
- EPIT is well tolerated with fewer and less-severe adverse reactions compared with OIT but efficacy is unpredictable without available serum biomarkers to gauge efficacy.

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