

# Advances in the Treatment of Food Allergy



## Sublingual and Epicutaneous Immunotherapy

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### KEYWORDS

- Allergen immunotherapy (AIT) • Sublingual immunotherapy (SLIT)
- Epicutaneous immunotherapy (EPIT) • Food allergy • Desensitization
- Oral tolerance • Sustained unresponsiveness

### KEY POINTS

- Food allergies have continued to increase in prevalence in the past decade and have become a significant health issue.
- In the search for efficacious, yet well-tolerated therapies, sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT) are being explored for the treatment of food allergy.
- SLIT and EPIT can increase threshold doses, which may provide at least partial protection against accidental exposures without suffering severe symptoms.
- More research is needed to define the optimal doses and administration protocol before these therapies can be offered to patients in clinical practice.

### INTRODUCTION

Food allergies have continued to increase in prevalence in the past decade and have emerged as a significant health issue.<sup>1</sup> Three percent to 6% of the population in the United States suffers from food allergy (FA),<sup>2</sup> and its prevalence in children has increased by 18% in the past decade.<sup>3</sup> Although 85% of patients may outgrow

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cow's milk and egg allergies, only approximately 20% of peanut-allergic and 10% of tree nut-allergic patients outgrow their allergies.<sup>4,5</sup>

The current standard of care in treating FA is a strict elimination diet and being prepared to treat allergic reactions owing to accidental exposures of trigger foods with medications such as antihistamines and self-injectable epinephrine. Despite careful avoidance, life-threatening reactions can still occur secondary to accidental exposures,<sup>6</sup> and the unpredictability of these acute reactions can significantly decrease the quality of life of individuals with FA.<sup>7</sup> A strict elimination diet can also lead to severe malnutrition in infancy and early childhood<sup>8</sup> when there is a higher nutritional demand for adequate growth and development.<sup>9,10</sup> For these reasons, safe and effective therapies for FA are necessary.

Allergen-specific immunotherapy (AIT) has the most potential for treating FA.<sup>11</sup> It relies on administering incremental doses of allergen by various routes, such as the subcutaneous, oral, sublingual, or epicutaneous.<sup>11</sup> The goal of AIT is to reorient the immune system; however, the precise mechanisms through which AIT affects this change are incompletely understood.<sup>11</sup> Evidence from studies suggest that AIT is involved in suppressing mast cell and basophil reactivity, reducing allergen-specific immunoglobulin (Ig)E while increasing allergen-specific IgG4 antibodies, skewing T-helper (Th)2 responses toward a Th1 phenotype, and stimulating the production of regulatory T cells (Tregs) that seem to be fundamental in inducing long-term tolerance.<sup>12,13</sup>

Food immunotherapy relies on the concept of desensitization and sustained unresponsiveness. The goal of early clinical trials in food immunotherapy was to desensitize patients to a maintenance dose, thus increasing the antigen threshold that can lead to an allergic reaction.<sup>11</sup> Studies being performed now are aimed at achieving a more sustained protective effect, termed sustained unresponsiveness, where patients have the ability to consume a large amount of an allergenic food without adverse reactions after discontinuing immunotherapy.<sup>14,15</sup> Permanent tolerance, in the context of FA immunotherapy, remains to be demonstrated.

Trials investigating immunotherapy to treat FA using subcutaneous administration of peanut extract were first conducted in the early 1990s.<sup>16,17</sup> However, subcutaneous immunotherapy (SCIT) was largely abandoned owing to the high level of anaphylactic reactions.<sup>17,18</sup> Since then, research in food immunotherapy has surged in the past 10 years.<sup>18</sup> Many studies have investigated oral immunotherapy (OIT), and the technique seems to be efficacious; however, a high rate of adverse reactions leading to patient withdrawal continues to drive the search for safer therapeutic options such as sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT).<sup>11</sup> In this article, we review the advances in SLIT and EPIT for the treatment of food allergies.

## SUBLINGUAL IMMUNOTHERAPY

SLIT uses the tolerogenic environment of the oral mucosa and is a well-established method of modulating the aberrant immune responses in individuals with allergic rhinitis.<sup>19</sup> Allergens in the form of drops or tablets are held under the tongue, using the immunogenic properties of the oral mucosa, thus promoting tolerance to the allergen.<sup>19</sup> The sublingual route of administering AIT was first studied in 1986 for the treatment of dust mite allergy.<sup>20</sup> Since then, numerous randomized, controlled trials have confirmed the safety and efficacy of SLIT in both adults and children for the treatment of environmental allergies.<sup>21–23</sup> Although the primary indication for SLIT remains allergic rhinoconjunctivitis, it is currently being explored for the treatment of FA.<sup>19,24</sup>

Since the first reported use of SLIT in FA in 2003,<sup>25</sup> several clinical trials have shown promising results. Studies examining SLIT for specific foods are described herein and listed in [Table 1](#).

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### **Kiwi**

SLIT was first used for the treatment of FA in a 29-year-old woman with a severe kiwi allergy.<sup>25</sup> During the 5-week buildup phase, the patient kept incremental doses of kiwi extract under her tongue for 1 minute and then swallowed. The patient reached a 3 times daily maintenance treatment regimen and tolerated consuming 1 cm<sup>3</sup> of fresh kiwi after sublingual application of the food for 1 minute. After 5 years, owing to other health concerns, the patient discontinued daily kiwi intake. She was able to resume kiwi consumption without any adverse effects 4 months later.<sup>25,26</sup>

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### **Hazelnut**

In 2005, Enrique and colleagues<sup>27</sup> performed the first double-blind, placebo-controlled (DBPC) SLIT trial. The study included 23 adults with hazelnut allergy, who were randomized to receive either hazelnut extract (n = 12) or placebo (n = 11). Although all subjects were positive on initial DBPC food challenge (DBPCFC) to hazelnut, 54.5% had oral allergy syndrome (OAS). The subjects held the extract under their tongue for 3 minutes and then spit it out. During the 4-day buildup phase, 11 of the 12 individuals (92%) from the active group were able to reach the target dose of 188.15 µg of major hazelnut allergen Cor a1 and 121.9 µg of Cor a8. They continued maintenance dosing at home for 8 to 12 weeks, and 5 of 11 individuals (45%) were able to ingest 20 g of hazelnut (about 15–20 hazelnuts) in a posttreatment DBPCFC without any symptoms. The mean tolerated dose in the treated individuals increased from 2.29 to 11.56 g.<sup>27</sup> Consistent with the desensitization, actively treated subjects had significantly increased levels of interleukin (IL)-10 in the peripheral blood compared with the placebo treated subjects. During a 1-year follow-up study, a subsequent DBPCFC was performed, and the mean tolerated dose further increased to 14.57 g and 5 of the 7 reached the highest planned dose of 20 g. Although SLIT seemed to be an effective tool in this study for desensitization, the high rate of OAS in the subjects (54.5%) makes it difficult to interpret the success in patients with hazelnut-induced anaphylaxis.<sup>27,28</sup>

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### **Milk**

In 2006, de Boissieu and colleagues<sup>29</sup> included 8 children (age 6–17 years) with cow's milk allergy in an open-label, pilot study. After reacting to an initial milk challenge, the subjects underwent milk SLIT to a goal dose of 1 mL/d of cow's milk over 6 months. The milk extract was kept under the tongue for 2 minutes and then spit out. Although 6 of the 8 children (75%) completed the protocol, only 3 (38%) were able to consume 200 mL of milk without symptoms during a posttreatment DBPCFC. The children did, however, have a higher posttreatment mean challenge threshold that increased from 39 to 143 mL.<sup>29</sup>

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### **Peach**

In 2008, Fernandez-Rivas and coworkers<sup>30</sup> conducted a DBPC trial for treatment of peach allergy with SLIT. Fifty-six adult subjects were randomized to receive active treatment (n = 37) or placebo (n = 19). A large number of the patients (63%) had only OAS to peach. The individuals underwent a 5-day inpatient buildup, which was followed by a maintenance dosing schedule of 3 times a week administration of 10 µg of the peach lipid protein Pru p 3 for 6 months. The doses were placed under

**Table 1**  
**Studies examining SLIT and EPIT for the treatment of food allergy**

| Study (Year)                              | Food     | Modality | Design                  | No. of Patients (Age Range) | Withdrawals/ Active Group | Maintenance Dose                                    | Challenge Dose | Duration         | Clinical Outcome                                                        | Adverse Events                                                                                                     |
|-------------------------------------------|----------|----------|-------------------------|-----------------------------|---------------------------|-----------------------------------------------------|----------------|------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| <b>SLIT</b>                               |          |          |                         |                             |                           |                                                     |                |                  |                                                                         |                                                                                                                    |
| Enrique et al, <sup>27</sup> 2005         | Hazelnut | SLIT     | DBPC RCT                | 23 (19–53)                  | 1/12                      | 13.25 mg/d                                          | 20 g           | 8–12 wk          | 5/11 completed OFC; ↑ threshold                                         | Systemic reactions 0.2% of total doses (1466); local reactions 7.4% of total doses (1466)                          |
| Fernandez-Rivas et al, <sup>30</sup> 2009 | Peach    | SLIT     | DBPC RCT                | 56 (18–65)                  | 4/37                      | 0.01 mg 3×/wk                                       | 3249 µg        | 6 mo             | ↑ threshold                                                             | Systemic reactions 0.4% and local reactions 39% of total doses (3378)                                              |
| De Boissieu & Dupont <sup>29</sup> 2006   | Milk     | SLIT     | Prospective case series | 8 (6–17)                    | 1/8                       | 1 mL/d                                              | 200 mL         | 6 mo             | 3/8 completed OFC; ↑ threshold                                          | No systemic reactions; 75% of patients reported subjective local symptoms                                          |
| Keet et al, <sup>34</sup> 2012            | Milk     | SLIT/OIT | Open RCT                | 30 (6–17)                   | 2/10                      | 7 mg (SLIT)<br>1000 mg/d (OITA)<br>2000 mg/d (OITB) | 8 g            | 60 wk (off 6 wk) | 1/10 SLIT vs 14/20 OIT completed OFC; 9/15 (OIT) sustained unresponsive | Systemic reactions 0.10% (buildup) and 0.02% (maintenance); OP reactions 26.82% (buildup) and 27.99% (maintenance) |
| Kim et al, <sup>31</sup> 2011             | Peanut   | SLIT     | DBPC RCT                | 18 (1–11)                   | 0/11                      | 2000 µg/d                                           | 2.5 g          | 12 mo            | ↑ threshold                                                             | Reactions 11.5% and OP itching 9.3% of total doses (4182)                                                          |

|                                        |        |          |          |                        |              |                                    |                                           |                     |                                                                                                                      |                                                                                                    |
|----------------------------------------|--------|----------|----------|------------------------|--------------|------------------------------------|-------------------------------------------|---------------------|----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| Chin et al, <sup>35</sup><br>2013      | Peanut | SLIT/OIT | DBPC RCT | 27 (2–11)<br>23 (3–10) | 0/27<br>5/23 | 2 mg/d (SLIT)<br>4000 mg/d (OIT)   | 2.5 g<br>5 g                              | 12 mo               | 8/27 SLIT vs 16/18 OIT<br>completed OFC                                                                              | No serious events<br>(SLIT), No epi<br>used (SLIT)                                                 |
| Fleischer<br>et al, <sup>32</sup> 2013 | Peanut | SLIT     | DBPC RCT | 40 (12–37)             | 3/20<br>5/17 | 1386 µg<br>3696 µg                 | 5 g                                       | 68 wk<br>44 wk      | 5/15 SLIT (low dose,<br>68 wk) vs 0/17<br>(high dose,<br>44 wk); ↑<br>threshold                                      | No severe<br>symptoms; OP<br>reactions 37.3%<br>of initial total<br>SLIT doses (5825);<br>31.4% in |
| Narisety<br>et al, <sup>38</sup> 2015  | Peanut | SLIT/OIT | DBPC RCT | 21 (7–13)              | 3/10<br>4/11 | 3.7 mg/d (SLIT)<br>2000 mg/d (OIT) | 10 g                                      | 12 mo (off<br>4 wk) | 5/10 SLIT vs 4/6 OIT<br>completed OFC; 1/<br>10 SLIT and 3/11<br>(OIT) sustained<br>unresponsiveness;<br>↑ threshold | No severe<br>symptoms;<br>reactions in 9%<br>of total doses<br>(4578); No epi<br>used (SLIT)       |
| EPIT                                   |        |          |          |                        |              |                                    |                                           |                     |                                                                                                                      |                                                                                                    |
| Dupont<br>et al, <sup>47</sup><br>2010 | Milk   | EPIT     | DBPC RCT | 18 (0.3–15)            | 0/10         | 1 mg 3 ×<br>48 h/wk                | 20 mL                                     | 3 mo                | 12-fold increase in<br>dose (20 mL)                                                                                  | Reactions 25% and<br>OP itching 20%<br>of total doses<br>(470)                                     |
| MILES (2014)<br>[NCT02223182]          | Milk   | EPIT     | DBPC RCT | 150 (2–17)             | NA           | 150 µg,<br>300 µg, or<br>500 µg/d  | 1444 mg<br>cumulative<br>reactive<br>dose | 24 mo               | Ongoing study                                                                                                        | Ongoing study                                                                                      |
| ARACHILD-2010<br>[NCT01197053]         | Peanut | EPIT     | DBPC RCT | 54 (5–18)              | NA/28        | 100 µg/d                           | 1 g                                       | 18 mo<br>reported   | ↑ threshold                                                                                                          | Ongoing study                                                                                      |
| CoFAR6 (2013)<br>[NCT01904604]         | Peanut | EPIT     | DBPC RCT | 75 (4–25)              | NA           | 100 µg/d<br>250 µg/d               | 5044 mg                                   | 30 mo               | Ongoing study                                                                                                        | Ongoing study                                                                                      |

(continued on next page)

**Table 1**  
(continued)

| Study (Year)                        | Food   | Modality | Design   | No. of Patients (Age Range) | Withdrawals/ Active Group | Maintenance Dose     | Challenge Dose | Duration | Clinical Outcome                                                                                          | Adverse Events                              |
|-------------------------------------|--------|----------|----------|-----------------------------|---------------------------|----------------------|----------------|----------|-----------------------------------------------------------------------------------------------------------|---------------------------------------------|
| VIPES (2012)<br>[NCT01675882]       | Peanut | EPIT     | DBPC RCT | 221 (6–65)                  | NA/55                     | 50, 100, or 250 µg/d | 1 g            | 12 mo    | Response rate (10-fold increase or tolerate 1 g): placebo-, 25%; 50 µg, 45.3%; 100 µg, 41.1%; 250 µg, 50% | No serious events in active groups reported |
| OLFUS-VIPES (2013)<br>[NCT01675882] | Peanut | EPIT     | DBPC RCT | 170 (6–65)                  | NA                        | 250 µg/d             | 1 g            | 36 mo    | Ongoing study                                                                                             | Ongoing study                               |

**Abbreviations:** ↑, increased; DBPC, double-blind placebo-controlled; epi, epinephrine; EPIT, epicutaneous immunotherapy; NA, not applicable; OFC, open food challenge; OIT, oral immunotherapy; OITA, oral immunotherapy group A (goal dose 2 g/d), OITB, oral immunotherapy group B (goal dose 1 g/d); OP, oropharyngeal; RCT, randomized, controlled trial; SLIT, sublingual immunotherapy.

the tongue and then swallowed. After 6 months of therapy, 33 active subjects (89%) were rechallenged and demonstrated up to a 9-fold higher threshold to elicit local symptoms compared with baseline. No changes were observed within the placebo group. Because a large portion of the patients had only OAS (63%), the success of SLIT in desensitizing patients with peach-induced anaphylaxis is unclear.<sup>30</sup>

### **Peanut**

Two randomized, DBPC trials for peanut SLIT have been published in the past several years.<sup>31,32</sup> The first study, conducted by Kim and colleagues,<sup>31</sup> enrolled 18 children (ages 1–11 years) randomized to SLIT ( $n = 11$ ) or placebo ( $n = 7$ ) groups. Each dose was kept under the tongue for 2 minutes and then swallowed. Over a 6-month period, all subjects in the active group achieved a goal daily dose of 2500  $\mu\text{g}$  in the dose escalation phase and continued for an additional 6 months in the maintenance phase. After completing the maintenance phase, the subjects underwent a DBPCFC. Although baseline thresholds were not established with a pretreatment oral food challenge, the treatment group safely ingested 20 times more peanut protein (1710 mg) than the placebo group (85 mg).<sup>31</sup>

Two years later, Fleischer and colleagues<sup>32</sup> reported the results of the first multicenter, randomized, DBPC clinical trial of peanut SLIT. The group randomized 40 individuals (age 12–37 years) equally to either active treatment with peanut SLIT or placebo after a study initial 2 g peanut DBPCFC, during which subjects had to react to qualify for study entry. In the first blinded phase of the trial, after 44 weeks on a goal dose of 1386  $\mu\text{g}/\text{d}$ , the subjects underwent a 5 g DBPCFC to peanut. During this challenge, 14 of 20 individuals (70%) were considered to be “responders,” which was defined as the ability to tolerate either 5 g of peanut or a 10-fold higher amount than their baseline DBPCFC. The median tolerated dose in the active group increased from 3.5 to 496 mg. During the second unblinded phase of the trial, the original active group continued an additional 24 weeks months of maintenance therapy, and the placebo-treated subjects crossed over to a higher active peanut SLIT dose of 3696  $\mu\text{g}$  daily. After completing 68 weeks of therapy, the median tolerated peanut dose increased further to 996 mg for the original active group. For the placebo-treated subjects who crossed over to higher dose SLIT, after 44 weeks of active therapy, 7 of 20 subjects (35%) were “responders,” with the median dose increasing from 71 mg at the baseline challenge to 603 mg. The authors concluded that the longer duration of treatment was more efficacious than the higher dose based on the results of the DBPCFCs.<sup>32</sup> The study continued with a 3-year open-label period of active peanut SLIT with annual DBPCFCs, after which time analyses were performed to further evaluate long-term safety and efficacy outcomes.<sup>33</sup> For subjects who passed any 10-g DBPCFC during the study, SLIT therapy was discontinued, and the subjects were rechallenged 8 weeks later with a 10-g DBPCFC, followed by an open serving of peanut if challenge negative. Only 4 of the original 40 subjects (10%) demonstrated what has been termed sustained unresponsiveness, the ability to consume without symptoms a predetermined amount of protein after a period of abstinence from immunotherapy. The authors did not find outcome differences between the groups on 1386 versus 3696  $\mu\text{g}$  of daily peanut protein.<sup>33</sup>

### **SUBLINGUAL IMMUNOTHERAPY VERSUS ORAL IMMUNOTHERAPY**

Three studies to date have directly compared OIT and SLIT. In 2012, in a randomized, open-label protocol, Keet and colleagues<sup>34</sup> compared OIT versus SLIT in children with milk allergy. Thirty children (ages 6–17 years), who reacted at initial DBPCFC,

underwent at least 6 weeks of initial SLIT to a goal dose of 3.7 mg of milk protein daily, held under the tongue for 2 minutes and then swallowed. The group was then randomized equally into 3 groups: SLIT (goal dose 7 mg/d), OITA (goal dose 2 g/d), and OITB (goal dose 1 g/d). The children continued on the maintenance dose, and after 12 and 60 weeks, underwent DBPCFCs to 8 g of cow's milk protein. Children who passed this challenge were then instructed to stop therapy and were challenged 1 and 6 weeks later. The results showed that after SLIT therapy the challenge threshold increased in all 3 groups from baseline, but therapy with SLIT followed by OIT was much more effective at desensitization than SLIT alone. After the full 60 weeks of maintenance therapy, the median fold increase in threshold increased 40-fold for SLIT (10 subjects), 54-fold for OITA (9 subjects), and 159-fold for OITB (9 subjects). One patient from the SLIT group tolerated the full challenge dose, compared with 8 in OITA and 6 in OITB. After discontinuing therapy for 1 week, 2 subjects from OITB group failed rechallenge. After discontinuing therapy for 6 weeks, 1 subject from the SLIT (10%), 5 from OITA (50%), and 3 from OITB (30%) demonstrated sustained unresponsiveness.<sup>34</sup>

In a second study published the following year, Chin and colleagues<sup>35</sup> performed a retrospective comparison of peanut SLIT versus OIT using data from 2 previously published SLIT and OIT protocols for peanut allergy.<sup>36,37</sup> Twenty-seven children underwent peanut SLIT to a goal dose of 2 mg/d, and 23 children were treated with peanut OIT to a goal dose of 4000 mg/d. After 12 months of therapy, the children underwent a DBPCFC to 2500 mg (SLIT) and 5000 mg (OIT). Among the children who underwent OIT, 70% passed the DBPCFC, in contrast with the SLIT group where only 30% passed the 1-year DBPCFC.<sup>35</sup> Similar to Keet and colleagues,<sup>34</sup> the authors found that OIT was more efficacious than SLIT for inducing desensitization to peanut protein.<sup>35</sup>

A third DBPC trial comparing peanut OIT and SLIT performed by Narisety and colleagues<sup>38</sup> was published recently. In this study, 21 children (ages 7–13 years) with peanut allergy were randomized to receive active SLIT versus placebo OIT or active OIT versus placebo SLIT. Doses were escalated to 3.7 mg/d (SLIT) or 2000 mg/d (OIT), and the patients were rechallenged after 6 and 12 months of maintenance. At this point, the subjects were unblinded, and patients received an additional 6 months of therapy. The patients who passed challenges at 12 or 18 months were taken off therapy for 4 weeks and rechallenged. The results showed that 16 of the 21 subjects (76%) had a greater than 10-fold increase in challenge threshold after 12 months, which was significantly greater in the active OIT group compared with the SLIT group (141-fold vs 22-fold, respectively). At study completion, 1 subject in the SLIT group and 3 from the OIT group demonstrated sustained unresponsiveness. The authors concluded that OIT seemed far more effective than SLIT for the treatment of peanut allergy.<sup>38</sup>

## Safety

In the studies described herein, the superior safety of SLIT compared with OIT has been proven repeatedly, which is largely owing to the site of immunotherapy administration. Human oral tissues have low numbers of mast cells, eosinophils, and basophils, making them an ideal site for AIT. This results in decreased release of proinflammatory mediators and fewer adverse reactions.<sup>18,19</sup>

The adverse reactions that occur in 7.4% to 29% of SLIT doses tend to be local, mild, and transient,<sup>29</sup> and observed at a similar frequency in both SLIT and placebo groups.<sup>30</sup> Almost 99% of the reported reactions are local, and of these, the majority of reactions ( $\leq 95\%$ ) are restricted to the oral cavity, presenting as oropharyngeal

itching.<sup>27,30</sup> When oropharyngeal symptoms were excluded, Fleischer and colleagues<sup>32</sup> found that 94% of the received doses were symptom free.

Systemic symptoms in SLIT are very rare, and most adverse reactions occur during the initial buildup phase.<sup>27,31,32</sup> In their study, Enrique and colleagues<sup>27,28</sup> reported only 0.2% systemic reactions, whereas Fernandez-Rivas and associates<sup>30</sup> reported 13.5%, but in both studies the reactions were mild and resolved either spontaneously or with antihistamines, antacids and sometimes omeprazole.<sup>27,28,30</sup>

The studies that compared OIT with SLIT for FA found that OIT caused nearly 4 times more multisystem symptoms.<sup>34,38</sup> Symptoms with OIT also were more likely to require more  $\beta$ -agonist, antihistamine, and injectable epinephrine for treatment.<sup>34,35,38</sup> A greater number of treatment withdrawals owing to intolerable symptoms were also noted in the OIT groups (10%–40%)<sup>34,38</sup> compared with SLIT groups (0%–30%).<sup>34,38</sup>

### ***Immune Mechanisms***

The underlying immune mechanisms involved in SLIT have been investigated in several studies.<sup>19</sup> SLIT uses the unique tolerogenic property of the oral mucosa.<sup>19</sup> Regulatory myeloid dendritic cells, which are predominantly oral mucosal Langerhans cells, seem to be the primary target cells of SLIT.<sup>19</sup> It has been proposed that oral mucosal Langerhans cells remain immature after SLIT and do not rapidly migrate to the lymph node, but present to T cells directly in the mucosa instead,<sup>19</sup> thus promoting sustained unresponsiveness. Oral mucosal Langerhans cells further contribute to a tolerogenic environment by producing the regulatory cytokines IL-10 and transforming growth factor- $\beta$ 1 once they have taken up the allergen.<sup>19</sup> Peripheral myeloid dendritic cells can also be involved in cytokine production by allergen-specific T cells and promote a tolerogenic environment after SLIT.<sup>19</sup>

After therapy with SLIT, the myeloid dendritic cells drive the polarization from the proallergic Th2 to the Th1 response.<sup>19</sup> A late phase of the immune response to SLIT shows significantly decreased IL-4 production but increased interferon- $\gamma$  production, indicating a shift toward a Th1 phenotype.<sup>39</sup> In their peanut study, Kim and colleagues<sup>31</sup> noted decreased IL-4 production but did not find any significant differences in interferon- $\gamma$  production. Additionally, induction of Tregs is an important aspect of AIT,<sup>40</sup> because through transforming growth factor- $\beta$  and IL-10 production, Tregs suppress effector immune responses.<sup>41</sup> IL-10 was found to be significantly increased in some FA SLIT studies,<sup>27,28</sup> but not all.<sup>31</sup>

AIT is also proposed to function through inhibiting allergen-specific IgE production and enhancing allergen-specific IgG4 production, both of which are mediated by IL-10 and can be markers of clinical efficacy after SLIT.<sup>19,42</sup> Decreased allergen-specific IgE levels after SLIT for FA have been seen in several studies<sup>25,26,31,34,35,38</sup>; however, clinical improvement was not always associated with this decrease.<sup>32</sup> Increased IgG4 levels have also been observed in multiple studies,<sup>25,27,28,30,31,35,38</sup> but they did not always correlate with clinical outcome.<sup>32,34</sup>

### **EPICUTANEOUS IMMUNOTHERAPY**

EPIT is another method that is being explored currently for the treatment of FA.<sup>11</sup> The allergen delivery through EPIT is limited to active immune cells of the epidermis.<sup>43</sup> In this process, the allergen is contained within a skin patch in soluble form. After the patch's application, the allergen is absorbed into the stratum corneum.<sup>11</sup> The first case study on successful EPIT was reported in 1921 by Vallery-Radot.<sup>44</sup> He was able to successfully reduce systemic allergic symptoms in patients allergic to horses

after allergen administration on scarified skin.<sup>44</sup> Several studies have since been performed in Europe that show successful results and fewer side effects compared with SCIT.<sup>45</sup> Nonetheless, the method fell out of favor owing to the uncomfortable process of skin scarification.<sup>46</sup>

Recently, EPIT has experienced a revival in the treatment of FA. Viaskin (DBV Technologies SA, Paris, France) is a new epicutaneous delivery system (EDS) that allows the application of allergens on intact skin and facilitates diffusion of allergens into the stratum corneum.<sup>46</sup> Mondoulet and colleagues<sup>46</sup> initially used EPIT with Viaskin for FA on intact skin in a pilot study with mice sensitized to egg and peanut. They concluded that EPIT was as efficacious as SCIT,<sup>46</sup> and also provided a reassuring safety profile. To date, 1 DBPC pilot study investigating EPIT in children has been published.<sup>47</sup> There are several other EPIT trials in milk and peanut sensitized subjects that are currently ongoing or waiting to be published, having been presented as abstracts at the American Academy of Allergy, Asthma and Immunology (AAAAI) as well as the European Academy of Allergy and Clinical Immunology (ECAAI) meetings.<sup>48,49</sup> Studies examining EPIT for specific foods are described elsewhere in this article and in [Table 1](#).

### ***Milk***

In 2010, Dupont and colleagues<sup>47</sup> conducted a 3-month-long bicenter, DBPC study to assess the efficacy and safety of EPIT administered using Viaskin EDS after its initial success in animal models.<sup>46</sup> The study enrolled 18 children with cow's milk allergy who were randomized to either active treatment with EPIT ( $n = 10$ ) or placebo ( $n = 8$ ). The treatment included three 48-h applications of the EDS per week for 3 months. Active EDS contained 1 mg of cow's milk powder that was applied onto intact skin in the interscapular area. An oral food challenge was performed after 3 months of therapy, which showed an increase in the threshold dose from 1.77 mL to 23.61 mL, a 12-fold increase in the active group. The mean cumulative dose did not vary in the placebo group.<sup>47</sup>

In 2014, the currently ongoing MILES trial, a multicenter, DBPC, randomized phase I/II trial to evaluate the efficacy and safety of Viaskin Milk, was initiated. The study has enrolled 150 children (ages 2–17 years) with cow's milk allergy. Part A of the MILES trial involves daily administration of 3 doses of Viaskin Milk (150, 300, and 500  $\mu\text{g}$  of cow's milk protein) versus placebo for 3 weeks to assess safety and determine dosing for Part B. Part B will evaluate the safety and efficacy of 3 selected doses of Viaskin Milk compared with placebo. After 12 months of therapy, all subjects will be unblinded and will continue therapy for another 12 months at the highest tolerated dose [NCT02223182].

### ***Peanut***

The Epicutaneous Immunotherapy in Peanut Allergy in Children (ARACHILD) trial was a multicenter, DBPC, randomized, pilot trial conducted in France in 2010. Fifty-four patients (ages 5–18 years) were enrolled and randomized into 2 treatment arms to assess 100  $\mu\text{g}$  of Viaskin peanut ( $n = 28$ ) compared with placebo ( $n = 26$ ). After 6 months of therapy, patients in the placebo arm crossed over to Viaskin peanut without unblinding, followed by an open-label period of 30 months. DBPCFCs were performed at 6, 12, and 18 months after onset of therapy. Successful therapy was defined as the ability to tolerate at least 1 g of peanut protein (4 peanuts) or a 10-fold higher dose than the baseline reactive dose. In the active group, 7.4%, 20% and 40% of subjects were able to consume at least 10 times more peanut protein compared with the beginning of the trial at 6, 12, and 18 months, respectively

[NCT01197053]. In children, there was a higher response rate of 12.5%, 33.3%, and 66.7% at the same time points.

In 2010, another multicenter, DBPC, phase Ib, randomized, clinical trial was initiated with Viaskin peanut in the United States to assess safety. The trial recruited 100 peanut-allergic subjects (ages 6–50 years) that were randomized to receive treatment for 2 weeks with 250  $\mu$ g or 500  $\mu$ g of Viaskin peanut or with placebo. The study found that adolescents and adults tolerated 500  $\mu$ g of Viaskin peanut well, whereas children tolerated the 250  $\mu$ g better [NCT01170286]. There were no serious adverse events in the trial owing to Viaskin patch.

The Efficacy and Safety of Several Doses of Viaskin Peanut in Adults and Children With Peanut Allergy (VIPES) study, a multicenter, DBPC, phase IIb, clinical trial of Viaskin peanut was initiated in 2012 in North America and Europe to study efficacy of the therapy. The largest clinical trial in peanut allergy desensitization ever completed, the VIPES trial enrolled 221 peanut-allergic individuals (ages 6–55 years) who were randomized into 4 treatment arms ( $n = 55$  per treatment group) to assess 3 doses of Viaskin Peanut (50, 100, and 250  $\mu$ g peanut protein) compared with placebo. Successful therapy, defined after 12 months of therapy as the ability to tolerate at least 1 g of peanut protein or a 10-fold higher dose needed to elicit a reaction, was seen in all 3 groups (45.3%, 41.1%, and 50%, respectively). If the criteria were changed to stricter endpoint of 10-fold and minimum of 1000 mg, the study was successful with response rate of 6.5% in the placebo, 28.6% (50  $\mu$ g), 30.8% (100  $\mu$ g), and 32.1% (250  $\mu$ g.) [NCT01675882]. The change in cumulative reactive dose of peanut that elicited a reaction at 12 months of therapy was +62.8 mg in placebo, +471.2 mg at 50  $\mu$ g, +617.5 mg at 100  $\mu$ g, and +1121 mg at 500  $\mu$ g dose in the children less 12 years of age. In comparison, the adolescent and adults had less effect but with a trend toward better response with higher dose of EPIT with cumulative reactive dose of 528, 619, 842, and 837 mg for placebo and increasing doses of peanut EPIT.<sup>48,49</sup> These data suggest a significant response to EPIT therapy for peanut.

The VIPES Open-Label Follow-up Study (OLFUS), a phase IIb clinical trial, was initiated in 2013 to assess the safety and efficacy of Viaskin peanut after 36 months of therapy. It included 170 (82%) of the patients who completed 12 months of therapy in the VIPES trial. Patients who show desensitization after 36 months discontinue therapy to evaluate for sustained unresponsiveness [NCT01955109]. The data from this study have not been presented at the current time.

In 2013, another randomized, DBPC trial was initiated by the Consortium of Food Allergy Research to evaluate Viaskin peanut. The trial enrolled 75 patients who were randomized to 2 doses of Viaskin (100 and 250  $\mu$ g) or placebo. After 52 weeks of therapy, oral food challenges are to be performed. Patients who successfully complete the desensitization protocol will undergo another DBPCFC after 30 months of therapy. Those who pass the challenge will discontinue therapy for up to 20 weeks to assess for sustained unresponsiveness. The placebo group will crossover to active therapy after 52 weeks and a DBPCFC will be performed after 30 months. The anticipated duration of the study is 4 years and has not been presented at the current time [NCT01904604].

## Safety

Studies evaluating EPIT for FA have displayed an excellent safety profile.<sup>46–48</sup> The epidermis does not contain blood vessels; therefore, allergen delivery to the epidermis does not cause a large release of allergens into the blood stream,<sup>43</sup> leading to a low risk of systemic reactions. From the only fully published trial, the pilot milk EPIT study by Dupont and colleagues<sup>47</sup> the authors concluded that EPIT is well tolerated and

local reactions did not require treatment with epinephrine. Based on data presented in abstracts at the AAAAI and ECAAI on the VIPES and ARACHILD studies, there are no systemic reactions owing to Viaskin patch and only well-tolerated localized reactions to EPIT with 2 patients withdrawing owing to localized dermatitis.<sup>48,49</sup>

### ***Immune Mechanisms***

The goal of EPIT is to safely and effectively administer allergen to the epidermis.<sup>11</sup> Several mouse studies have elucidated the mechanism by which EPIT modulates the immune system.<sup>46,50,51</sup> Application of EDS on intact skin enhances the skin hydration through sweat and promotes allergen diffusion through the superficial layers of the skin. Subsequently, dermal dendritic cells uptake the allergen, which becomes concentrated inside the stratum corneum, without free passage through the skin.<sup>43,46,50</sup> Dermal dendritic cells and Langerhans cells are involved in transporting antigen from the epidermis to afferent lymph nodes to activate immune responses.<sup>43</sup> Repeated applications down-regulate local eosinophil recruitment and decrease systemic allergen-specific immune responses while increasing Tregs.<sup>43</sup>

Previous studies show an association between AIT and Tregs.<sup>13,52</sup> CD4<sup>+</sup> Tregs include inducible Tregs and naturally occurring Tregs.<sup>13</sup> Inducible Tregs consist of different subsets and they each suppress the immune response differently.<sup>13</sup> These include IL-10–producing Tr1 cells (Tr1), transforming growth factor- $\beta$ –inducing Th3 cells, and CD4<sup>+</sup> CD25<sup>+</sup> Foxp3<sup>+</sup> Tregs (Foxp3<sup>+</sup>).<sup>13,53</sup> Different immunotherapy routes may induce different Tregs.<sup>13</sup> SCIT and SLIT induces a transient increase in Tr1, followed by an immune deviation toward the Th1 response.<sup>13,39</sup> EPIT increased peripheral Foxp3<sup>+</sup> CD4<sup>+</sup> T cells and expression of Foxp3, which leads to a decrease in the allergen-specific cytokine production.<sup>13,43,51</sup>

Dioszeghy and colleagues<sup>43</sup> showed that EPIT-induced Tregs play an important role in developing tolerance. EPIT induces both effector and naïve Foxp3<sup>+</sup> Tregs, but not IL-10<sup>+</sup> Tr1 cells (which differs from SCIT and SLIT).<sup>50</sup> Foxp3 is critical for the stability of Tregs and allows CD4<sup>+</sup> CD25<sup>+</sup> Foxp3<sup>+</sup> Tregs to persist potentially for a longer period of time. The suppressive activity of Tregs is maintained even after the cessation of EPIT.<sup>13</sup>

In their research involving mouse models, Mondoulet and colleagues<sup>46</sup> found that in sensitive treated animals, EPIT decreased Th2-related cytokines (IL-4 and IL-5) and eotaxin, in addition to decreasing eosinophil infiltration in serum and Bronchoalveolar lavage (BAL). EPIT also strongly influences specific antibody levels.<sup>46</sup> Mouse IgG2a, which is the human equivalent of IgG4, was increased after treatment with food allergens.<sup>46</sup> Although SLIT also increases IgG2a after therapy, it is significantly higher with EPIT.<sup>50</sup> These changes reflect the switch of the immune response from a Th2 to a Th1 profile.<sup>50</sup> Compared with SLIT, EPIT induces a stronger reduction of the Th2 response with a greater decrease in IL-4, IL-5, IL-10, and IL-13.<sup>50</sup>

### **SUMMARY**

Over the past several years, there has been an increase in studies investigating the best modality to treat food allergies. Although SCIT is known to be the most efficacious route for the treatment of environmental allergies, it has not been adopted into practice for FA treatment owing to the high rate of systemic side effects. OIT has shown promising results and is able to induce desensitization, but it too is accompanied by an increased risk of systemic reactions compared with SLIT and EPIT. In the search for efficacious, yet well-tolerated therapies, both SLIT and EPIT have great potential.

SLIT improves the safety of the therapy, but its efficacy remains uncertain and seems lower compared with OIT. As it presently stands, SLIT may be useful as a bridging technique before initiating OIT, or it may need to be optimized with adjuvants to make it more efficacious when used alone. EPIT seems to be more promising owing to a potentially better safety profile, but there are limited data at this time with respect to this and its efficacy, because the data have only been presented as abstracts and have not been peer reviewed. Both SLIT and EPIT show that patients can theoretically increase their threshold doses to a food allergen, thus providing at least partial protection against accidental exposures without suffering severe symptoms. Additionally, several strategies are currently being investigated to improve the immunologic properties of both SLIT and EPIT.<sup>24,45</sup>

More research is needed to define the optimal doses and administration protocol for both SLIT and EPIT. Little is known about the long-term efficacy of these therapies, which can potentially expose treated patients to a high risk of subsequent reactions even with brief lapses in exposure.<sup>34</sup> Although emerging evidence suggests that SLIT and EPIT may be effective in the treatment of FA, further studies are needed before these therapies can be offered to patients in clinical practice.

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