



# Sublingual immunotherapy for food allergy and its future directions

Stephen A Schworer<sup>1</sup>  & Edwin H Kim<sup>\*,1</sup> 

<sup>1</sup> Department of Medicine, Division of Rheumatology, Allergy & Immunology, University of North Carolina School of Medicine, Chapel Hill, NC 27599, USA

\*Author for correspondence: [edwinkim@email.unc.edu](mailto:edwinkim@email.unc.edu)

Food allergy is an important medical problem with increasing prevalence throughout the world. Different approaches of food immunotherapy are being investigated including oral, epicutaneous and sublingual routes. Sublingual immunotherapy (SLIT) for food allergy involves placement of glycerinated allergen under the tongue daily to achieve allergen-specific desensitization. SLIT has been studied in the treatment of hazelnut, peach, apple, milk and peanut allergies with substantial focus on the treatment of peanut allergy. Phase II studies have shown SLIT for treatment of peanut allergy increases the tolerated dose of peanut by a substantial margin with fewer and less severe side effects than other modalities. This review discusses the mechanisms of SLIT, early studies of its use in food allergy and larger randomized controlled trials for treatment of peanut allergy. Future directions using the mechanisms involved in SLIT include oral mucosal immunotherapy for peanut allergy.

First draft submitted: 3 May 2020; Accepted for publication: 22 June 2020; Published online: 2 July 2020

**Keywords:** desensitization • food allergy • peanut allergy • sublingual immunotherapy

IgE-mediated food allergy is an increasingly common condition with rising prevalence in adult and pediatric populations [1]. Multiple studies identified the prevalence of food allergy in different populations. The HealthNuts cohort in Australia demonstrated a challenge-confirmed prevalence of food allergy of 11% at age 1 and 3.8% at age 4 [2]. A cross-sectional survey of the US adult population estimated a prevalence of food allergy at 10.8% [3]. Prevalence in the adult and pediatric populations the National Health and Nutrition Examination Survey (NHANES) database, was estimated at 7.6% [4]. Furthermore, the prevalence is increasing over a period of the past 20–30 years [1,5].

Food allergy impacts the daily life of an individual through unexpected reactions from accidental ingestion, severe reactions such as anaphylaxis and modification of behavior shown to have effect on overall quality of life [6,7]. Accidental exposures occur through unintentional intake of a causative allergen, errors in reading labels and cross-contact or cross-contamination [6]. These ingestions lead to severe symptoms in 11.4% of reactions. In a study of adult food allergy patients, half experienced an accidental ingestion over a 1-year period [8]. Label reading alone was not sufficient to prevent these accidental reactions in many circumstances. Symptoms ranged from oropharyngeal itching to severe symptoms in the respiratory and gastrointestinal systems. The dose of allergen in the accidental exposure varied but in the case of peanut, the largest ingestion was about half of one peanut kernel [8,9]. Accidental ingestions occur at home, school, work, restaurants and at friends' houses. In addition to the medical risks of accidental exposures, food allergy patients have been shown to have a decreased quality of life, specifically related to the risk of accidental exposure leading to anxiety and limitations on the child and parental social life [7,10].

In the absence of a curative therapy for food allergy, prevention of the initial allergic sensitization has recently been investigated. The LEAP study demonstrated that early introduction of peanut resulted in less frequent allergic sensitization compared with avoidance in a randomized controlled trial [11]. Early introduction of the most common allergenic foods in exclusively breast-fed infants also led to a reduced rate of food allergy in per-protocol analysis [12]. The optimal window for this introduction is not clear and may be challenging to achieve on a population level. Furthermore, peanut allergy persists beyond 12 years of age in nearly three quarters of individuals [13]. With the prevalence of peanut allergy in the range of 1.9% as seen in the HealthNuts study [2], millions of individuals will be living with peanut allergy in the absence of a cure. Given the issues related to adverse reactions with accidental ingestions and impact on quality of life, advancing a treatment for food allergy is imperative [14].

Until early 2020, no US FDA-approved therapy for food allergy existed and treatment consisted only of avoidance [1]. Over the past decade, the approach of allergen specific immunotherapy has been studied most thoroughly for treatment of food allergy. Similar to the treatment protocol for subcutaneous immunotherapy for environmental allergens, immunotherapy for food entails beginning with a low dose of specific allergen followed by a dose escalation phase then a maintenance phase. In food immunotherapy, dose escalation occurs over a period of a few weeks up to several months depending on the route of exposure. Upon achieving the target treatment dose, the patient is continued daily on the maintenance dose for the duration of therapy. Subcutaneous immunotherapy to peanut has been limited by a high rate of systemic side effects [15] and as a result alternative modalities of delivery have been studied for food desensitization, specifically oral immunotherapy (OIT), epicutaneous immunotherapy (EPIT) and sublingual immunotherapy (SLIT) [16–18]. OIT involves ingestion of the allergen in the form of a flour mixed with a vehicle food. Epicutaneous immunotherapy is applied as a patch and food allergen is absorbed through skin pores. SLIT involves administration of liquid glycerinated allergen extracts under the tongue. OIT for peanut allergy has progressed furthest through the FDA approval process and now the first peanut OIT product is approved for treatment of peanut allergy in patients ages 4 to 17 [19,20].

While OIT has been effective for peanut allergy desensitization, there have been concerns regarding multiple drawbacks to therapy including treatment associated adverse reactions, specifically gastrointestinal side effects and a risk for severe reactions and practical aspects of the OIT protocol including limitations on exercise after dosing that may prove challenging for individual patients [21,22]. SLIT addresses some of the limitations of OIT through its unique mode of delivery. The purpose of this review is to examine the use of SLIT for food allergen immunotherapy by discussing its immunologic characteristics, previous studies investigating this therapy and future directions.

### Immunologic mechanisms of sublingual immunotherapy

The goal of immunotherapy is to redirect the immune response so it does not activate allergic inflammation when confronted by a specific allergen. SLIT induces a local immune response in the oral cavity to promote a tolerogenic environment, shifting immune responses away from allergic Th2 polarization [23,24]. The mechanistic understanding of SLIT is largely derived from investigations of grass pollen immunotherapy for the treatment of allergic rhinitis. Current data support a model where antigens delivered by SLIT are taken up by a myeloid dendritic cell population in the oral mucosa, oral Langerhans cells [23–25]. Uptake of allergen by oral Langerhans cells leads to IL-10 release, which promotes T-cell production of tolerogenic cytokines including IL-10 and TGF- $\beta$  [26]. FOXP3-positive T regulatory cells are induced and Th2 cytokines including IL-4 are downregulated [26–29]. Whether the long-term control of the immune response is mediated directly by regulatory T cells and production of cytokines such as IL-10 [27] or a skewing of the immune response to Th1 with an interferon- $\gamma$  signature remains uncertain [28]. Changes in T-cell phenotype are accompanied by a humoral immune response to inhibit an allergen-specific IgE response. SLIT promotes an allergen-specific production of IgG<sub>4</sub> and IgG<sub>1</sub> in treatment of grass pollen allergy, which function to competitively inhibit antigen-specific IgE binding [27,30]. The importance of IgG<sub>4</sub> and IgG<sub>1</sub> as blocking antibodies has also been demonstrated in SLIT as treatment for birch related food allergy in a study of Mal d 1 SLIT [31]. While the magnitude of IgG<sub>4</sub> increase in SLIT is not as large as in subcutaneous immunotherapy (SCIT), the clinical relevance of the IgG<sub>4</sub> level is not clear [24]. Additionally, an increase in allergen-specific IgA has been observed in individuals using SLIT for treatment of grass pollen allergy [27]. Allergen-specific IgA likely prevents allergen uptake and presentation to specific IgE.

These immunologic changes are accompanied by a change in clinical response when the immune system responds to specific allergens. Treatment with 2 years of grass pollen SLIT led to a significant increase in allergen-specific IgG<sub>4</sub> at 10 and 22 months accompanied by clinical improvement in allergic rhinoconjunctivitis symptoms [32]. Furthermore, the duration of SLIT has implications on the immunologic as well as the clinical response. In a study of therapy with grass pollen SLIT for 2 years followed by evaluation after 1 year off therapy, there was a temporal relationship between the decrease in allergen-specific Th2 cells, increase in antigen specific IgG<sub>4</sub> and decrease in symptoms during therapy [33,34]. Symptom recurrence 1 year off therapy was associated with an increase in peripheral blood allergen-specific Th2 cells. There was a decrease in antigen specific IgG<sub>4</sub> off therapy but the serum level remained elevated above baseline. In a separate study, treatment with 3 years of grass pollen SLIT produced a sustained clinical efficacy that persisted for 2 years off of immunotherapy and was accompanied by a persistently elevated allergen-specific IgG<sub>4</sub> level and neutralization of the allergen-specific IgE response [35].

### SLIT in pollen-food allergy syndrome & early descriptions in food allergy

As discussed above, SLIT for environmental allergens demonstrated efficacy for treatment of allergic rhinoconjunctivitis [34,35]. SLIT for food allergy treatment was first described in kiwi fruit allergy in 2003. A single patient with anaphylaxis to kiwi fruit was successfully desensitized using increasing concentrations of diluted kiwi extract with associated increases in specific IgG4 and decreases in size of skin prick test size and specific IgE [36,37]. The patient was able to tolerate a 1-cm cube of kiwi fruit, which was then continued as maintenance therapy. Additionally, after a period of 4 months off therapy the patient was able to restart at the maintenance dose without adverse effects.

The first randomized, double-blind, placebo-controlled trial using SLIT for treatment of food allergy was in hazelnut allergy [38]. Participants were enrolled in this study if they experienced either symptoms of oral itching consistent with oral allergy syndrome or anaphylaxis. After 8–12 weeks the treatment group tolerated fivefold greater quantity than before treatment with no change seen in the placebo group. The primary side effect was oral itching in 7.4% of doses and rare cutaneous side effects treated with antihistamines.

A randomized, double-blind, placebo-controlled trial on peach allergy examined the impact of 6 months of SLIT with peach extract on participants with oral allergy syndrome or anaphylactic allergy to peach [39]. It demonstrated an increase of three- to nine-fold quantity of peach tolerated with concomitant decrease in skin prick test size and increase in Pru p 3-specific IgG4. These initial randomized trials demonstrated the efficacy of SLIT and also its safety as the majority of adverse effects were described as local oropharyngeal itching without systemic adverse effects requiring treatment with epinephrine. However, over half the participants in each of these studies described oral allergy syndrome rather than anaphylaxis as their allergic reaction to the food, limiting the generalizability of these studies to other food allergens.

In a more recent randomized controlled trial, SLIT for the treatment of birch pollen-related apple allergy was evaluated using recombinant Mal d 1 and Bet v 1 [40]. A total of 60 participants with birch pollen-related apple allergy were placed on SLIT with recombinant Mal d 1, Bet v 1, or placebo for a period of 4 months. There were no systemic reactions to therapy and adverse effects were primarily oropharyngeal. Interestingly, treatment with Mal d 1 SLIT led to an increase in the dose of Mal d 1 required to elicit symptoms in 70% of individuals whereas treatment with Bet v 1 increased the dose in 44%, which was not significantly different from a 42% increase in placebo. This study demonstrated efficacy in treatment of birch pollen-related apple allergy with SLIT using the major apple allergen but not using the primary birch allergen.

### SLIT in cow's milk allergy

A trial comparing SLIT alone to SLIT plus OIT in children with cow's milk allergy evaluated 30 participants between the ages of 6 and 17 years for 60 weeks [41]. In the SLIT alone group, a maintenance dose of 7 mg was used and compared with two different SLIT plus OIT groups, using 1 or 2 g of OIT maintenance in addition to SLIT. After 60 weeks of therapy, 60% of the SLIT group and 90% of the SLIT plus OIT groups increased their tolerated dose of milk by tenfold during an oral food challenge (OFC) compared with before treatment. One out of ten in the SLIT alone group passed an 8 g milk OFC compared with six out of ten in the SLIT plus 1 g OIT group and eight of ten in the SLIT plus 2 g OIT group. Adverse effects were noted in all groups. During the maintenance phase, the SLIT alone group experienced oropharyngeal side effects in 28% of doses compared with 22 and 24% in the low- and high-dose SLIT plus OIT groups, respectively. Gastrointestinal side effects were reported in 0.38% of SLIT alone doses compared with 8% of doses with SLIT plus high-dose OIT and 3% of doses with SLIT plus low-dose OIT during the maintenance phase. Epinephrine was used four times by participants in the SLIT plus OIT groups compared with twice in the SLIT alone group, both of these SLIT alone episodes being associated with aspiration of the SLIT liquid by the same participant. Immunologic changes were observed in all three treatment arms with a decrease in skin prick test size and basophil activation coupled with an increase in milk specific IgG4. In the SLIT plus OIT groups, there was a significant decrease in milk specific IgE after sixty weeks of maintenance therapy. In the SLIT alone group, milk specific IgE slightly decreased by 60 weeks of maintenance but this did not reach statistical significance. This study demonstrated that SLIT alone at the dosage given was less effective in increasing the amount of milk tolerated when compared with SLIT plus OIT. There were fewer GI side effects with SLIT alone and fewer severe symptoms that prompted administrations of epinephrine. This study highlights that OIT has the ability to allow for high quantities of allergen to be ingested after therapy, but with more side effects, not only during dose escalation but also during maintenance therapy.

Overall, these early studies demonstrated that SLIT provides desensitization when used as immunotherapy for different foods. While the magnitude of allergen threshold was not as great as OIT, there was a multiple-fold

increase in dose of allergen tolerated in SLIT with milk, peach and hazelnut, whereas side effects largely were limited to the oropharynx. Furthermore, immunologic changes associated with desensitization were noted with SLIT to support these clinical findings.

### Peanut SLIT

Peanut allergy treatment is the most thoroughly studied application of food SLIT. Three randomized controlled trials have investigated this therapy in different age groups. Peanut SLIT was compared with placebo in a multicenter, randomized, double-blind controlled trial of 40 participants aged 12–37 years, with a median age of 15 years [42]. At 44 weeks of treatment at a maintenance dose of 1.386 mg, 70% of participants receiving peanut SLIT met criteria as responders in the trial by passing a 5 g OFC or increasing the successfully tolerated peanut dose by tenfold over their pretreatment threshold. The successfully consumed dose in the treatment group increased from 3.5 to 496 mg of peanut protein. When treatment was extended to 66 weeks with a maximum maintenance dose of 3.696 mg, the median successfully consumed dose increased to 996 mg. Immunologic parameters reflected desensitization including an increase in peanut-specific IgG<sub>4</sub> and a decrease in basophil reactivity.

In this study, side effects were largely oropharyngeal itching (37% of doses) and when these symptoms were excluded, 94.7% of doses were symptom-free. One dose of epinephrine was administered in the treatment group for diffuse cutaneous pruritus not responsive to oral antihistamine. Follow-up of this study at 2 to 3 years of therapy demonstrated ongoing immunologic changes and a favorable safety profile [43]. However, there was a large dropout rate in the long-term study, with only four of 37 participants completing the final OFC after 3 years of therapy. The ability to achieve permanent immune tolerance after treatment with food immunotherapy has remained unclear in part due to a lack of accepted clinical and immunological markers. As a proxy for tolerance, sustained unresponsiveness has been assessed in food immunotherapy defined as the ability to tolerate OFC without clinical symptoms after the immunotherapy has been withdrawn for an arbitrary period of time [44]. Notably, each of the four participants completing the SLIT trial not only passed a 5-g oral peanut challenge but also demonstrated sustained unresponsiveness by again passing a 5-g oral peanut challenge after 8 weeks off immunotherapy.

To directly compare the clinical effect, immunologic changes and side effects profiles of SLIT to OIT, a randomized controlled trial was conducted comparing these treatment modalities in peanut allergy [45]. Individuals aged 7–13 years (mean age of 11) were treated with a maintenance dose of peanut SLIT at 3.7 mg or OIT at 2000 mg for 1 year. This treatment was followed by evaluation of the tolerated dose of peanut by OFC. In the SLIT group, the mean cumulative dose tolerated increased from 21 to 496 mg, whereas in OIT, this dose increased from 21 to 7246 mg. Peanut-specific IgG<sub>4</sub> significantly increased with treatment in both groups but the magnitude of change was markedly greater with OIT. After 12 months in the study, participants were unblinded and therapy was adjusted based on their response to OFC. Participants who tolerated a 5 or 10 g OFC continued on their current treatment. Those who reacted at doses less than 5 g both continued the current therapy and had the alternative treatment arm added to their regimen. Full dose 3.7 mg SLIT was added to the OIT group, while in the SLIT group OIT was initiated at 10% of the dose to which the individual reacted and escalated to 2000 mg. All of the participants in the SLIT arm had OIT added to their regimen based on this protocol. In the OIT arm four out of seven participants passed the 5 g OFC and the remaining three added SLIT.

This study benefited from the ability to compare adverse events in the two treatment arms. In the active SLIT group, 9% of doses were associated with symptoms, the majority being oropharyngeal (3.9% of total doses) and gastrointestinal (3.2% of total doses). In the OIT group, symptoms were noted in 43% of doses, with about half of these symptoms reported as oropharyngeal and one quarter as gastrointestinal. Five doses of epinephrine were given during the trial, all in the OIT group. Overall, this study demonstrated that both OIT and SLIT increase the median tolerated amount of peanut at OFC. OIT had larger fold-increases in peanut tolerated at 141-fold after 6 and 12 months while SLIT increased the tolerated dose 14-fold after 6 months and 22-fold after 12 months. It was noted by the authors that while the magnitude of increase from baseline was much greater with OIT, SLIT provided a substantial fold-increase as well. The OIT treatment groups also had more frequent and severe symptoms associated with dosing.

A third trial demonstrated the efficacy and side effect profile of peanut SLIT in young children, aged 1–11 years (median age 6.5 years) [46,47]. The first phase of the study compared peanut SLIT to placebo for 6 months of dose escalation followed by 6 months of maintenance. The extended maintenance phase then continued these individuals on 2 mg SLIT for 3–5 years. After 6 months of maintenance therapy, the treatment group ingested a significantly increased dose of peanut, median of 1710 mg compared with 85 mg. After 3 to 5 years of therapy, two-thirds

of participants (32 out of 48) consumed 750 mg or more during a double-blind, placebo-controlled OFC and 25% passed a 5000 mg OFC. These clinical changes were accompanied by statistically significant increases in peanut-specific IgG<sub>4</sub> and decreases in basophil reactivity, peanut-specific IgE and skin prick test size. Symptoms were noted during 4.8% of doses. Oropharyngeal itching accounted for 75% of these symptoms. Epinephrine was not administered for any symptoms during the study and antihistamines were given in 0.2% of total doses. This study demonstrated clinical efficacy in the majority of participants with a favorable side effect profile, largely limited to oropharyngeal symptoms. In these three clinical trials of peanut SLIT, a younger median age appeared to correlate with more peanut protein tolerated in food challenges, suggesting that implementing this therapy earlier in life may be beneficial (Table 1).

### Benefits & drawbacks of SLIT

In the absence of curative therapy, SLIT, OIT and EPIT provide potential options for desensitization to food allergens. These therapies require daily dosing of maintenance allergen and do not appear to achieve long-term tolerance [17]. Some individuals on SLIT and OIT may develop sustained unresponsiveness, but which individuals will achieve this state and the duration of the absence of clinical reactivity is not known [47,48]. With a daily therapy that will be potentially life-long and no known cure for food allergy, the goals of treatment for each individual patient will help to identify the best option for treatment. A sampling of caregiver and patient goals identified the major goal of food immunotherapy to be creating a buffer for unintentional food exposure [49]. However, how much is enough when creating this buffer has not been well defined. In peanut allergy, a modelling study suggested that increasing the reaction threshold above 300 mg would reduce the risk of a reaction by 95% and above 1000 mg would further reduce this risk [50]. As discussed above, the three randomized studies on peanut SLIT demonstrated the median successfully consumed cumulative dose to increase to 496 mg after 1 year [42,45] and 996 mg after 2–3 years [43] and two-thirds of participants aged 1–11 years tolerated 750 mg or greater with a mean cumulative dose of 1750 mg [47]. In the Phase III trial of EPIT, 35% of the treatment group were classified as responders, which was defined as increasing the tolerated cumulative dose to 444 mg in participants who reacted to less than 10 mg and to 1444 mg in those who reacted to doses between 10 and 300 mg. The PALISADE study of AR101 peanut OIT found that 76% of children ages 4–17 tolerated a cumulative dose of 443 mg, 67% tolerated 1043 mg and 50% tolerated 2043 mg at the conclusion of the study [19]. While on the whole, OIT has provided a higher dose threshold [45], the majority of patients treated with SLIT would likely meet the 300 mg threshold to reduce a substantial amount of the risk of unexpected reactions. How the impact of the increase in reaction threshold affects quality of life in real-world treatment scenarios will be of interest to better inform patients going forward.

Another important consideration for use of a daily medication for the treatment of food allergy is the frequency and severity of symptomatic doses. The characteristics of these symptoms will likely impact quality of life and long term adherence. In studies on peanut SLIT, the percentage of doses that elicited symptoms ranged from 3.8 to 37% with the vast majority of symptoms localized to the oropharynx, as detailed above [42,45–47]. Severe symptoms were rare as was the administration of epinephrine to treat these severe symptoms. In contrast, OIT, despite its proven efficacy in many studies, elicits more frequent and more severe side effects with dosing [45]. Many factors have been shown to reduce the reaction threshold in OIT, leading to reaction on doses an individual may have tolerated for weeks before, including febrile illness, dosing without eating in the previous 2 h and exercise within 2 h after dosing [22]. A retrospective analysis of OIT studies found adverse reactions in 80% of participants [51]. These symptoms included gastrointestinal symptoms in 49% and systemic symptoms in 42% of participants for which 12% required epinephrine. In a more recent systematic review, the risk ratio of anaphylaxis in participants receiving OIT compared with placebo or avoidance was 3.12 (95% CI: 1.76–5.55) [21]. As the daily dosing of allergen in OIT (ranging from 300 to 4000 mg) is substantially greater than in SLIT (1.3–7 mg), the increased frequency and severity of adverse symptoms with each dose is not unexpected [52].

As ongoing daily therapy will be needed to maintain desensitization, compliance is a major factor for therapeutic success in OIT and SLIT. In the four largest studies of peanut SLIT, the percentage of participants who withdrew varied. In a population of individuals aged 12–37 years, over 50% withdrew from the study before the 3 year follow-up study was completed [42,43]. The majority of participants withdrew because of participant decision and the most cited reason was that daily dosing was too difficult to maintain. Only two of the 40 randomized participants withdrew because of symptoms with dosing. In the study in younger participants, ages 1–11 years on study entry, the rate of participant withdraw was only 23% (11 out of 48) at 3–5 years [47]. Whether this difference is a function of age or other factors is not certain. With the low reports of side effects and relative ease of dosing with SLIT,

| Table 1. Randomized trials of sublingual immunotherapy for food allergy. |                       |                                       |                                |                       |                    |                                        |                                                    |                              |                          |                                    |      |
|--------------------------------------------------------------------------|-----------------------|---------------------------------------|--------------------------------|-----------------------|--------------------|----------------------------------------|----------------------------------------------------|------------------------------|--------------------------|------------------------------------|------|
| Study (year)                                                             | Allergen              | Study participants (active treatment) | Median participant age (years) | Maintenance dose (mg) | Treatment duration | Treatment responders (desensitization) | Median cumulative tolerated dose at challenge (mg) | % doses with adverse effects | Treatment group dropouts | Dropouts related to adverse events | Ref. |
| Enrique (2005)                                                           | Hazelnut <sup>†</sup> | 12                                    | 29.2 <sup>‡</sup>              | 13.25                 | 8–12 weeks         | Not reported <sup>¶</sup>              | Fivefold increase                                  | 7.6                          | 1                        | 0                                  | [37] |
| Fernández-Rivas (2009)                                                   | Peach <sup>†</sup>    | 37                                    | 29.1 <sup>‡</sup>              | 0.01 <sup>§</sup>     | 6 months           | Not reported <sup>¶</sup>              | Three- to ninefold increase                        | 39.8                         | 4                        | 1                                  | [38] |
| Fleischer (2013)                                                         | Peanut                | 20                                    | 15                             | 1.386                 | 44 weeks           | 14/20 (70%) <sup>#</sup>               | 371                                                | 37                           | 5                        | 1                                  | [40] |
| Narisety (2015)                                                          | Peanut                | 10                                    | 11                             | 3.7                   | 12 months          | 7/10 (70%) <sup>#</sup>                | 496                                                | 9                            | 1                        | 1                                  | [43] |
| Kim (2011)                                                               | Peanut                | 11                                    | 5.8                            | 2                     | 6 months           | Not reported <sup>¶</sup>              | 1710                                               | 11.5                         | 0                        | 0                                  | [44] |
| Kim (2019)                                                               | Peanut                | 48                                    | 6.5                            | 2                     | 3–5 years          | 32/48 (67%) <sup>††</sup>              | 1750                                               | 4.8                          | 11                       | 2                                  | [45] |

<sup>†</sup> Includes patients with oral allergy syndrome.  
<sup>‡</sup> Mean age.  
<sup>§</sup> Pru P 3 antigen quantity.  
<sup>¶</sup> No threshold for responders was defined in this study.  
<sup>#</sup> Responders defined as tenfold increase from baseline [40,43] or 5 g oral food challenge [40].  
<sup>††</sup> Responders defined as tolerating 750 mg oral food challenge.

the relatively high withdrawal rates from these two studies was surprising. In a larger study population, the Phase III trial of AR101 peanut OIT had a withdraw rate of 20%, of which 11.6% in the treatment group were due to adverse events [19]. Within this group, gastrointestinal symptoms were the most prominent factor, affecting 6.5% of the treatment group. While SLIT for food allergy has not yet been studied in a large Phase III trial, compliance has been analyzed in its use for allergic rhinitis. In comparing SLIT to SCIT for treatment of allergic rhinitis, compliance for each over a 3-year period of therapy was found to be low [53]. Patients prescribed SCIT showed 23% compliance for 3 years of therapy with a median duration of 1.7 years compared with a 7% compliance over 3 years a median duration of 0.6 years in SLIT. One reason for this low compliance with environmental allergen SLIT may have been a perceived lack of efficacy in the treatment of rhinitis symptoms [54,55]. In the case of SLIT for food allergy, where the purpose of daily dosing is to prevent symptoms rather than control symptoms that are already present, it is not known how this trend will translate.

Important questions for future investigations and for individual patients and families remain. What increase in reaction threshold is enough? Which combination of side effects versus efficacy is ideal? Overall, a balance of clinical efficacy and symptoms with dosing will determine the ideal immunotherapy modality for individual patients. Whether the compliance in real world dosing of SLIT for food allergy will resemble that of SLIT for environmental allergy is to be determined. The impact daily of therapy on the individual and family in terms of benefits and adverse effects will need to be weighed in each circumstance. The decision if and by what modality to pursue immunotherapy for food allergy will be a shared decision between the patient, family and prescriber.

### Future perspective

SLIT for the treatment of food allergy has shown efficacy in Phase II clinical trials [42,43,45–47]. Daily dosing of glycerinated liquid extracts under the tongue promotes desensitization to food allergens and elicits a shift in the Th2 immune response toward an IgG<sub>4</sub> and regulatory T-cell phenotype associated with decreased clinical reactivity to food allergens [47]. Adverse effects of SLIT dosing are primarily limited to oropharyngeal itching with rare gastrointestinal and systemic symptoms.

Despite these promising results, OIT has progressed more quickly in development for the treatment of peanut allergy likely due to early studies demonstrating stronger desensitization with OIT when compared with SLIT [41]. With today's clearer understanding of the risks and potential difficulties with OIT as well as a shift in treatment goals from tolerance to protection against accidental ingestions, alternatives such as SLIT have garnered renewed interest and may deserve further investigation. In comparison with trials of the newly FDA-approved peanut OIT product (AR101/Palforzia), Phase II trials of SLIT for peanut allergy show fewer side effects but also do not achieve as high of a cumulative tolerated dose after therapy [19,41,45]. A subpopulation of participants in peanut SLIT studies demonstrate sustained unresponsiveness after three to 5 years of therapy but markers or clinical characteristics to predict this response are not known [47].

Future directions for sublingual approaches to immunotherapy are under development with the goal to increase the daily dose applied to the oral mucosa without compromising the side-effect profile [56]. The proposed mechanism of SLIT takes advantage of the tolerogenic oral Langerhans cells within the oral mucosa by applying a liquid formulation to the sublingual area of the mouth [57]. Biopsy of human tissue has demonstrated the highest density of these cells in the vestibular mucosa, buccal mucosa and gingiva with the lowest concentration in the sublingual region. A novel delivery platform termed oral mucosal immunotherapy (OMIT) aims to deliver allergen to the regions of the oral mucosa with the highest concentration of oral Langerhans cells [56]. Peanut INT301 is a developmental product utilizing OMIT as a fully functional toothpaste [E Berglund, Personal Communication, 10 March 2020]. The goal of this product is to deliver specific allergen to a greater area of oral mucosa than SLIT, taking advantage of the areas of the mouth with a higher concentration of oral Langerhans cells. This product aims to address the concern of low compliance with SLIT seen in allergic rhinitis studies by incorporating immunotherapy into the daily activity of tooth brushing. The delivery system of INT301 has the capacity to deliver at least 50 mg of peanut product per dose (compared with 2–3.7 mg per dose in SLIT) and thus could potentially achieve a greater maximal tolerance of allergen. There are not published studies with food allergen immunotherapy using OMIT.

One pilot study has investigated OMIT in treatment of environmental allergy in rhinoconjunctivitis [56]. This study included 24 adults and compared SLIT with glycerinated drops to OMIT toothpaste in multi-allergen immunotherapy. Adherence, which was defined as received over 90% of doses over a 12-month period, was 80% in OMIT and 62% in SLIT. This difference did not reach statistical significance. The number and severity of

adverse events also were not significantly different between these groups and were largely oropharyngeal swelling and itching. SLIT and OMIT elicited similar increases in allergen-specific IgG4 production while on therapy.

As OMIT for food allergy treatment moves forward into clinical trials, a key question will be whether it can achieve the positive effect of higher levels of desensitization while maintaining the favorable side effect profile of SLIT. In all of these therapies, real-world compliance will be of great concern given the known challenges with long-term adherence to environmental allergen SCIT and SLIT related to perceived ineffectiveness at the initiation of therapy, cost and side effects [58]. Incorporating food allergy treatment into the daily routine of tooth brushing is an intriguing approach to this challenge.

### Executive summary

#### Immunologic mechanisms of sublingual immunotherapy

- Sublingual immunotherapy (SLIT) promotes a tolerogenic immunologic response to allergens.
- Specialized oral Langerhans cells take up allergen in the oral mucosa.
- Immune responses to SLIT are characterized by IL-10, regulatory T cells and IgG<sub>4</sub>.

#### SLIT in pollen-food allergy syndrome & early descriptions in food allergy

- Trials of SLIT for treatment of hazelnut and peach allergy demonstrated effectiveness in randomized controlled trials. These studies were limited by the inclusion of patients with oral allergy syndrome.

#### SLIT in cow's milk allergy

- SLIT was not as effective as oral immunotherapy in achieving desensitization to cow's milk but was associated with fewer side-effects.

#### Peanut SLIT

- Randomized controlled trials demonstrate efficacy of SLIT for peanut allergy treatment.
- The highest tolerated dose of peanut allergen was noted in the study investigating younger participants and a longer duration of SLIT.

#### Benefits & drawbacks of SLIT

- SLIT desensitizes individuals to a degree that will protect from doses typically encountered by accidental ingestion of an allergen.
- Adverse effects are less common in SLIT than oral immunotherapy and are typically limited to the oropharynx.

### Author contributions

SA Schworer and EH Kim reviewed the literature and wrote the paper.

### Acknowledgments

Personal communication approved by E Berglund.

### Financial & competing interests disclosure

EH Kim reports clinical medical advisory board membership with DBV Technologies; consultancy with Aimmune Therapeutics, DBV Technologies, AllerGenis, Allakos, Ukko and Vibrant America; and receives grant support to his institution from the National Institute of Allergy and Infectious Diseases (NIH/NIAID), National Center for Complementary and Integrative Health (NIH/NCCIH), FARE and the Wallace Research Foundation. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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