



Current Status of Potential Therapies for IgE-Mediated Food Allergy

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Abstract

Purpose of Review The goal of this review is to provide the reader with an updated summary of published trial data regarding the use of oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT) for treatment of IgE-mediated food allergies.

Recent Findings Data from phase 2 trials for treatment of peanut allergy with OIT and EPIT reveal an increase in the threshold of reactivity for peanut-allergic children. Compared to EPIT, OIT promotes a greater increase in the threshold of reactivity; however, adverse events are more common with OIT.

Summary OIT, EPIT, and SLIT appear to modulate the immune response for some food-allergic individuals. Data regarding utility for treatment of food allergies regardless of modality is limited to few foods, as is investigation into treatment of food-allergic infants, young children, and adults. Future trials are likely to focus on young children, food allergies other than peanut, and treatment of multifood-allergic individuals.

Keywords Food allergy · Oral immunotherapy · OIT · Epicutaneous immunotherapy · EPIT · Sublingual immunotherapy · SLIT · Peanut allergy · Milk allergy

Introduction

Food allergy affects 5–10% of the population in the developed world and typically is present in early childhood [1, 2]. Symptoms following ingestion may be limited, or they may progress to life-threatening anaphylaxis. A number of factors may influence reaction severity, including the amount of the allergenic food ingested, presence or degree of asthma control, and individual sensitivity [3]. There are no surrogate markers that allow for prediction of reaction severity or the threshold of reactivity. Though fatalities due to food allergy are rare, its potentially life-threatening nature and the challenges associated with constant vigilance to avoid accidental ingestion create a significant burden on the quality of life for affected individuals

and their caretakers [4]. At the present time, there are no FDA-approved therapies for treatment of food allergies. While most food allergies resolve naturally without intervention, individuals allergic to peanut, tree nuts, fish or shellfish may expect to be allergic throughout their life in the absence of therapy.

Over the past decade, investigation into interventional therapies aimed at treating IgE-mediated food allergies has accelerated rapidly. The most commonly investigated modality involves feeding milligram to gram quantities of food protein through the oral route, termed oral immunotherapy (OIT). OIT has consistently been shown to significantly change the threshold of reactivity, but it also carries the greatest risk of having an adverse reaction among therapies currently under investigation. Epicutaneous immunotherapy (EPIT) and sublingual immunotherapy (SLIT) utilize microgram to milligram quantities of protein to mitigate the allergic response, and systemic reactions using either approach is rare; however, efficacy is variable and neither approach has been sufficiently studied at the time of this publication to predict their long-term potential as a reliable therapeutic approach to treatment of food allergy. This review will focus on the current literature regarding OIT, SLIT, and EPIT as interventional therapeutic approaches for the treatment of IgE-mediated food allergies.

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OIT

OIT has been increasingly studied in recent years, with evidence of efficacy for several foods. In general, OIT protocols consist of an initial escalation phase (multiple doses over a single day), a buildup phase (daily dose slowly increased at regular intervals), and a maintenance phase after a target dose is achieved. Desensitization, a temporary state of immune unresponsiveness requiring ongoing allergen exposure, is assessed with an oral food challenge (OFC) during or at the end of maintenance. If passed, an additional OFC after a period of abstinence may be performed to assess for sustained unresponsiveness (SU), which refers to an absence of an allergic response upon exposure to the allergenic food after a prolonged period of avoidance. OIT decreases activation of mast cells and basophils, induces humoral changes (increased allergen-specific IgG4 and IgA and initially increased then decreased allergen-specific IgE), and alters function of both regulatory and effector T cells. While the general efficacy of OIT using these principles is increasingly evident for the most common food allergens, questions remain, especially regarding adverse effects and durability of effects.

Peanut OIT

Case reports of successful desensitization with peanut OIT were first published in 2006 [5, 6]. In 2011, the first multicenter randomized double-blind placebo-controlled (DBPC) peanut OIT study used a maintenance dose of 4000 mg peanut protein (1 peanut = approximately 250–300 mg of protein) (J. Baumert and S. Taylor, Food Allergy Research and Resource Program, personal communication, September 23, 2016) for 48 weeks [7]. Sixteen of 19 children (1–16 years) achieved desensitization (passed a 5000-mg DBPCFC). The other three withdrew due to allergic side effects. SU after peanut OIT was first reported in 12 of 24 subjects after up to 5 years treatment with 4 g daily followed by 4 weeks avoidance [8]. Four-week SU rates were lower (27% by intention-to-treat analysis) in a study designed primarily to compare peanut OIT versus SLIT [9]. SU is often lost with prolonged avoidance [10], implying that at least some level of continued allergen exposure may be required for ongoing unresponsiveness.

Successful secondary prevention of peanut allergy in high-risk infants sensitized to peanut was seen in the LEAP study [11]. This hints at a possible “early window” in which the immune response to peanut may be more malleable. In a randomized double-blinded trial in preschool children (9 to 36 months) of high-dose versus low-dose OIT for 3 years, 29 of 37 (78%) achieved 4-week SU, versus 91% (29 of 32) in per protocol analysis [12•]. It remains unclear whether this apparent higher efficacy is attributable to the young age at intervention or to other factors such as low peanut-specific IgE. There was no significant difference in safety or efficacy

between the 3000 and 300 mg maintenance dose. Phase 3 clinical trials of a commercial peanut OIT product in peanut-allergic individuals (4–55 years) with a 300-mg maintenance dose are ongoing (NCT02635776). A phase 2 study of the same product showed successful desensitization to ≥ 443 and 1043 mg in 79 and 62%, respectively, by ITT (versus 19 and 0% in placebo groups) [13••].

Milk OIT

In uncontrolled case series and studies of milk OIT, most subjects successfully achieve desensitization [14–19]. The first randomized controlled trial of milk and egg OIT showed desensitization in 64 versus 35% in the control group, illustrating the importance of control groups in assessing the impact of OIT in settings where natural food allergy resolution is common [20]. Two-month SU occurred in 36% of the OIT subjects. Skripak et al. published the first randomized placebo-controlled study of milk OIT, with 13 weeks treatment with 500 mg milk protein increasing the median OFC threshold from 40 to 5140 mg [21]. In open-label follow-up, the dose was escalated to a median of 7000 mg, with 6 of 13 patients tolerating an OFC of 16,000 mg [22].

As in peanut OIT, the effects of milk OIT have limited durability. Keet et al.’s open-label RCT of milk OIT versus SLIT showed superior desensitization rates with OIT, but the 6-week SU rate was only 40% by ITT, with two patients losing desensitization after 1 week of OIT abstinence [23]. In a long-term follow-up of an open-label study, 14 (58.3%) of 24 children were consuming ≥ 200 ml of milk daily 7 years after completing OIT, although three (21.4%) still had symptoms with ingestion [24]. In long-term follow-up of the Keet and Skripak studies, less than a third of OIT subjects fully tolerated milk 3 to 5 years after OIT completion [25]. If ongoing allergen exposure is required to maintain unresponsiveness, then regimens with less frequent dosing may be preferable, but evidence is lacking to support this approach. One study found no difference in efficacy between daily and twice-weekly maintenance dosing while allowing other milk products ad lib, but this study did not assess desensitization or SU with OFCs [26].

Egg OIT

Early egg OIT studies showed desensitization in a majority of patients in small case series [14, 15], and subsequent studies have shown high rates of desensitization and low rates of SU. Five of 7 (71%) patients passed an 8 g OFC after 24 months egg OIT with 300 mg egg white protein, but only two (29%) achieved 3-month SU [27]. With individualization of maintenance dose (median 2400 mg), six of eight (75%) achieved 4-week SU. In the first DBPC randomized multicenter study of egg OIT (2 g egg white powder daily), 30 of 40 (75%) were

desensitized at 22 months, but only 11 (27.5%) had 6–8-week SU [28]. Four- to 6-week SU increased to 50% (20 of 40) after 4 years of long-term follow-up [29], and other studies have shown SU of 31 to 37% after shorter treatment durations [30, 31].

OIT with Baked Milk and Baked Egg

Many patients with milk and/or egg allergy tolerate these foods if extensively heated or baked [32, 33], and this tolerance has been associated with resolution of allergy [34, 35]. This has inspired baked egg (BE) and baked milk (BM) OIT studies with disappointing results to date. In an open label, uncontrolled study of BM OIT in severely milk-allergic children who previously failed to tolerate unbaked milk OIT, adverse reactions prevented 11 of 14 patients from tolerating 1300 mg of baked milk after 1 year [36]. In a pilot study of baked egg OIT, 53% (8 of 15) tolerated the target dose of 6.25 g of egg protein (one biscuit) daily, and five others were able to incorporate trace amounts of egg protein into their diet [37]. A recent DBPC trial of OIT using hydrolyzed egg white showed no significant difference in efficacy between the OIT and placebo groups [38].

OIT with Other Foods

While the base of knowledge on OIT for milk, egg, and peanut has grown over recent years, data remains relatively limited on other foods. In an open-label, non-controlled, real-life OIT study of wheat OIT (WOIT) in six wheat-allergic patients (sensitized to α -amylase but not omega-5-gliadin), five of six (83.6%) tolerated a maintenance dose of 100 g [39]. In another open-label prospective study using historical controls, 16 of 17 (94.4%) tolerated 5.2 g of wheat protein daily, and 2-week SU was 61.1% [40]. Recent results of a large randomized, placebo-controlled multicenter WOIT study with high-gluten wheat flour were less promising [41]. Twenty-three patients in the WOIT group received up to 1445 mg daily, with 12/23 (52.2%) meeting the primary end-point (tolerating ≥ 4443 mg in DBPCFC) at 1 year, and only 7/23 (30.4%) fully desensitized (successfully consumed dose (SCD) 7443 mg) after 2 years. Only three (13%) achieved SU. The placebo group crossed over to high-dose WOIT (max 3870 mg daily) and 12/23 (57.1%) were desensitized. These results illustrate the variability in OIT success patterns with different foods and even different patterns of sensitization to the same food.

Multiple-Food OIT

While single foods are the target for most OIT trials, as many as 30% of children with food allergy react to multiple foods,

and this subset of children tends to have more persistent food allergy [42]. This lower likelihood of natural food allergy resolution makes effective treatment more desirable. Peanut OIT has no effect on tree nut- and sesame-specific IgE levels [43], indicating that in order to treat allergies to multiple foods, OIT would be needed for each food. A phase 1 pilot study of multiple-food OIT (peanut and up to four other foods) showed no significant difference in adverse effects versus peanut OIT alone [44]. Results were similar with omalizumab pretreatment and rush OIT to multiple foods [45]. Further studies on multiple-food OIT will be needed to clarify its efficacy, risks, and benefits.

Adverse Reactions to OIT

Despite the mounting evidence that OIT often effectively induces desensitization, safety concerns remain. Adverse effects (AEs) are common and may be immediate and IgE-mediated (urticaria, flushing, wheezing, emesis, anaphylaxis) or chronic and isolated to the gastrointestinal (GI) tract (abdominal pain, nausea vomiting, dysphagia, eosinophilic esophagitis [EoE]). Data on OIT safety is limited by the relative lack of large studies with a primary focus on detailed safety assessment.

AEs are most common with initial dose escalation and buildup, but they still occur during maintenance. Hofmann et al. reported upper respiratory symptoms, abdominal symptoms, and wheezing in 79, 68, and 18% of 28 patients during initial dose escalation for peanut OIT [46]. AEs (mostly upper respiratory tract or cutaneous) occurred with 46% of buildup phase doses, and 3.5% of home maintenance doses. Eighty-nine percent of 352 patients undergoing OIT in a clinical setting experienced IgE-mediated symptoms, with over 57% experiencing multisystem reactions and epinephrine use rates of 12% during buildup and 6% during maintenance [47]. To date, the largest OIT safety analysis was performed retrospectively on pooled data from three pediatric peanut OIT trials [7, 8, 48], and found that 80% of 104 patients had mild (85%) to moderate (15%) treatment-related AEs during OIT [49••]. AEs occurred in 72% of patients during buildup (2.8 per 100 dosing days) and 47% of patients during maintenance (0.4 per 100 dosing days). Over 90% occurred at home. Twenty-two percent of all AEs (occurring in 61% of subjects) required treatment. Systemic reactions were seen in 42% of patients (10% of all AEs), and 12% of patients received epinephrine during the trial. Interestingly, for 97 AEs, the authors deemed that epinephrine was warranted but not administered, highlighting the inadequacy of epinephrine use as a proxy measure for OIT safety.

Infection, exercise, pollen allergy, uncontrolled asthma, menstruation, and dosing with an empty stomach have all been identified as factors that augment the risk of AEs during OIT [20, 47, 50]. OIT protocols typically include instructions aimed at mitigating these factors, for example limiting

physical activity after dose administration, holding doses with acute illness, dosing with meals, and trying to ensure asthma control. Virkud et al. also identified allergic rhinitis as a predictor of AEs, especially during maintenance phase and peak pollen months, and noted associations between larger peanut SPT wheal size and both overall AEs and isolated GI symptoms [49••].

Persistent GI symptoms (abdominal pain, nausea, vomiting, dysphagia) are common in OIT. A meta-analysis estimated the prevalence of EoE in OIT at 2.7% [51]. However, this may be an underestimate as symptoms typically resolve with cessation of dosing, and most patients do not undergo endoscopic evaluation. Virkud et al. found that 49% of patients experienced GI symptoms, 33% of all AEs included GI symptoms, and 26% of AEs involved isolated GI symptoms [49••]. Ten of 13 (77%) symptomatic withdrawals were secondary to GI symptoms, representing 10% of the study population overall. Three underwent endoscopy and two had EoE. Only peanut SPT wheal size was identified as a risk factor for isolated GI symptoms (1.8-fold increase in risk for each 5-mm increase in SPT wheal). However, a separate single-center analysis of 794 subjects undergoing milk, peanut, egg, and/or sesame OIT found that recurrent GI symptoms (present in 8.2%) were associated with higher baseline peripheral eosinophil counts, greater increase in eosinophil counts during treatment, and higher maximum eosinophil counts. These symptoms resolved with reduction or cessation of dosing and did not recur in 42 of 45 patients who resumed dosing. All three patients who underwent endoscopy had EoE.

Future Treatments

OIT + Probiotics

Given the questions regarding the durability of OIT's effects and relatively low rates of SU, investigators have sought ways to increase the tolerogenicity of OIT. Use of tolerogenic adjuvants has shown promise in studies of subcutaneous and sublingual immunotherapy for allergic rhinitis [52–56]. *Lactobacillus rhamnosus* CGMCC 1.3724 has been shown to induce immune responses thought to promote tolerance [57–61]. Based on this information, a DBPC randomized trial of *Lactobacillus rhamnosus* CGMCC 1.3724 and peanut OIT (probiotic and peanut oral immunotherapy [PPOIT]) was undertaken with the hypothesis that the probiotic would have an adjuvant tolerogenic effect resulting in improved SU [62]. Fifty-six children (1 to 10 years) were randomized equally to PPOIT with *Lactobacillus rhamnosus* CGMCC 1.3724 (at a dose equivalent to 20 tubs of yogurt daily) and peanut flour (maintenance dose of 2 g peanut protein) or placebo for 18 months. There were no probiotic only or

OIT only groups and no entry DBPCFC to confirm peanut allergy. Desensitization occurred in 26/29 children (89.7%) in the PPOIT group and 2/28 (7.1%) in the placebo group, while 2-week SU occurred in 23/28 (82.1%) in the PPOIT group and 1/28 (3.6%) in the placebo group. Those who achieved 2-week SU were instructed to continue peanut ingestion ad libitum.

Four years after study completion, 48 of 56 (86%) patients were surveyed on interim peanut consumption and reactions and offered a DBPCFC to assess 8-week SU [63]. Sixteen of 24 (67%) participants in the PPOIT group reported eating peanut at 4-year follow-up, all of whom had achieved 2-week SU at the end of the parent study. Four (20%) of the 20 who had achieved 2-week SU and participated in the follow-up study stopped eating peanut in the interim: 1 due to dislike of peanut taste, 2 due to symptoms with peanut ingestion, and 1 due to social circumstances. Rates of 8-week SU were 58% (7 of 12) in the PPOIT group and 7% (1 of 15) in the placebo group. Of those who failed the DBPCFC in the PPOIT group, two were peanut-allergic (did not attain 2-week SU after parent study and had not continued eating peanut), one was re-sensitized 26 months after the parent study, and two had been eating peanut ad lib but reacted at a cumulative dose of 4 g. Given that the parent study assessed 2-week SU and the follow-up assessed 8-week SU, it is unclear if the allergic status of the last two actually changed or not. These results need to be interpreted with caution given the limitations of the study design.

While these findings do show somewhat higher rates of SU than studies of OIT alone, 11 reactions occurred after intentional peanut ingestion in four participants who achieved 2-week SU in the initial study, compared to nine reactions in six patients in the placebo group after accidental ingestions. Quality of life was significantly improved in the PPOIT group up to 12 months after the initial trial [64]. A recent economic analysis based on the initial study and using Markov modeling suggested that the treatment was likely cost-effective but would likely cause more anaphylactic events that it would prevent [65]. Further studies with more rigorous design are needed to confirm the benefits seen and define whether they were due to OIT, the probiotic, or a synergistic effect of the combination.

OIT + Anti-IgE Therapy

Omalizumab is a humanized monoclonal antibody (mAb) that targets circulating IgE, decreasing its levels and also leading to downregulation of IgE receptors on mast cells and basophils. An early study showed that a similar mAb (TNX-901) increased the threshold of reactivity to peanut, and subsequent studies confirmed that omalizumab had the same effect [66–68]. The first use of omalizumab prior to

and concurrent with OIT was an open-label pilot study of 11 patients, 9 (82%) of whom successfully achieved rapid desensitization to milk with mostly mild adverse effects [69]. In a similar study with peanut, 12 of 13 (92%) passed an 8-g OFC after 12 weeks pretreatment with omalizumab, successful rush OIT, dose escalation to 4 g daily, then 12 weeks OIT maintenance dosing after cessation of omalizumab [70]. A larger DBPC milk trial in 57 subjects showed no significant difference in rates of desensitization (88.9% with omalizumab, 71.4% with placebo) but significantly less frequent and less severe reactions in the omalizumab group during dose escalation and maintenance [71]. A trend toward higher 8-week SU was noted in the omalizumab group (48.1%) versus the placebo group (35.7%). In the first randomized DBPC study of omalizumab with peanut OIT, 79% were successfully desensitized to 2 g peanut protein versus 12% in the placebo group [72]. Rates of AEs did not significantly differ, but omalizumab-treated subjects were ingesting much higher doses of peanut. Of note, two of the omalizumab-treated subjects had symptoms consistent with EoE, with biopsy confirmation in one. The only report of egg OIT in conjunction with omalizumab was a single-center collection of cases of subjects who previously failed egg OIT then achieved desensitization with concurrent omalizumab. However, all had recurrence of symptoms several months after omalizumab discontinuation [73]. This loss of desensitization was not seen in other studies. In a single-center phase 1 trial, omalizumab facilitated rush OIT to up to five food allergens, with 19 (76%) tolerating the full initial escalation day and all except three dropouts due to non-adherence reaching their target maintenance dose of 4 g protein per allergen at a median of 18 weeks [45]. Reaction rates were similar to those in a similar multiple-food OIT study by the same team in which subjects needed a median of 85 weeks to achieve the same maintenance dose [44].

Altogether, these studies demonstrate that omalizumab allows higher initial OIT doses, facilitates more rapid desensitization with fewer doses needed to achieve target dose, and reduces the rate and severity of IgE-mediated reactions during OIT. These features are particularly appealing for the 30% of patients with food allergies who react to multiple-food allergens. Anti-IgE therapy is not effective in the treatment of EoE, and unsurprisingly seems ineffective in preventing OIT-related EoE. Further study is needed to clarify the ideal duration of omalizumab treatment (pre-OIT and total duration) as well as whether or not omalizumab can significantly affect rates of SU.

IT with Modified Allergens

Another approach to improve the safety of food-specific immunotherapy is allergen modification. Results of baked milk

and egg and hydrolyzed egg OIT studies were discussed above. In a murine model of peanut OIT, CpG-coated poly(lactic-co-glycolic acid [PLGA]) nanoparticles containing peanut extract appeared safe and effective [74]. This approach combined a nanoparticle delivery system intended to optimize transport across the gut barrier and limit mast cell/basophil activation together with CpG, a Toll-like receptor (TLR) agonist intended to enhance the shift of the allergen-specific response toward Th1. Major peanut allergens modified to decrease IgE-binding while maintaining their ability to stimulate a lymphocyte response showed promise in a murine model [75, 76]. However, in a phase 1 study of modified recombinant Ara h 1, Ara h 2, and Ara h 3 encapsulated in heat/phenol-killed *E. coli* administered rectally, 5 of 10 adults were unable to complete dosing due to adverse reactions and two had anaphylaxis [77]. Parvalbumin has also been modified into a hypoallergenic form [78] but has not yet been studied in IT.

EPIT

EPIT takes advantage of allergen presentation to Langerhans cells in the epidermis as a potential route for safely modulating the immune response. Systemic side effects are minimized secondary to the absence of vascularity in the epidermis. The mechanism of EPIT is not clearly defined; however, it is agreed upon that local and peripheral Foxp3⁺ Treg cells are essential in EPIT [79]. It has been shown in a mouse model that antigen is taken up by Langerhans cells in the superficial layers of the stratum corneum, transported to draining local lymph nodes, and generate gastrointestinal-homing latency-associated peptide (LAP+) regulatory T cells [80]. Induction of regulatory T cells is associated with down-modulation of allergen-specific responses [81].

Milk

In 2010, a pilot study using egg and peanut-sensitized mice concluded that EPIT was as efficacious as SCIT in a murine model [82]. This led to the first EPIT RDBPC study evaluating 19 children (ages 3 months–15 years) with cow's milk allergy [83]. The study concluded that there was a tendency toward an increased cumulative tolerance dose ($p = 0.13$), although it was not powered to study efficacy. Currently, there is an ongoing phase 2 trial (NCT02223182) assessing efficacy in milk-allergic patients randomized to placebo or 150, 300, or 500 µg milk protein for 12 months.

Peanut

In 2016, a phase 1 study of peanut EPIT demonstrated safety and tolerability in 100 peanut-allergic patients during a 2-

week treatment period [84]. Of patients who received peanut EPIT, 52.5% experienced a treatment emergent adverse event, compared to 45% of placebo. No severe reactions were reported, and no epinephrine was used.

Jones et al. reported results from the National Institutes of Allergy and Infectious Diseases sponsored Consortium on Food Allergy Research (CoFAR) phase 2 trial including 74 peanut-allergic patients (ages 4–25 years) assigned to 100 or 250 µg peanut protein, or placebo for 52 weeks [85]. The primary outcome was passing a 5044-mg protein OFC or achieving ≥ 10 -fold increase in SCD from baseline to week 52. Compared to 12% of placebo-treated participants, 46% of the 100-µg dose participants and 48% of the 250-µg dose participants met the primary outcome ($p = 0.005$ and 0.003 , respectively), although this was significant only because of an increased tenfold threshold in SCD compared to baseline rather than via passing a 5044-mg challenge. The median SCD was 144 mg in both treatment groups. The majority of adverse reactions were mild and limited to the patch site. A follow-up study will be forthcoming, which will evaluate long-term results through 130 weeks. Lastly, although not powered to study specific age differences, this study demonstrated a greater effect in participants less than 11 years [85].

Another recent phase 2 trial showed similar results. Two hundred twenty-one peanut-allergic subjects (ages 6–55 years) were randomized to 50, 100, or 250 µg peanut protein, or placebo [86••]. The primary outcome was passing a 1000-mg peanut protein OFC or achieving ≥ 10 -fold increase in SCD from baseline to week 52. There was a significant difference in response rate reported between the 250-µg group and placebo group ($p = 0.01$) with a mean cumulative reactive dose of 1117.8 mg for the 250-µg group and 469.3 mg for the placebo group. Consistent with prior reports, further stratification demonstrated that only in the 6- to 11-year age group was there was a significant difference between the 250-µg group versus the placebo group (34.2%), although this study was not designed to detect an age effect independent of a treatment effect. Nevertheless, these reproducible results have prompted ongoing studies to focus on a younger population [86••]. Results from the open-label portion of this study are pending and will assess efficacy after 36 months of treatment (NCT01955109). This follow-up study will also measure SU after 2 months without treatment in subjects who are desensitized with therapy.

Currently, results are pending from a completed phase 2 trial in France (NCT01197053) which randomized 52 peanut-allergic children (ages 5–17 years) to either 100 µg peanut protein or placebo, followed by 12 months of open treatment for all patients in the active arm. Enrollment is complete for a phase 3 study (NCT02636699) evaluating peanut-allergic children (ages 4–11 years) after 12 months of 250 µg peanut protein, with a follow-up study (NCT03013517) assessing patients who use 250 µg peanut protein for an additional

2 years. Lastly, a phase 3 trial (NCT03211247) is investigating the efficacy of peanut EPIT in peanut-allergic children (ages 1–3 years) who will receive 12 months of 100 or 250 µg peanut protein, or placebo.

Conclusion

Studies thus far have shown EPIT is safe; the risk of a systemic reaction is low, and the major adverse effect has been well-tolerated localized patch-site reactions. Studies have also concluded that EPIT may increase threshold doses to peanut, and ongoing studies are targeting children younger than 11 years old as preliminary phase 2 data suggests a more robust response in this age group.

SLIT

SLIT involves placing allergen in the form of drops or tablets under the tongue and uses the unique immunogenic properties of the oral mucosa to promote tolerance. The regulatory myeloid dendritic cells seem to be the primary target cells of SLIT and are proposed to present to T cells directly in the mucosa instead of rapidly migrating to the lymph node [87]. Although it has been approved for allergic rhinoconjunctivitis, more recent studies have focused on food allergies.

Hazelnut

In 2005, the first DBPC SLIT trial randomized 23 hazelnut-allergic adults to hazelnut or placebo. After 8 to 12 weeks of maintenance therapy, 5 of 11 (45%) in the active cohort were able to ingest 20 g of hazelnut with the mean tolerated dose increasing from 2.29 to 11.56 g. Of note, 54.5% patients had only oral allergy syndrome on initial food challenge [88, 89].

Milk

In 2006, an open-label pilot study evaluated eight children (ages 6–17 years) with cow's milk allergy. After 6 months, only three (38%) were able to consume 200 ml of milk without symptoms. However, their mean post-treatment challenge threshold increased from 39 to 143 ml [90]. An ongoing trial (NCT00874627) is currently evaluating the reactive milk dose at inclusion, 6 and 12 months of therapy.

Peach

In 2008, a DBPC trial studied 56 peach-allergic adults. After 6 months of maintenance therapy, 33 (89%) patients were rechallenged and were able to tolerate up to ninefold higher threshold compared to baseline, although the mean changes in

threshold doses were not reported. Of note, 63% of patients had only oral allergy syndrome on initial food challenge [91].

Peanut

In 2011, the first DBPC trial randomized 18 peanut-allergic children (ages 1–11 years) to placebo or peanut SLIT. After a goal daily dose of 2500 µg peanut protein over a 6-month period and an additional 6 months of maintenance, the active group safely ingested 20 times more peanut protein (1710 mg) than the placebo group (85 mg), although the ranges were very wide in the active group ($p = 0.011$) [92].

In 2013, 40 subjects (ages 12–37) were randomized to peanut SLIT or placebo for 44 weeks. Compared to 3 of 20 (15%) in the placebo cohort, 14 of 20 (70%) in the peanut cohort met the primary outcome of tolerating either 5000 mg of peanut or a tenfold higher amount than baseline threshold ($p < 0.001$). Subsequently, the peanut cohort continued an additional 24 weeks of maintenance therapy; their SCD increased from 496 mg after the first maintenance period to 996 mg after the additional 24 weeks of maintenance. In addition, the placebo-treated cohort crossed over to 3639 µg daily for 44 weeks; 7 of 16 (44%) patients met the aforementioned primary outcome [93]. A subsequent study followed this peanut cohort for two additional years, but only 4 of 37 patients (11%) demonstrated SU, which was defined as the ability to consume an open serving of peanut 8 weeks after passing a 10,000-mg DBPCFC [94]. Of note, this conclusion needs to be interpreted cautiously, as there was a high rate of drop out (~62%), which was largely because of “participant decision” or “nonadherence” and not because of significant adverse reactions.

One ongoing SLIT study for peanut allergy (NCT01373242) is assessing tolerance after 48 months of therapy and then the subjects are randomized to study a tolerance period of 1–17 weeks. Another trial (NCT02304991) is studying peanut SLIT in 1- to 4-year-old subjects with the primary outcome being reaction thresholds after 36 months of treatment. Lastly, a study (NCT00429429) is evaluating the effectiveness of SLIT via negative DBPCFC to 8000 mg of peanuts after 2 years of treatment.

Conclusion

SLIT studies have demonstrated the sublingual route to be very safe, as almost 99% of reported reactions are local, and the majority of these reactions are restricted to the oral cavity. Systemic symptoms in SLIT are very rare, with one study reporting 0.2% of all reactions [88]. It is also significantly safer than OIT in milk and peanut-allergic patients, although the change in threshold doses of reactivity is overall less than what is seen with OIT [95, 96]. Future studies are warranted

and may include investigations into the use of adjuvants and multi-allergen SLIT.

Conclusions

While the past decade has provided additional support for promising approaches to treating IgE-mediated food allergies, broad interpretability is limited by variable study design utilizing a variety of outcome measures, maintenance doses, and small study populations. Ongoing phase 3 studies for OIT and EPIT will provide high-quality evidence to inform allergists regarding the best approach to treating our peanut-allergic patients. Limited evidence in treating other foods suggests that each food may respond differently to each approach, and it is unlikely that we will have a clear pathway to treatment of multifood-allergic patients in the near future. At the present time, evidence weighs in favor of food allergen avoidance and use of auto-injectable epinephrine when needed following accidental ingestion.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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