

Immunotherapy for Food Allergy: Are We There Yet?



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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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List of Design Committee Members: Yael Gernez, MD, PhD, and Anna Nowak-Węgrzyn, MD

Learning objectives:

1. To describe current approaches to food immunotherapy under study.
2. To understand efficacy and side effects for various routes of food immunotherapy.
3. To distinguish desensitization from permanent tolerance.

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Current clinical research focuses on food allergen-specific immunotherapy through oral (OIT), sublingual (SLIT), or epicutaneous (EPIT) routes. Immunotherapy relies on the delivery of gradually increasing doses of specific allergens to induce desensitization (defined as temporary antigen hyporesponsiveness that depends on regular food ingestion) and, ultimately, tolerance (defined as the ability to ingest food without symptoms despite prolonged periods of avoidance or irregular intake). Although the majority of the patients treated with OIT achieve desensitization, only a minority achieves tolerance. OIT involves higher maintenance doses of food protein (300 mg-4g) compared with SLIT (2.5-7.5 mg) and EPIT (250-500 mcg). OIT efficacy is higher compared with SLIT, but OIT is associated with higher rate of systemic adverse events compared with SLIT and EPIT. OIT is also associated with a minor risk of eosinophilic esophagitis. Combined treatment of OIT

and anti-IgE monoclonal antibody has improved safety but not efficacy compared with OIT alone. Early initiation of peanut OIT in peanut-allergic infants and young children may afford superior efficacy and safety. In this review, we discuss the allergen-specific strategies currently explored for the treatment of food allergy, including immunotherapy with native and heat-modified food proteins. Additional research employs strategies to improve the safety and efficacy of allergen immunotherapy through modifications of allergen structure and addition of immunomodulatory adjuvants. © 2017 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2017;5:250-72)

Key words: Food allergy; Immunotherapy; Food immunotherapy; OIT; Oral immunotherapy; SLIT; Sublingual immunotherapy; EPIT; Epicutaneous immunotherapy

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Abbreviations used

AE- Adverse event
AR- Allergic rhinitis
DBPC- Double-blinded placebo-controlled
DBPCFC- Double-blinded placebo-controlled food challenge
EoE- Eosinophilic esophagitis
EPIT- Epicutaneous immunotherapy
FA- Food allergy
GI- Gastrointestinal
HydE- Hydrolyzed egg
OFC- Oral food challenge
OIT- Oral immunotherapy
QoL- Quality of life
SLIT- Sublingual immunotherapy
SPT- Skin prick test
SCD- Successfully consumed dose
SU- Sustained unresponsiveness
Treg- T regulatory cell
VP100- Viaskin peanut 100 µg
VP250- Viaskin peanut 250 µg

Food allergy (FA) is a global health problem affecting approximately 5% of adults and 8% of young children.¹ IgE-mediated FA is associated with risk of fatal anaphylaxis, yet there is no currently approved immunomodulatory treatment. Food avoidance and immediate treatment of anaphylactic reactions with epinephrine remain the mainstay of management.^{2,3} However, accidental exposures are common and food avoidance has been shown to decrease the quality of life (QoL).^{4,5} There is, therefore, an unmet need for effective therapies. In the past decade, significant advances have been made in the field of specific food immunotherapy, including oral (OIT), sublingual (SLIT), and epicutaneous immunotherapy (EPIT).³

Allergen immunotherapy entails a risk of an allergic reaction. Indeed, in the 1990s, a high rate of systemic reactions occurred with peanut subcutaneous immunotherapy (SCIT) in peanut-allergic adults.⁶ Therefore, subsequent studies have focused on alternative routes of delivery or modification of allergic proteins to improve safety and efficacy.

In this review, we discuss allergen-specific strategies currently explored for the treatment of FA, including immunotherapy with native and modified food proteins. [Figure 1](#) summarizes diverse therapies undergoing active investigation.⁷⁻¹⁵

OUTCOMES OF FOOD IMMUNOTHERAPY: DESENSITIZATION VERSUS TOLERANCE

Food immunotherapy entails the delivery of gradually increasing doses of allergens with the objective of inducing desensitization, and ultimately, tolerance ([Figure 2](#)). Desensitization is a state of temporary antigen hyporesponsiveness that develops relatively early during immunotherapy. Desensitization depends on regular food exposure; when dosing is interrupted (eg, due to illness or nonadherence), the protective effect of desensitization is lost. The exact mechanism underlying desensitization is not well understood, but there is an increase in allergen-specific IgG₄ antibodies, observed as early as 8 weeks after starting OIT, followed by decreases in specific IgE.¹⁶⁻¹⁹ Basophil activation is suppressed by IgG antibodies, and this inhibition can be blocked by antibodies against FcγRII.²⁰ Peanut OIT induces hyporesponsiveness in basophils consistent with

pathway-specific anergy previously described *in vitro*, suggesting that effector cell anergy could contribute to clinical desensitization.²¹

In the rapid high-dose milk OIT combined with 8 weeks of omalizumab pretreatment, within a week of starting OIT, the CD4⁺ T-cell response to milk was nearly eliminated, suggesting anergy or deletion of milk-specific CD4⁺ T cells, with no detectable increase in T regulatory cells (Tregs).¹⁹

Permanent tolerance is defined as the ability to ingest food without symptoms despite prolonged periods of avoidance or irregular intake. Potential mechanisms underlying oral tolerance are presented in [Figure 3](#).

Because there is no agreement on the exact period of food avoidance after treatment, defining tolerance, the studies report on sustained unresponsiveness (SU) as a surrogate for permanent oral tolerance.^{10,11,17,22-33}

MECHANISMS OF OIT

An overview of the immune changes associated with OIT is presented in [Figure 4](#).

Effector cells

In the early stage of OIT, a decrease in nonspecific reactivity of basophils and mast cells is observed.^{10,25,28,33-37} The decrease in basophil and mast cell reactivity could be secondary to a decreased surface expression of high-affinity IgE receptors³⁸ or generation of IgG blocking antibodies.²⁰

Humoral changes

OIT is associated with reduced serum levels of food-sIgE and increased levels of food-sIgG₄ and -IgA.^{10,25,28,33-37,39,40} Peanut OIT is associated with an increased frequency of peripheral blood peanut-binding B cells expressing mutated and isotype-switched antibodies.⁴¹

T lymphocytes

Increased Tregs have been observed from 9 to 32 months after starting OIT,⁴² but the exact changes in induced T-effector cells remain unknown. Successful OIT caused an expansion of allergen-specific CD4⁺ T cells and shift toward an anergic Th2 phenotype, largely absent in pretreatment allergic subjects and healthy controls.⁴³ Similarly, within 1 week of starting a high-dose rapid milk OIT after 8 weeks of omalizumab pretreatment, the CD4⁺ T-cell response to milk was greatly reduced, indicating anergy or deletion of milk-specific CD4⁺ T cells.¹⁹

OIT TO NATIVE FOOD PROTEINS

OIT utilizes the pathways underlying oral tolerance that is the physiologic response to ingested food proteins. Although there is considerable variability among the published trials, most OIT protocols include 3 phases: (i) an initial dose escalation day (up to 8 doses in 1 day), followed by (ii) a gradual build-up every 2 weeks until a target dose is reached (usually within 6-12 months), and (iii) maintenance dose (months-years) ([Figure 2](#)). Although many trials established desensitization as the primary outcome, fewer have evaluated permanent tolerance, referred to as SU.^{10,11,17,22-33} [Table I](#) summarizes selected clinical trials of peanut, milk, egg, and wheat OIT.

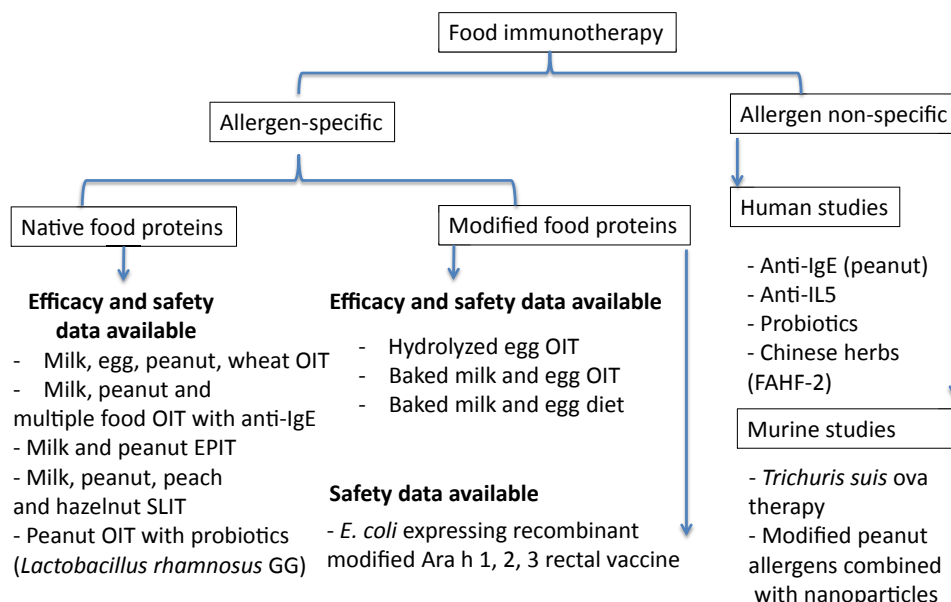


FIGURE 1. Diverse approaches to food allergy therapy tested in clinical trials.⁷⁻¹⁵ EPIT, Epicutaneous immunotherapy; FAHF-2, food allergy herbal formula 2; OIT, oral immunotherapy; SLIT, sublingual immunotherapy

OIT ASSOCIATED WITH ANTI-IgE MONOCLONAL ANTIBODY THERAPY (OMALIZUMAB)

Treatment with anti-IgE monoclonal antibody was shown to increase the threshold for clinical reactivity in peanut-allergic patients.^{57,58} Considering the high cost of the long-term, potentially life-long treatment with anti-IgE monoclonal antibody, an alternative approach has been explored. Six studies investigated the safety and efficacy of combining OIT with omalizumab (Table II).^{7-10,59,60} During the escalation day, patients treated with omalizumab tolerated significantly higher doses of the food and overall developed significantly fewer adverse effects (AEs) than the placebo-treated group.^{7-10,60} In the rapid peanut OIT preceded by 12 weeks of omalizumab, 23 of 29 (79%) of the subjects randomized to omalizumab tolerated 2000 mg of peanut protein 6 weeks after stopping omalizumab versus 1 of 8 (12%) subjects receiving placebo, $P < .01$.⁶⁰ The combination of OIT and omalizumab enhances safety of OIT but appears to have no significant effect on efficacy. Further studies are needed to fully evaluate the efficacy versus the cost and the optimal duration of combined treatment.

OIT TO MULTIPLE FOODS

Most of the OIT trials targeted individual foods; however, up to 30% of the children are allergic to multiple foods and tend to have more persistent food allergies, thus most in need of an effective therapy.⁶¹ There is a great interest in developing simultaneous multiple food OIT. The limitation is that OIT has to provide sufficient dose of each individual food protein while maintaining safety. In a pilot phase 1 study, 25 children were pretreated with omalizumab followed by OIT with up to 5 foods (cow milk, egg, peanut, tree nuts, grains, and sesame seed)⁷ (Table II). The rate of AEs observed in the rush-OIT group was similar to a group with the same eligibility and demographic

undergoing multiple food OIT in a previous study without using omalizumab.⁶² A double-blinded, placebo-controlled food challenge (DBPCFC) multicenter trial of multiple food OIT is ongoing and will provide additional evidence about safety and efficacy of this approach.

OIT SAFETY

Almost all patients experience AEs during the initial dose escalation day or the build-up phase; the frequency of AEs decreases during the maintenance phase. Most of the AEs are mild (eg, oropharyngeal pruritus) and resolve without treatment or with oral antihistamines. Many patients report gastrointestinal (GI) symptoms, in particular, abdominal pain, nausea, vomiting, or reflux.^{23,24,53} These symptoms may occur without close temporal proximity to the dose administration. GI discomfort is the main reason for OIT discontinuation. The GI symptoms decrease over time,^{28,35} but approximately 2.7% of the subjects treated with food OIT in clinical trials develop eosinophilic esophagitis (EoE) as determined by a meta-analysis.^{10,49,63} In the rapid peanut OIT preceded by 12 weeks of omalizumab, 8% of the subjects (2 treated with omalizumab and 1 treated with placebo) developed symptoms of EoE (biopsy confirmed in 2 cases); in all 3, symptoms resolved with discontinuation of peanut OIT. This suggests that omalizumab does not moderate the risk of EoE in OIT, especially with rapid up-dosing.⁶⁰ Further studies should clarify whether OIT incites or unveils a pre-existing EoE.

The risk of an acute AE increases with exercise and ingesting OIT dose on an empty stomach (may be secondary to increased intestinal permeability and enhanced absorption of partially digested food protein),^{29,56,65} illness/fever (inflammation),⁶⁶ menstruation (not completely understood, likely secondary to hormonal changes), with poorly controlled or acutely exacerbated asthma and or pollen allergy (lower threshold for the end-

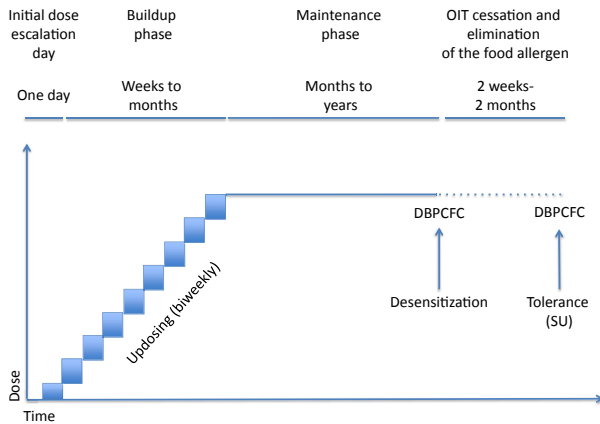


FIGURE 2. Typical protocol of food OIT tested in clinical trials. Initial rapid escalation generally starts at a subthreshold dose, which is rapidly increased every 30 minutes over the course of several hours to identify the highest tolerated dose. The patient returns on the following day for a single administration of the highest tolerated dose during the initial rapid escalation day to confirm that it can be safely ingested every day at home. During the build-up phase, the daily dose is increased at typically every 2-week interval until the target dose or highest tolerated dose (maintenance dose) is reached. The dose reached at the end of the build-up phase is continued daily during the maintenance phase. After a period of maintenance, ranging from months to years, DBPCFC to the OIT food is performed to assess for desensitization. To assess for tolerance, daily dosing is then discontinued for a period of 4 to 12 weeks and reintroduced during tolerance DBPCFC. If the food is ingested without any adverse reaction, this state is defined as sustained unresponsiveness (SU), which is a term used as a surrogate for permanent tolerance. *DBPCFC*, Double-blind, placebo-controlled food challenge; *OIT*, oral immunotherapy.

organ reactivity).^{26,67} To minimize the risk of AEs,⁶⁵ OIT doses are ingested around the same time of the day, following a meal or snack and with restricted physical activity within 1 to 2 hours of dosing. OIT is suspended during febrile illness or viral gastroenteritis; depending on the number of missed doses, OIT may be restarted at the same dose at home or under supervision in the office, or OIT dose needs to be reduced. Acute AEs can occur during a prodromal phase of a viral illness without any apparent inciting trigger. Therefore, all patients are provided with an emergency action plan, prescribed an epinephrine autoinjector, and instructed to avoid the offending food during OIT. Asthma and allergic rhinitis (AR) should be managed appropriately to ensure adequate control of chronic airway inflammation.⁵⁶

Real-life experience with OIT

Five practices reported their combined experience with peanut OIT. Among 352 patients (age range: 3-24 years) who received 240,351 doses of peanut, peanut butter, or peanut flour, 55 experienced 95 reactions (angioedema, severe cough, or respiratory distress), which were treated with epinephrine.⁶⁸ This clinical practice experience with peanut OIT confirms that anaphylaxis may occur during OIT but is relatively uncommon. However, these results may be biased due to lack of food

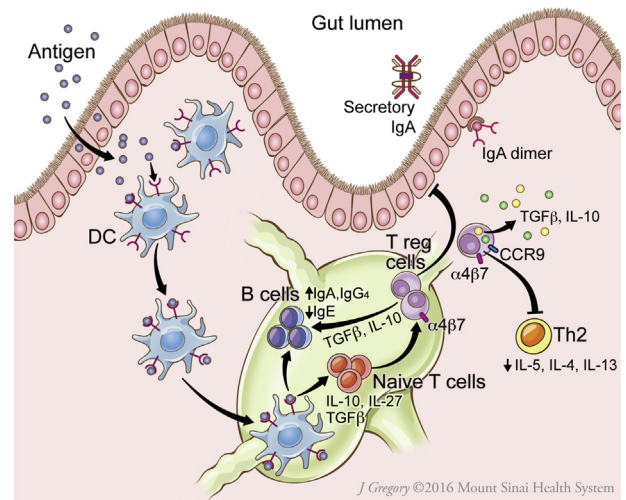


FIGURE 3. Putative mechanisms of oral tolerance in the gut. On passage through the epithelial barrier, food protein allergen is captured by the dendritic cell (DC). The DC migrates to the nearby mesenteric lymph nodes and produces TGF- β , IL-10, and IL-27, which induce secretion of IgA/IgG4 by B cells and generation of Tregs. Tregs express CCR9 and $\alpha 4\beta 7$, the homing molecules that direct them to migrate to the gut. Tregs secrete IL-10 and TGF- β that further induce and reinforce tolerance. *DC*, Dendritic cell; *Treg*, T regulatory cells.

challenges to confirm peanut allergy before initiating OIT in a subset of patients, lack of standardized criteria for challenge positivity in those who underwent an open peanut challenge, and lack of standardized reporting of AEs. Risk factors were identified as uncontrolled asthma, exercise close to the dose ingestion, ingestion of the dose on an empty stomach, and viral illness.

Low-dose OIT

A wide range of maintenance dosing has been explored in clinical trials (Table 1). A small, single-center, case-control study performed desensitization to low dose of milk (3 mL = 102 mg of milk protein).³¹ The majority, 58.3% (7/12), of the patients were desensitized to 3 mL of milk compared with 13.8% (4/25) of control subjects after 1 year of treatment, $P = .001$, intention to treat analysis. In preschool children, peanut OIT with 300 mg maintenance dose of peanut protein had comparable efficacy and improved safety compared with OIT with 3000 mg maintenance dose.⁴⁸

OIT EFFICACY

The percentages of patients who complete OIT course and achieve desensitization have been reported to be from 35% to 100% (intention to treat). Direct comparisons among studies are hampered by the heterogeneity of study design and primary endpoint definition. The small size of the skin prick test (SPT) wheal, low serum food-sIgE levels, and controlled asthma are associated with a favorable response to OIT.⁵² Significantly fewer patients achieve SU. The long-term data from patients discharged from clinical trials are scarce, but the available limited evidence is somber, especially regarding milk OIT. Because of the frequent, predominantly GI AEs, many patients stopped eating the foods on regular basis and lost desensitization.^{24,28,69}

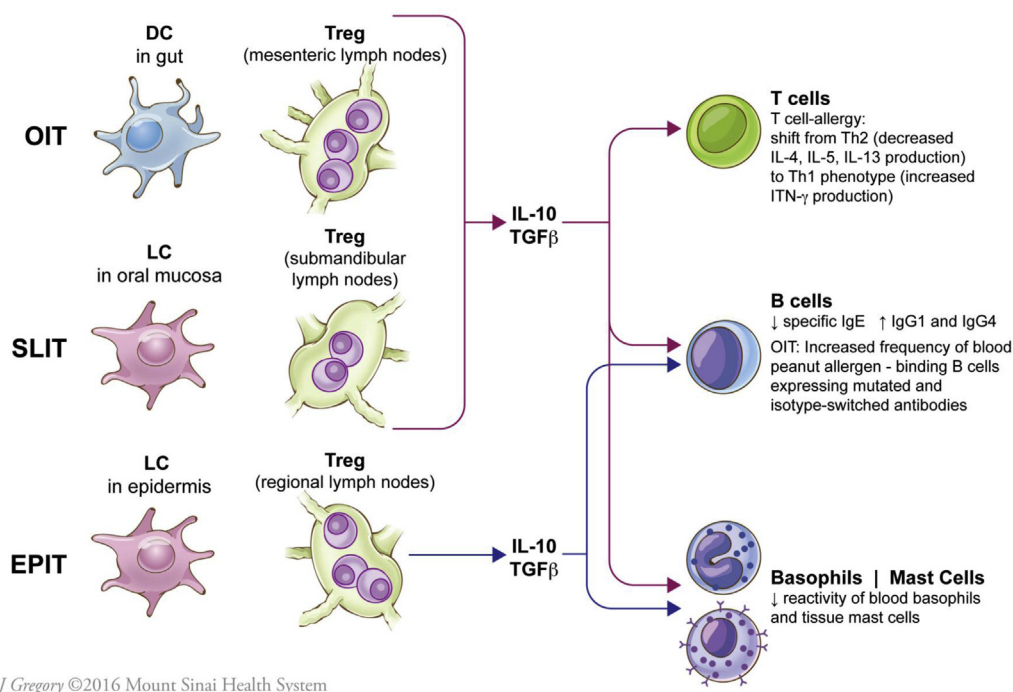


FIGURE 4. Potential mechanisms of immunomodulation operative in different forms of food allergen immunotherapy. High-dose OIT may be associated with deletion of allergen-specific CD4⁺ T cells without development of allergen-specific FoxP3⁺ Tregs.¹⁹ OIT and SLIT enhance Tregs in the gut and in oral mucosa, respectively. The activation of Tregs will (i) decrease the production of cytokines by Th2 cells (such as IL-4, IL-5, and IL-13); (ii) decrease the production of IgE by B cells and induce secretion of IgA, IgG₁ and IgG₄; and (iii) will decrease reactivity of blood basophils and tissue mast cells. EPIT has been shown to stimulate Tregs in the regional lymph nodes, which will also (i) decrease the production of food allergen-sIgE and increase the production of sIgG₄ as well as (ii) decrease the reactivity of blood basophils and tissue mast cells. DC, dendritic cell; EPIT, epicutaneous immunotherapy; LC, Langerhans cell; OIT, oral immunotherapy; SLIT, sublingual immunotherapy; Treg, T regulatory cell.

In the long-term follow-up of milk OIT, 22% (7/32) patients reported limiting their consumption because of symptoms, 9% (3/32) because of anxiety, and 13% (4/32) because of the taste aversion; 16% (5/32) continued to strictly avoid milk after the cessation of milk-OIT trial.⁶⁹

Vickery *et al* evaluated SU in peanut-allergic children, median age at enrollment 57.5 months (range: 12–111 months), who underwent peanut OIT.^{17,70} Of the original 39 patients, 24 (61.5%) were taking a daily dose of 4000 mg peanut protein for 3 to 5 years. After discontinuing OIT for 4 weeks, 12 of 24 (50%) of patients passed a DBPCFC to 5 g of peanut protein and were declared as having achieved SU to peanut.¹⁷ Over a median 40 months after OIT cessation, all but one patient reported regular peanut consumption and no allergic reactions.

In the intent-to-treat analysis, the majority (78%, 29/37) of preschool peanut-allergic children treated with peanut OIT for 3 years, 17 of 20 of patients on low-dose OIT and 12 of 17 patients on high-dose OIT for 3 years, achieved SU after 4 weeks of peanut avoidance.⁴⁸ Per-protocol, the overall proportion achieving SU was 91% (29/32).⁴⁸

Percentage of patients achieving SU appears to increase with longer duration of OIT. After 22 months of egg OIT, 28% egg-allergic children achieved SU,²⁵ compared with 50% who achieved SU by year 4.²⁸ However, the study was blinded and placebo-controlled only through year 1, potentially introducing a bias in favor of long-term OIT.

CAN WE IDENTIFY RESPONDERS?

Favorable response to OIT is determined by the phenotype of the patient, severity of food allergy,⁷¹ pretreatment food-sIgE levels,^{39,72} and kinetics of the serologic responses during OIT, as well as the concomitant allergic conditions such as asthma and AR.⁷² Improved rates of SU are seen with peanut OIT initiated in young children and with longer duration of OIT.⁴⁸

Food allergy phenotype

Patients were more likely to experience adverse reactions during egg OIT if they reacted to a lower dose of egg white protein on an initial dose escalation day.⁷² Patients were more likely to discontinue OIT immunotherapy if they had asthma or high egg white-, ovalbumin-, and ovomucoid-sIgE.⁷² In contrast, lower pretreatment egg white- and ovomucoid-sIgE as well as increased egg white-sIgG₄, sIgA, and sIgA₂ over the course of egg OIT were associated with SU.³⁹ If patients did not require epinephrine administration during induction or if they could tolerate starting dose >30 mL of milk, they were more likely to have a successful milk OIT.⁷¹ Patients were more likely to fail if they had large SPT to milk (>9 mm).⁷³ Subjects who achieved SU after 3 to 5 years of peanut OIT had smaller baseline and post-treatment peanut SPT; lower peanut-, Ara h1-, and Ara h 2-sIgE levels; and lower peanut-sIgE/total IgE ratios compared with subjects not achieving SU.¹⁷ In combined analysis of 3 peanut-OIT trials, baseline AR, asthma, and peanut SPT were

TABLE I. Selected OIT clinical trials

Authors, year	Design; daily maintenance dose (DMD) mg protein/d; duration of the study	Sample size (N); age range (y)	Safety	Primary outcome
<i>Peanut OIT</i>				
Blumchen et al, 2010 ⁴⁴	Randomized open label DMD: ≥500 mg of peanut protein Duration: 7-d escalation/rush 8-wk maintenance	N = 23 Age 4-13	35% (8/23) dropped out AEs were frequent: OIT discontinued in 4 patients due to AEs Rush protocol: 7.9% of OIT doses associated with objective AEs Build-up: 2.6% of OIT doses associated with objective AEs	<i>Desensitization</i> 64% (14/22) reached maintenance dose. Median tolerated dose after completion of OIT: 1000 mg of peanut protein
Varshney et al, 2011 ⁴⁵	Randomized placebo controlled DMD: 4000 mg of peanut protein Duration: 48 wk	N = 28 Active: 19 Placebo: 9 Age 1-16	3 dropouts in the active group (due to side effects) AEs common but mostly mild <i>Active:</i> Initial day of escalation: 47% of patients with objective AEs Build-up: AEs in 1.2% of 407 build-up doses <i>Placebo:</i> Initial day of escalation: no AEs During final peanut DBPCFC: 33% (3) required epinephrine	<i>Desensitization</i> 84% (16/19) passed 5000 mg of peanut OFC
Anagnostou et al, 2014 ⁴⁶	Randomized controlled DMD: 800 mg of peanut protein Duration: OIT or observational control for 26 wk Crossover from the control group to the OIT group	N = 39 in the first phase and 46 in the second phase of OIT Age 7-16	Similar number of AEs in the 2 groups after treatment; most of them mild (oral itching in 6.3%) <i>Active:</i> 4 subjects did not reach maintenance dose at 6 mo; 1 withdrawal <i>Control:</i> 5 patients did not reach maintenance dose at 6 mo; 3 withdrawals	<i>Desensitization</i> Active: 62% (24/39) tolerated 1400 mg peanut protein OFC Control: 0% (0/46) Difference: P < .001
Vickery et al, 2014 ¹⁷	Open label DMD: 400 mg up to 4000 mg, median Duration: 5 y	N = 24 Age 1-16	15% (6/39) dropouts because of the side effects and 23% (9/39) for personal or other reasons This was the first study to demonstrate sustained unresponsiveness after peanut OIT No description of side effects	<i>Desensitization</i> 62% (24/39) completed the protocol 100% of the 24 patients, who completed the protocol successfully ingested 5000 mg of protein <i>SU at 4 wk following OIT cessation</i> 50% (12/24 per protocol) or 31% (intent to treat) to 5000 mg of peanut protein
Bird et al., 2015 ⁴⁷	Unblinded peanut OIT pilot study MD: 2000 mg of peanut protein (median of 895 mg/d) Median duration of maintenance: 41 wk	N = 11 Age 7-16	2 dropouts Only 7.9% of doses (264/3265) associated with a reported AEs All AEs mild except for 2 severe reactions <i>Build-up:</i>	<i>Desensitization</i> 100% (9/9) children who received a 2000 mg DMD passed a 5000 mg challenge 66% (6/9) no reactions during the challenge, and they achieved DMD in a median time of 41 wk

(continued)

TABLE I. (Continued)

Authors, year	Design; daily maintenance dose (DMD) mg protein/d; duration of the study	Sample size (N); age range (y)	Safety	Primary outcome
			94% (249/264) of the reactions; most of the reactions were skin reactions followed by throat clearing and then sneezing <i>Maintenance:</i> One patient required epinephrine (2 h after dosing after 131 d of therapy, 200 mg) One patient vomited, not related to dosing, but stopped vomiting after cessation of OIT	
Vickery et al, 2016 ⁴⁸	Randomized, double blinded MD: 3000 mg of peanut protein daily (high dose) vs 300 mg of peanut protein daily (low dose) Duration: 3 y	N = 40, 20 in each group 9-36 mo old	5/37 dropouts All subjects included: 95% of doses had AEs (mostly GI and upper airway reactions) 85% mild 15% moderate None severe 0 epinephrine administered Moderate-severity AEs were significantly more likely in the low-dose compared with the high-dose group overall ($P = .04$) and during the build-up phase ($P = .02$) <i>High dose:</i> 100% (17/17) of doses associated with AEs <i>Low dose:</i> 90% (18/20) of doses associated with AEs	<i>Desensitization</i> 81% (30/37) overall: High dose: 76% (13/17) Low dose: 85% (17/20) SU at 4 wk: Overall (intention to treat): 78% (29/37) High dose: 71% (12/17) Low dose: 85% (17/20)
Peanut OIT with probiotics				
Tang et al, 2015 ¹¹	Randomized double blind, placebo controlled Trial of peanut and probiotic <i>Lactobacillus rhamnosus GG (LGG)</i> CGMCC 1.3724 DMD: 2000 mg of peanut protein Duration: 18 mo	N = 62; 31 patients in each group Age: 1-10 Active: median age 6.1 Placebo: median age 5.8	Active (peanut OIT with LGG): 7% dropouts (2/29) 1 severe AE to probiotics 45% AEs Placebo (placebo OIT with placebo probiotic): 10% dropouts (3/29) 32% AEs No significant difference in severe AEs per subject between groups ($P = .9$) Limitations: no DBPCFC at the beginning (only 40% of patients had open challenge), no controls with OIT alone or probiotic alone SU challenges at median 2.3 wk (range: 2-5.3 wk) after cessation of OIT + probiotics	<i>Desensitization</i> Active: 90% (26/29) to 4 g peanut Placebo: 7% (2/28) to 4 g peanut SU—Median 2.3 wk (range: 2-5.3 wk) weeks off OIT Active: 79% (23/29) Placebo: 3% (1/26)
Egg OIT				
Buchanan et al, 2007 ²³	Open label DMD: 300 mg of egg white protein Duration: 24 mo	N = 7 Age 1-16	<i>Rush:</i> all patients had mild objective AEs <i>Build-up:</i> 1 patient experienced abdominal pain <i>Maintenance:</i> No subjects reported AEs	<i>Desensitization</i> 57% (5/7) passed 8 g OFC SU 3 mo (cessation of OIT and egg restricted diet) 29% (2/7)

Vickery et al, 2010 ²⁴	Open label DMD: 300 mg of egg white protein Duration: 18-50 mo	N = 8 Age 3-13	<i>Rush</i> : 83% (5/6) had objective AE 2 patients dropped out <i>Build-up</i> : 50% (3/6) experienced objective AEs (abdominal pain ± vomiting) 1 patient had urticaria and 1 had runny nose <i>Maintenance</i> : no AEs	<i>SU 4 wk after cessation of OIT but with egg in the diet</i> 75% (6/8)
Burks et al, 2012 ²⁵	Randomized, placebo controlled DMD: 2000 mg of egg protein Duration: 22 mo	N = 55 OIT: 40 Placebo: 15 Age 5-11	5 in OIT and 2 in placebo group dropped out <i>Active: First 10 mo</i> 25% AEs out of 11860 OIT doses <i>Active: After 10 mo</i> 8.3% of 15,815 doses <i>Placebo: first 10 mo</i> 9% AEs out of 4018 placebo doses No information in the following 10 mo <i>Cessation of OIT, egg in their diet</i> : No AEs	<i>Desensitization</i> : <i>Active</i> : 75% (30/40) passed 8 g OFC <i>Placebo</i> : 0% (0/15) <i>Difference</i> : $P < .001$ <i>SU at 8 wk after cessation of OIT (had egg in their diet)</i> : <i>OIT</i> : 28% (11/40) <i>Placebo</i> : 0 <i>Difference</i> : $P = .03$
Jones et al, 2016 ²⁸ Goal 4-y follow-up	Long-term follow-up of the randomized, placebo-controlled study by Burks in 2012 ²⁵ DMD: 2000 mg of egg protein Goal: 4-y follow-up of the actively treated subjects	N = 40 (initial study) N = 22 at 2 y	8 dropouts For those subjects still dosing during years 3 and 4, mild AEs were present in 54.5% (12/22) of subjects	<i>Desensitization (10 mo)</i> <i>OIT</i> : 55% (22/40) <i>Placebo</i> : 0/40 <i>Difference</i> : $P = .006$ <i>SU at year 2 after egg avoidance for 4-6 wk</i> 27.5% (11/40) <i>SU at year 3 after egg avoidance for 4-6 wk</i> 18% (18/40) <i>SU by year 4</i> : 50% (20/20)
Carminiti et al, 2015 ²⁶	Randomized, placebo controlled, double blind (OIT/placebo) DMD: 4000 mg of egg protein Duration: 4 mo (continued egg consumption 3 times per week for 6 mo)	N = 31 OIT: 17 Placebo: 14 Age 4-10	1 dropout in OIT and 1 dropout in placebo <i>Desensitization phase (do not precise otherwise)</i> <i>Active</i> : 17% (3/17) patients had AEs <i>Placebo</i> : 0 AEs <i>Active</i> : 2 patients had mild gastrointestinal AEs <i>Placebo</i> : 0 AEs	<i>Desensitization</i> : <i>OIT</i> : 94% (16/17) <i>Placebo</i> : 0% (0/14) <i>Difference</i> : $P < .001$ <i>SU at 3 mo of cessation of OIT, continued egg consumption</i> : <i>OIT</i> : 31% (5/17)
Escudero et al, 2015 ²⁷	Open label (OIT/egg avoidance) DMD: 1 undercooked egg (fried egg, scrambled or undercooked omelet) every 2 d Duration: 3 mo (then observed for one more month to assess SU)	N = 61 OIT: 30 (OIT for 3 mo and then egg avoidance for 1 mo) Control: 31 (egg avoidance for 4 mo) Age 5-17	OIT group: 145 reactions <i>Dose escalation day</i> : 14% of total reactions <i>Build-up</i> : 53% of total reaction <i>Maintenance</i> : 31% of total reaction 70% of patients had >1 reaction One patient required epinephrine	<i>Desensitization</i> : <i>OIT</i> : 93% (28/30) <i>Placebo</i> : not assessed <i>SU 1 mo after OIT cessation and egg avoidance</i> : <i>OIT</i> : 37% (22/30) <i>Placebo</i> : 3% (1/31) <i>Difference</i> : $P = .003$
OIT using hydrolyzed egg				
Giavi et al, 2016 ³⁴	Double blind, placebo controlled Hydrolyzed egg white (HydE)	N = 29 OIT: 15	4 dropped out <i>Active</i> : 7 AEs <i>Placebo</i> : 2 AEs	<i>Desensitization</i> <i>OIT</i> : 36% (4/11) <i>Placebo</i> : 21% (3/14)

(continued)

TABLE I. (Continued)

Authors, year	Design; daily maintenance dose (DMD) mg protein/d; duration of the study	Sample size (N); age range (y)	Safety	Primary outcome
	DMD: 9 g HydE Duration: 6 mo	Placebo: 14 Age 1-5.5	<i>Desensitization</i> Active: all patients, except 1 experienced at least 1 AE during the course of the treatment; no epinephrine treatment Active: 7 AEs (4 related to the product) Placebo: 2 AEs (unrelated to the study)	No significant difference in maximum tolerated dose between active OIT (median = 1.2 g) and placebo (median = 0.3 g) group, $P = .35$
Milk OIT				
Staden et al, 2007 ²⁹	Randomized controlled (milk or egg OIT vs milk or egg elimination diet) DMD: 3300 mg milk protein or 1600 mg of hen's egg Duration: 21 mo (range: 11-59 mo)	N = 39 Egg or milk OIT: 25 14 milk 11 egg Elimination diet: 20 10 with milk allergy 10 with egg allergy Age < 1-12	11 dropouts Active group: 100% of subjects had AEs, 21 had mild reactions and 4 had moderate reactions Control group: 20% (5/20) of subjects had AEs due to accidental exposure to milk	<i>Desensitization</i> Active group: 64% (16/25) Control group: 35% (7/20) Difference in desensitization between the 2 groups: $P = .05$ <i>SU after 2-mo elimination diet</i> Active: 36% (9/25) 12% (3/25) tolerance with regular intake
Skripak et al, 2008 ¹⁶	Randomized, placebo controlled DMD: 500 mg of milk protein Duration: 13 wk	N = 19 OIT: 12 Placebo: 7 Age 6-17	1 dropout Active group: 45.4% (1107/2437 doses) AEs Placebo group: 11.2% (134/1193 doses) AEs Local reactions were the most frequent	<i>Desensitization</i> OIT: median OFC threshold increased from 40 to 5140 mg ($P < .002$) Placebo: no change in threshold ($P < .16$) Difference between groups: $P < .003$
Narisety et al, 2009 ⁴⁹	Open label (follow-up of the Skripak et al study ⁵⁰) 14 patients were able to escalate with maximum dose from 1000 to 1600 g (median 7000 mg) Duration: 13-75 wk (median: 17 wk)	N = 15 (13 completed the study) Age 6-16	AEs were common and unpredictable, but overall decreased overtime 17% (419/2465) local AEs 0.2% (6 doses in 4 patients) reactions treated with epinephrine One patient developed eosinophilic esophagitis	<i>Desensitization</i> OFC performed on 13 patients: 6 tolerated 1600 mg 7 tolerated 3000-1600 mg
Pajno et al, 2010 ⁵¹	Randomized, placebo controlled DMD: Group A: 150-200 mL of milk every day Group B: 150-200 mL twice weekly Duration: 1 y	N = 30 Group A: 15 children Group B: 15 children Age 4-10	2 dropped out of group A and 1 out of group B Group A/Active 53% of AEs 3 severe reactions No reaction after reaching 32 mL Group B/Control 64% of AEs No difference in % of AEs between these 2 groups	<i>Desensitization</i> Active: 67% (10/13) tolerant to 200 mL of cow's milk Control: 0% The only study to date to report on maintenance dosing 2 times per week as opposed to daily dosing
Kivisto et al, 2015 ⁵²	Open-label, noncontrolled, real-life OIT study DMD: 2000 mg of milk protein	N = 74 Age 5-15	Risk factors associated with 6-mo induction failure Uncontrolled asthma ($P = .026$) Higher milk-specific IgE (>100 kIU/L) before OIT	<i>Desensitization at 6 mo</i> 82% (61/74) were able to consume at least 200 mL of milk or 6400 mg of milk protein a day

	Duration: The aim of this study was to evaluate the impact of OIT on milk consumption during the first 2.5 y after a start of OIT. 6-mo induction phase 2-y maintenance 2.5-y trial follow-up (data in 57 children)		AEs during OIT were more prevalent among those who failed to complete the protocol IM epinephrine was needed by 4% of the children during the 6-mo induction phase and by 6% during the 2-y maintenance phase of free daily milk or milk product use	<i>Desensitization at 24 mo</i> 49.1% (28/57) were consuming 200 mL of milk or 6400 mg of milk protein a day
Paassilta et al, 2016 ^{53,54}	Long-term efficacy and safety of OIT in school children (follow-up study) Special attention was paid to milk consumption and reactions DMD: milk (≥ 200 mL) or milk products (protein ≥ 6400 mg) Duration: 7 y Initial study: randomized, double-blind, placebo-controlled OIT study	N = 28 (data for 24) Age: 6-15	Long-term efficacy study 21.4% (5/24) reported AEs associated with milk consumption (mostly GI reactions)	Initial study <i>Desensitization</i> 92.9% (26/28) completed the 6-mo escalation phase 89.3% (25/28) used milk at 12 mo and 24 85.7% (23/28) at 36 mo This long-term efficacy study <i>Desensitization at 7 y</i> Data were available at the 7-y point for 24 children 58.3% (14/24) continued to consume milk
Elizur et al, 2016 ³⁵	Long-term efficacy and safety of OIT Follow-up 6 mo after cessation of milk OIT DMD: 7200 mg of milk protein during OIT On completion of OIT, all patients were instructed to consume a daily dose of at least 4500 mg (150 mL) indefinitely	N = 197/195 answered	51.3% (100/195) experiences AEs 29.2% (57/195): respiratory tract 8.7% (17/195): gastrointestinal tract 6.7% (13/195) required epinephrine AEs rate were decreasing over time: 0.28/mo to 0.21/mo to 0.15/mo for 6-15 mo, 15-30 mo, or >30 mo after treatment decreased respectively ($P < .01$) Trigger: viral infections and physical exercise	<i>Desensitization/tolerance</i> 92.3% (180/195) were consuming milk protein regularly after 6 mo of finishing OIT
Baked egg and baked milk OIT				
Bravin et al, 2016 ⁵⁵	Pilot study Baked egg DMD: Target maximum dose of 6.25 g of egg protein Duration: 60 d	N = 15 Age: 6-17	AEs: 2 could not tolerate the first dose without reactions and thus remained on strict egg-free diets All adverse reactions were mild and could be controlled by oral antihistamines where needed	<i>Desensitization</i> : 53% (8/15) <i>Partial tolerance at days 10-47</i> : 33% (5/15) Include previously avoided trace amounts of egg into their diets.
Golberg et al, 2015 ³⁶	Open label uncontrolled Baked milk DMD: 1300 mg of baked milk protein Duration: 12 mo	N = 15 Age 6-12	53.3% (8/15) did not complete desensitization due to IgE-mediated reactions <i>Build-up</i> 60% (9/15) had a reaction the first day <i>Overall</i> 86.6% (13/15) experienced AEs 26.6% (4/15) had skin reactions 33% (5/15) had GI reactions 40% (6/15) had upper respiratory reactions 20% (3/15) used epinephrine	<i>Desensitization</i> : 21% (3/15)
Wheat OIT				
Rodriguez del Rio et al, 2014 ⁵⁶	Prospective uncontrolled DMD: 100 g of wheat protein Duration: 6 mo	N = 6 Age 5-11	1 dropout due to persistent AE (abdominal pain) <i>Baseline DBPCFC</i> : 100% of patients experienced a reaction	<i>Desensitization to 100 g of wheat</i> : 83.6% (5/6)

(continued)

TABLE I. (Continued)

Authors, year	Design; daily maintenance dose (DMD) mg protein/d; duration of the study	Sample size (N); age range (y)	Safety	Primary outcome
66% (4/6) had an anaphylactic reaction (epinephrine) <i>Escalation:</i> 6.25% (6/96) doses <i>Maintenance:</i> 16.6% (1/6) exercise (urticaria)				
Sato et al, 2015 ³⁰	Prospective with historical control Goal: assess sustained unresponsiveness in patients with wheat-induced anaphylaxis up to 2 y of cessation of OIT DMD: 5.2 g of wheat protein Duration: 2 y	N = 29 OIT = 18 Historical controls = 11 Age 5.2-13.6	2 dropouts <i>Baseline DBPCFC:</i> 35.3% (6/17) required epinephrine and 11.1% (2/17) had anaphylactic shock <i>Rush:</i> 26.4% (42/143 dose) resulted in AEs (no epinephrine) <i>Maintenance:</i> not stated <i>Overall:</i> 6.8% (486/5778) doses associated with AEs (one treated with epinephrine)	<i>Desensitization</i> Active: 94.4% (16/17) <i>SU after 2 y</i> Active: 61.1% (11/17) Historical control group: 9.1% (1/11) Difference between groups: <i>P</i> = .008
Low-dose OIT				
Yanagida et al, 2015 ³¹ Milk	Single-center, case-control study DMD: 3 mL of milk Duration: 1 y	N = 37 OIT: 12 Control: 25 Age: 5.8-12.8	No dropouts after the start of the study AEs in different phases are not described <i>Active group</i> 57.1 (32/56 doses) of adverse reaction 23.2% (13/56 doses) mild 19.6 (11/56 doses) moderate 29.6% (11/56 doses) severe <i>Control group</i> 19.5% (729/3739 doses) AEs 17.5% (13/3739 doses) mild 2% (73/3739 doses) moderate 0.003% (1/3739 doses)	<i>SU after 2 wk of OIT cessation</i> Active group: 58.3% (7/12) were desensitized to 3 mL of milk 33.3% (4/12) were desensitized to 25 mL of milk Control group 13.8% (4/25) were desensitized to 3 mL of milk 0% (0/12) were desensitized to 25 mL of milk <i>SU after 2 wk of cessation</i> Differences between 2 groups 3 mL of milk: <i>P</i> = .001 25 mL of milk: <i>P</i> = .007
Multiple food OIT				
Begin et al, 2014 (Erratum in 2016) ⁷	Pilot study phase I Pretreatment with omalizumab for 8 wk before onset of OIT until 16 wk after the start of OIT OIT: 18 wk DMD: 400 mg of protein for each offending food (max 5 foods)	N = 25 Age 4.5-15.4	3 dropped out due to nonadherence <i>Rush phase:</i> 52% (13/25 patients), all mild <i>Escalation phase:</i> 5.7% reaction (13/277 doses), all mild <i>Home dosing</i> 5.3% (401/7530 doses) reaction 5.1 % (385/7530): mild 0.2% (15/7530): moderate 0.01% (1/7530): severe; epinephrine	<i>Desensitization</i> 76% (19/25)

AE, Adverse event; DBPCFC, double-blind, placebo-controlled food challenge; OFC, oral food challenge; OIT, oral immunotherapy; SLIT, sublingual immunotherapy; SU, sustained unresponsiveness.

TABLE II. Oral immunotherapy combined with anti-IgE treatment

Authors, year; food	Design; daily maintenance dose (DMD) mg protein/d; duration of the study	Sample size (N); age range (y)	Safety	Primary outcome
Nadeau et al, 2011 ⁸ Milk	Pilot study phase I Pre-treatment with omalizumab for 9 wk and was continued until week 16 for OIT Total duration of OIT: 24 wk DMD: 2000 mg of milk protein	N = 11 Age 7-17	2 dropouts 1.8% (41/2301) of total doses <i>Rush</i> : 51% (21/41 reactions) <i>Escalation</i> : 29.2% (12/41 reactions) <i>Maintenance</i> : 19.5% (8/34 reactions) <i>Severity</i> Most of the reaction were grade 1: 1.3% (29/2301 doses) 1 epinephrine dose during rush and 2 epinephrine doses were given at home	<i>Desensitization</i> : 82% (9/11) reached 1000 mg of milk protein (cumulative dose: 1992 mg)
Schneider et al, 2013 ⁹ Peanut	Pilot study phase peanut OIT Pretreatment with omalizumab for 12 wk, then DC at 20 wk OIT: 30-32 wk DMD: 4000 mg of peanut protein Duration: 32 wk	N = 13 Age 7-15	1 dropout 2% (72/3502) of total doses <i>Rush</i> : 8.33% (6/72) <i>Escalation</i> : 68% (49/72) <i>Maintenance</i> : 23.6% (17/72) <i>Severity per dose</i> 1.8% (63/3502) were mild 0.2% (7/3502) were moderate 0.06% (2/3502) were severe 25 reactions occurred in 1 subject, with supra-ventricular tachycardia (transient hypersalivation and nausea)	<i>Desensitization</i> : 92% (12/13)
Begin et al., 2014 (erratum in 2016) ⁷ Multiple foods	Pilot study phase I multiple food OIT Pretreatment with omalizumab for 8 wk and was DC at 16 wk OIT: 18 wk DMD: 400 mg of protein for each offending food (max 5 foods)	N = 25 Age 4.5-15.4	3 dropped out due to nonadherence <i>Rush phase</i> : 52% (13/25 patients), all mild <i>Escalation phase</i> : 5.7% reaction (13/277 doses), all mild <i>Home dosing</i> 5.3% (401/7530 doses) reaction 5.1% (385/7530): mild 0.2% (15/7530): moderate 0.01% (1/7530): severe; epinephrine	<i>Desensitization</i> : 76% (19/25)
Wood et al, 2016 ¹⁰ Milk	Omalizumab DBP, open label milk OIT Pretreatment with omalizumab/placebo until month 28 Escalation: 22-40 wk Maintenance OIT: 28 mo Patients who were desensitized continued for 8 wk Then, cessation of OIT, strict avoidance of food and rechallenged at 32 wk (SU) DMD: 3800 mg of milk protein	N = 57 Omalizumab: 28 Placebo: 29 Age: 8-15	<i>Dropouts</i> Omalizumab: 2 Placebo: 3 <i>Adverse reactions</i> <i>Escalation</i> (median percentage of doses per subject with any reactions): Active (omalizumab): 2.1% Placebo: 16.1% Omalizumab vs placebo, $P < .0005$ <i>Maintenance</i> : Omalizumab: 0.7% (110/15,418) doses	<i>Desensitization</i> : Active: 88.9% (24/27) Control: 71.4% (20/28) Differences between 2 groups: $P = .18$ <i>SU after 8 wk of OIT cessation and strict diet avoidance</i> : Active: 48.1% (13/27) Control: 35.7% (10/28) Differences between 2 groups, $P = .42$

(continued)

TABLE II. (Continued)

Authors, year; food	Design; daily maintenance dose (DMD) mg protein/d; duration of the study	Sample size (N); age range (y)	Safety	Primary outcome
	Total duration: 32 mo		1 epinephrine Placebo: 14.4% (1983/13,745) doses 10 epinephrine Epinephrine administration 0.04% (20 of 40,641 total doses) in 11 subjects Omalizumab: 2 doses in 2 omalizumab-treated subjects Placebo: 18 doses in 9 placebo-treated subjects (including 2 subjects on 5 occasions and 1 subject on 2 occasions) <i>Severity:</i> Reactions more frequent and more severe in the placebo group Omalizumab vs placebo: Mild reaction: median 0.5% vs 7.9% ($P = .0001$) Moderate reaction: median 0.0% vs 0.5% ($P = .005$)	
Martorell-Calatayud et al, 2016 ⁵⁹	Open label study Omalizumab for 9 wk; then OIT for 12 mo; omalizumab has been continued for 2 mo after reaching the final dose of the induction phase DMD milk: 200 mL of cow milk DMD egg: 17 mL egg white	N = 14 Cow milk: 5 Egg: 9	No dropouts <i>AEs:</i> <i>Rush:</i> 28% (4/14) had mild reaction <i>Early maintenance with omalizumab</i> 14% (2/14) had mild reactions <i>Late maintenance (omalizumab was discontinued for 2.5 mo):</i> 42% (6/14) had anaphylactic reactions	<i>Desensitization:</i> 100% (in egg and milk group)
MacGinnitie et al, 2016 ⁶⁰	Phase II randomized, double blind Omalizumab for 12 wk, then rapid desensitization. Omalizumab was continued until week 19. Open label: 8 patients (2 from active and 6 from control) who could not tolerate 250 mg of peanut protein after 8 wk of desensitization received open label omalizumab DMD: 2000 mg of peanut protein	N = 39 Active: 29 Control: 8 Open label study: 8 Age: 6-19	Dropouts: 3 (active group) Grade 2 reactions: Active: 14.2% (4/28) Control: 75% (6/8) Grade 1 reactions: Active: 57.1% (16/28) Control: 62.5% (5/8) Grade 3 reactions: Active: 10.71% (3/28) Placebo: 12.5% (1/8) Open label omalizumab: 37.5% (3/8) 14 reactions (in 8 patients) required Epipen 8% (3/37) cases of eosinophilic esophagitis (2 in active group and 1 in control)	<i>Desensitization 6 wk after withdrawal of omalizumab (2000 mg of peanut protein)</i> Active: 73.9% (23/29) Control: 12.5% (1/8) Difference between groups: $P < .01$ Open label study: 100% (8/8) <i>Desensitization 12 wk after withdrawal of omalizumab (4000 mg of peanut protein)</i> Active: 75.9% (22/29) Control: 12.5% (1/8) Difference between groups: $P = .002$

AE, Adverse event; DBPCFC, double-blind, placebo-controlled food challenge; OIT, oral immunotherapy; SLIT, sublingual immunotherapy; SU, sustained unresponsiveness.

TABLE III. Selected SLIT clinical trials

Authors, year	Design; Daily maintenance dose (DMD) (mg protein/day); duration of the study	Sample size (N); age range (y)	Safety	Primary outcome
Peanut SLIT				
Kim et al, 2011 ⁸⁸	Double-blind, placebo-controlled study DMD: 2 mg peanut protein Duration 1 y (6 mo of escalation and 6 mo of maintenance)	N = 18 Active: 11 Placebo: 7 Age 1-11	No dropout AEs: Active: 11.5% (480/4182) of peanut doses (transient oropharyngeal) Placebo: 8.6% (248/2875) of placebo doses (itchy) <i>Home doses requiring treatment:</i> Active: 0.26% (11/4182): antihistamine 0.02% (1/4182): albuterol No epinephrine Placebo: No reactions necessitated a treatment	<i>Desensitization:</i> OFC threshold 20 times greater SLIT vs placebo (median 1720 vs 85 g, $P = .011$)
Fleischer et al, 2013 ³⁷	Randomized, double-blinded, placebo-controlled study Placebo crossover subjects were escalated after unblinding at week 44 to higher-dose peanut SLIT up to 3696 mg/d Original peanut SLIT group maintained a maximum dose of 1386 mg/d peanut protein DMD: 3696 µg of protein	N = 40 (20 in each group) Age 12-37	At 44 wk, all reactions: Active: 41.1% (2394/5825) reactions 90% were transient oropharyngeal 1.1% treated with oral antihistamines (127/11,854), 1 each (0.01%) treated with albuterol or epinephrine Placebo: 99.4% of all doses were symptom-free Crossover high-dose group (65 wk) 33.7% AEs (167/5030) More than 95% were transient oropharyngeal 2.9% (147/5030) required treatment	<i>Desensitization at 44 wk:</i> Active 70% (14/20) (median successfully consumed dose [SCD] increased from 3.5 to 496 mg) Placebo: 15% (3/20) <i>Desensitization at 65 wk:</i> Active: median SCD increased to 996 Control: 43% (7/16) of crossover responded (increased from 21 to 496 mg)
Burks et al, 2015 ³²	Open label (3-y follow-up) DMD: 5000 µg of peanut or 10-fold increase compared with baseline Duration: 3-y follow-up	N = 37 Age 12-36	50% discontinued therapy 98% of the 18,165 doses were tolerated without adverse reactions beyond the oropharynx No severe reactions or uses of epinephrine Adverse reactions: 18.3% of doses in the high-dose crossover group after 44 wk of active 18.1% of doses received by subjects in the peanut SLIT group after 44 wk	<i>Desensitization:</i> 10.8% (4/37) <i>SU after 8 wk of cessation of SLIT therapy</i> (no peanut avoidance) 100% (4/4)
Hazelnut SLIT				
Enrique et al, 2005 ⁸⁷	Randomized, placebo controlled DMD: 1 mg corresponded to 1.84 mg of the allergen Cor a 8 and 2.88 mg of the allergen Cor a 1 Max dose was 20 mg Duration: 8-12 wk	N = 23 Active: 12 Placebo: 11 Age 9-17	1 dropped out Active: Build-up: 0.2% (3/1466) of systemic reactions 7.4% (109/1446) of local reactions Maintenance Local reactions only	<i>Desensitization</i> Active: 45% (5/11) Control: 10% (1/10) $P < .05$ Mean hazelnut quantity provoking objective reactions increased from

(continued)

TABLE III. (Continued)

Authors, year	Design; Daily maintenance dose (DMD) (mg protein/day); duration of the study	Sample size (N); age range (y)	Safety	Primary outcome
			Placebo: no reaction	2.29 g to 11.56 g ($P = .02$; active group) vs 3.49 g to 4.14 g (placebo; NS)
Comparison OIT vs. SLIT				
Keet et al, 2012 ³³	Randomized SLIT vs OIT	N = 30	2 dropouts (1 in OITA and 1 in OITB)	Desensitization
Milk	DMD: can tolerate at least 10-fold increase after 15 mo of maintenance therapy	SLIT: 10 OIT: 10 SLIT/SLIT: 10	Number of adverse events is similar between groups	SLIT/SLIT: 10%
	SLIT/OITA: SLIT then OIT (start 1000 mg)	Age 6-17	29% (1802/6246) reactions with SLIT doses and 23% (2402/10645) OIT doses (P-NS)	SLIT/OITB: 70%
	SLIT/OITB: SLIT then OIT (start 2000 mg)		More multisystem reactions in the OIT group (IRR, 11.5; $P < .001$)	SLIT/OITA: 90%
	Then for the one who passed the challenge, therapy was withdrawn; then OFC were repeated at 1 and 6 wk to assess for SU		Epinephrine 2 in SLIT group vs 4 times during OIT dosing (might have been also dosing error)	Challenge threshold at 12 wk SLIT/SLIT: 7 fold SLIT/OITB: 64 fold SLIT/OITA: 79 fold Challenge threshold at 60 wk SLIT/SLIT: 40-fold SLIT/OITB: 159-fold SLIT/OITA: 54-fold
				The challenge threshold increased by at least 10 times baseline at T5 for 60% of those randomized to SLIT and for 90% in each of the OIT groups (P5.053, SLIT vs OIT)
				SU after 6 wk of milk avoidance: SLIT/SLIT: 10% (1/10) SLIT/OIT: 30% (3/10) SLIT/OITA: 50% (5/10) patients
Narisety et al, 2015 ²²	DBPC SLIT vs OIT	N = 21	5 dropouts (3 in OIT active and 2 in SLIT active)	Desensitization
Peanut	Active OIT/placebo SLIT or active SLIT/OIT placebo	Active: 11 SLIT: 10	Adverse reactions were mild	OIT: 63.3% (7/11)
	DMD	Age 7-13	SLIT vs OIT	SLIT: 70% (7/10)
	OIT: 2000 mg of peanut protein	No difference	AEs higher in the OIT group (43% vs 9% of doses; $P < .001$)	Increase in median challenge threshold dose was significantly greater with OIT
	SLIT: 3.7 mg of peanut protein	between groups in	Most of the AEs were mild, although a few were severe (3.4% vs 1.3%; $P < .001$)	SLIT: 14- and 22-fold (6 and 12 mo)
	Duration: 12 mo of maintenance and then 4 wk of cessation of OIT/SLIT to assess for SU	terms of age, sIgE at baseline	Antihistamines used with 40.9% of OIT doses vs 23.1% of SLIT doses ($P < .001$)	OIT: 141- and 141-fold (6 and 12 mo)
			5 doses of epinephrine given to 4 subjects in the active OIT group (1 during build-up and 4 during maintenance) compared with 0 in the SLIT group	$P = .009$ and $P = .01$ SU after 4 wk of peanut avoidance 10% (1/10) in SLIT 27% (3/11) in OIT $P = .59$

AE, Adverse event; DBPCFC, double-blind, placebo-controlled food challenge; OFC, oral food challenge; OIT, oral immunotherapy; SLIT, sublingual immunotherapy; SU, sustained unresponsiveness.

significant predictors of higher overall AE rates. SPT predicted increased gastrointestinal AEs, whereas AR predicted increased systemic AEs.⁶⁷

Age of the patient

High rates of SU after peanut OIT were reported in preschool peanut-allergic children, median age 28.5 months (range: 9-16 months).⁴⁸ In the intent-to-treat analysis, after 3 years of peanut OIT, 78% (17/20 of patients on low dose and 12/17 patients on high dose) reached SU (Table I).⁴⁸ Per-protocol, the overall proportion achieving SU was 91% (29/32).

OIT AND QUALITY OF LIFE

Milk OIT significantly improved QoL, especially in children older than 4 years.⁷⁴ Among patients treated with peanut OIT, a significant improvement in QoL was found regarding allergen avoidance, dietary restrictions, risk of accidental exposure, emotional impact, food-related anxiety, and social and dietary limitations.^{46,75}

LIMITATIONS OF OIT

Many questions remain regarding OIT, including the optimal maintenance dose, the frequency of maintenance dosing, and OIT duration. There is no consensus on the uniform reporting of efficacy and safety outcomes; because of the considerable heterogeneity in the clinical protocols, it is difficult to compare and combine the data from different studies of small sizes. There are no standardized criteria for selecting optimal candidates for OIT and no biomarkers that reliably predict favorable outcomes. Therefore, it is unclear how to translate the results of clinical trials to an individual food-allergic patient.

The inclusion criteria for the OIT trials are extremely specific; most studies include patients reacting below 100 to 300 mg food protein during the baseline oral food challenge (OFC) and exclude patients with past life-threatening anaphylaxis, and persistent or uncontrolled asthma. However, in clinical settings, patients are considered allergic if they cannot tolerate approximately 5 g of the food protein, equivalent to a real-life serving.^{1,76}

Prior studies suggest that overall, during OFC, approximately 75% of the reactions occur at doses over 100 mg of food protein, and 55% of reactions occur at cumulative doses over 250 mg, with over 30% reacting at doses over approximately 1.5 g.⁷⁷⁻⁸⁴

Therefore, it is possible that the majority of patients with a milder phenotype of food allergy might achieve superior outcomes from OIT than reported from clinical trials. Finally, results from Vickery et al suggest that peanut OIT may be more efficacious and safer in infants than in older children, possibly due to a better plasticity of the infant immune system and generally lower serum food-specific IgE antibody levels that have been associated with more favorable outcomes of OIT.⁴⁸

OIT WITH MODIFIED ALLERGENS

Baked milk OIT has been attempted in 14 patients who failed native (nonbaked) milk OIT. After 12 months, 3 patients (21%) achieved the full dose of baked milk (1.3 g protein daily); 8 developed frequent immediate systemic reactions. These results confirm prior observations that patients with a more severe phenotype of milk allergy are likely to react to baked milk.³⁶ In contrast, among 15 children with IgE-mediated egg allergy, 53%

gradually introduced baked egg at home and tolerated an open OFC to 1 whole hard-boiled egg after 12 months.⁵⁵ Baked milk/egg OIT are different from diets incorporating baked milk and egg diets that include children tolerant to a substantial amount of baked milk (approximately 1.3 g) or egg protein (2.2 g).⁸⁵

In a pilot study, OIT with 9 g of hydrolyzed egg white was well tolerated, but after 6 months, there was no difference in tolerance of hard-boiled egg between active and placebo groups, although there was evidence of immunomodulation (see Table I). It is possible that a longer treatment period and/or a higher dose might improve the clinical outcome.³⁴

SUBLINGUAL IMMUNOTHERAPY

SLIT was initially reported in 1986 in patients with AR who received daily administration of a liquid grass or house dust mite extract.⁸⁶ Extract of food protein is also delivered sublingually, held for 2 minutes and swallowed. SLIT has been studied for hazelnut,⁸⁷ peanut,⁸⁸ milk,³³ kiwi,⁸⁹ and peach⁹⁰ (Table III). SLIT efficacy is limited by allergen dose due to low concentration of available extracts and the volume of liquid that can be held sublingually.

IMMUNOLOGIC CHANGES ASSOCIATED WITH SLIT

SLIT is associated with a decreased nonspecific basophil and mast cells reactivity.^{22,33,37,88} Serum peanut-sIgE levels initially increase and then decrease over 8 months, whereas peanut-sIgG₄ levels increase gradually.⁸⁸ Serum IL-5 is significantly lower, whereas Tregs are increased in the active group compared with placebo.⁸⁸

SAFETY AND EFFICACY OF SLIT VERSUS OIT

SLIT utilizes significantly lower doses and is generally better tolerated than OIT. Two randomized studies directly compared milk and peanut SLIT versus OIT^{22,91} (Table III). After 60 weeks of maintenance, 1 of 10 patients in the milk SLIT and 14 of 20 patients in the milk OIT passed an 8 g milk protein OFC ($P = .002$). The overall number of AEs was similar between groups. However, AEs in the OIT group were more likely to involve respiratory or GI tract and to be systemic compared with the local AEs in SLIT.⁹¹ In a double-blinded, placebo-controlled (DBPC) trial comparing peanut SLIT versus peanut OIT, doses were escalated to 3.7 mg (SLIT) and 2000 mg (OIT).²² Sixteen of 21 completed the 12-month double-blind phase and all patients on SLIT and OIT had a greater than 10-fold increase in challenge threshold. However, the increase in the threshold was greater in peanut OIT (141-fold increase) compared with peanut SLIT (22-fold increase). In the OIT group, the adverse reactions were more severe than the reactions in the SLIT group and required therapy more frequently.

SLIT SAFETY

SLIT is a safe route of desensitization as AEs predominantly consist of transient oropharyngeal pruritus and do not require treatment. No case of EoE has been reported with food SLIT; however, a case report of EoE postenvironmental SLIT has been described.⁹²

TABLE IV. EPIT studies

Authors, year; food	Design; daily maintenance dose (DMD) mg protein/d; duration of the study	Sample size (N); age range (y)	Safety	Primary outcome
Dupont et al, 2010 ⁵⁰ Milk	Pilot bicenter, double-blind, placebo-controlled study Active group: 3 patch application during 48 hours per week for a total of 3 mo DMD: 1 mg skimmed cow's milk powder	N = 19 Active: 10 Placebo: 9 Age: 3 mo to 15 y	2 dropouts in the active group and 1 in the placebo group Nonlocal AEs significantly more frequent in patients in the active group (total doses: 470): Active (470 doses total) vs placebo (316 doses total) Respiratory (cough, asthma, bronchitis): 0.4% (2/470) vs 0.1% (5/316), $P = .09$ GI (vomiting, diarrhea): 0.3% (16/470) vs 0% (0/316); $P < .001$ Local reactions significantly more frequent in patients in the active group: Active (470 doses total) vs placebo (316 doses total) 19% (93/470) vs 14.5% (46/316), $P = .07$ No anaphylactic reactions	The mean cumulative tolerated dose was significantly increased in active group: 12% vs 8% placebo ($P = .03$)
Jones et al, 2016 ⁶⁴ Peanut	Randomized, double-blind, placebo-controlled multicenter phase Ib study DMD: 500 µg of peanut protein Duration: 22 d	N = 100 Active: 80 Placebo: 20 Age 6-49	4 dropouts No difference in number of at least one nonlocal AE between treatment groups Active group: 52.5% (42/80) reported nonlocal adverse reactions: 41.3%: mild and transient (nonlocal pruritus/erythema/edema or urticaria) 11.3%: moderate severity (nonlocal pruritus/erythema/edema and urticaria) Placebo: 45% (9/20) reported nonlocal adverse reactions: 30%: mild 15%: moderate Patients on EPIT patch experienced more local-adverse reactions (local pruritus/erythema/edema and urticaria) compared with patients on placebo (84% vs 60%; $P < .21$, relative risk: 1.4; 95% CI, 0.99-2.08) <i>Severity</i> No anaphylaxis in the active group	<i>Safety study</i> Safe
Jones et al, 2016 ⁹³ Peanut	Randomized, double-blind, placebo-controlled multicenter phase II study DMD: patch of 100 or 250 µg Duration: 52 wk	N = 74 Active: VP100: 24 VP250: 25 Placebo: 25 Age 6-49	4 dropouts At least one nonlocal AE (% doses): Active group VP100: 0.2% (18/8121) VP250: 0.1% (6/9033) Placebo: 0.2% (17/8418) At least one local AE (% doses):	<i>Desensitization (10-fold increase in the successfully consumed dose [SCD]).</i> Active group: VP100: 46% (11/24) VP250: 48% (12/25) Control group: 12% (3/25)

Active group	Difference in desensitization between the different groups
VP100 79.8% (6479/8121)	VP100 vs placebo: $P = .005$
VP250: 79.7% (7203/9033)	VP250 vs placebo: $P = .3$
Placebo: 14.3% (1200/8418)	Median changes of SCD: Active group:
Severity	VP100: 43 mg of protein
No anaphylaxis	VP250: 130 mg of protein
	Placebo: 0 mg of protein
	Difference in median changes of SCD between the different groups:
	VP100 vs placebo: $P = .014$
	VP250 vs placebo: $P = .003$

AE, Adverse event; EPIT, epicutaneous immunotherapy; VP100, Viaskin peanut 100 µg; VP250, Viaskin peanut 250 µg.

SLIT LIMITATIONS

SLIT trials have excluded patients with a history of near-fatal anaphylaxis to the offending food. Therefore, as in OIT, the applicability of SLIT to the general population of food-allergic patients remains unknown. Longitudinal studies are needed to gain a better understanding of desensitization and SU in food SLIT.

EPIT

EPIT utilizes a novel antigen delivery through application of an allergen-containing patch designed to activate skin Langerhans cells with subsequent systemic downregulation of the effector cell responses. The epidermis is not vascularized, thereby reducing the risk of systemic AEs to EPIT. Peanut EPIT induced sustained protection against peanut anaphylaxis in a mouse model.⁹³ The mechanism of protection could be secondary to the generation of gut-homing LAP1+Foxp3+ Tregs.⁹³

In a pilot study, 18 milk-allergic children were treated for 3 months (Table IV).⁵⁰ AEs were almost exquisitely limited to the skin, for example, erythema or eczematous eruption at the patch application site. Currently, phase III multicenter international clinical trials of peanut and milk EPIT are ongoing.

EFFICACY OF EPIT

Jones et al⁹³ recently reported the efficacy of EPIT for the treatment of peanut allergy. In this phase II clinical trial, 46% of the patients on Viaskin peanut 100 µg (VP100) and 48% of the patients on Viaskin peanut 250 µg (VP250) were able to tolerate a 10-fold increase of their successfully consumed dose (SCD) (primary end point of this study) compared with 12% in the placebo-treated participants ($P = .005$ and $P = .003$ respectively, compared with placebo). Median change in SCD doses was 0, 43, and 130 mg of protein in the placebo, VP100 and VP250 groups ($P = 0.14$ and $P = .003$, respectively, compared with placebo). Treatment success was higher among younger children; 61% of those 4 to 11 years were considered treatment successes compared with 14.4% of those older than 11 years at the time of the enrollment, $P = .03$.

SAFETY OF EPIT

EPIT is expected to induce few systemic and GI symptoms, based on the pilot data and the very low dose of food allergen applied on the skin, for example, 250 to 500 mcg. The patch remains on the skin for 24 hours, and a new patch is applied in a different location on the upper back (younger children) or on the inner aspect of the upper arm (older children and teenagers) daily. A multicenter randomized, DBPC multicenter phase Ib study reported that peanut EPIT was safe and well tolerated (Table IV).⁶⁴ The most frequent^{19,47,50,51,54,63,87} AEs were localized erythema, pruritus, and urticaria⁶⁴; no anaphylaxis to active EPIT was observed.^{64,93} Table V directly compares OIT, SLIT, and EPIT.

OTHER FUTURE THERAPIES

Additional approaches to food immunotherapy involve proteins or peptides of decreased allergenicity, use of^{94,95} adjuvants to enhance efficacy and improve safety, and allergen nonspecific approaches such as Chinese herbs^{96,97} (Figure 1, Table VI).^{12,15,94,98-100}

TABLE V. Comparison of food allergen immunotherapy currently in clinical trials

	OIT	SLIT	EPIT
Daily maintenance dose	300-4000 mg	2-7 mg	50-500 µg, usually 250 µg
Food protein [*] ; specific foods studied	Peanut, cow's milk, egg, wheat	Peanut, cow's milk, hazelnut, peach	Peanut, cow's milk
Observed dosing	Up-dosing every 1 or 2 wk	Up-dosing every 1 or 2 weeks	Initiation and periodic observation
Safety	Less desirable	More desirable	More desirable
Adverse effects			
Oral	Frequent mild oropharyngeal pruritus	Majority of AEs are oropharyngeal (local)	None reported
Skin	Yes (urticaria)	Yes (urticaria)	Yes (local skin reactions: eczema, urticaria)
GI	Yes most of the adverse reactions are GI (abdominal pain, nausea)	Rare, less common	Rare, ongoing investigation
Severity/systemic/anaphylaxis	Can be systemic when associated with exercise, fever, URI, menstruation, dosing on empty stomach	Mild, rare systemic reactions	Mild, local reactions
EoE	Estimated at 2.7%-8% ^{59,63†}	Not reported	Not reported
Frequency of AEs	Almost everyone will react during the escalation phase	Less frequent Enrique et al ⁸⁷ : 7.4% (109/1466 doses) Keet et al ³³ : 29% (1802/6246 doses) Fleischer et al ³⁷ : 41.1% (2394/5825 doses)	Local reactions: Dupont et al ⁵⁰ : 19% (93/470 doses) Jones et al ⁶⁴ : 84% (67/80 patients) Jones et al ⁹³ : VP100: 79.8% (6479/8121) VP250: 79.7% (7203/9033) Nonlocal reactions: Dupont et al ⁵⁰ : 3.8% (18/470 doses) Jones et al ⁶⁴ : 52.5% (42/80 patients) Jones et al ⁹³ : VP100: 0.2% (18/8121 doses) VP250: 0.1% (6/9033 doses)
Activity restriction	Dose taken with meal; no physical activity for 2 h after dose administration; withhold with illness	Do not eat for 30 min after dose administration	None
Efficacy	More desirable	Less desirable	Ongoing investigation
Desensitization [‡]	Large effect (usually, the patients who finish the protocol achieve desensitization) Peanut: 62% ⁴⁶ to 100% ⁴⁷ Egg: 36% ³⁴ to 94% ²⁶ Milk: 67% ⁵¹ to 92.9% ⁵⁴ Wheat: only 2 studies 83.6% ⁵⁶ and 94.4% ³⁰	Moderate effect Peanut: 10.8% ²² to 70% ³² Milk: 10% (only 1 study) ³³	Ongoing investigation Peanut: only 1 study VP100: 46% (11/24) ⁹³ VP250: 48% (12/25) ⁹³
Intention to treat analysis			
Sustained unresponsiveness [‡]	Peanut: 50% ¹⁷ to 79% ¹¹ Egg: 27.5% ²⁶ to 75% ²⁴ Milk: 36% ²⁹ to 92.3% ³⁵ Wheat: 61.1% (1 study) ³⁰	Peanut: 10% ²² to 100% ³² (only 2 studies) Milk: 10% (only 1 study) ³³	Peanut: no data Milk: no data
Intention to treat analysis			
Long-term tolerance	Variable response Limited evidence	Ongoing investigation	Present
Immunomodulation	Significant	Present	Present in mice Present in human subjects
Adherence	Suboptimal primarily because of chronic GI AEs	Better than with OIT	Better than with OIT
Feasibility [§]	Difficult because of GI AEs and lifestyle modifications	Easy	Easy

AE, Adverse event; EoE, eosinophilic esophagitis; EPIT, epicutaneous immunotherapy; GI, gastrointestinal; OIT, oral immunotherapy; SLIT, sublingual immunotherapy; VP100, Viaskin peanut 100 µg; VP250, Viaskin peanut 250 µg.

^{*}Few studies explored less frequent (every other day or twice a week) maintenance dosing therapy with promising results.^{27,51}

[†]This study might have publication bias and this value might be falsely elevated.

[‡]Limitations: heterogeneity of study design and variable definitions of desensitization and sustained unresponsiveness.

[§]The feasibility of OIT is limited by (i) the requirement for frequent clinic visits, (ii) the need to observe the child for 2 h after OIT dose administration, (iii) parents might be anxious to give the offending food to their child, and (iv) the child may be apprehensive about eating the food.

TABLE VI. Selected future therapies for food allergy

Human studies				
Authors, year; treatment; food allergy	Design; dose; duration	Sample size (N); age range (y)	Safety	Primary outcome
Wang et al. ⁹⁴ ; Patil et al, 2011 ⁹⁵ FAHF-2 (food allergy herbal formula 2, a mix of 9 herbs) Peanut	Randomized, double-blinded, placebo-controlled, dose escalation, phase 1 trial 3 doses (FAHF-2 vs placebo) were studied 2.2 g (4 tablets), 3.3 g (6 tablets), and 6.6 g (12 tablets) 3 times a day for 7 d Duration: 7 d	Age range: 12-45 N = 19 Active: 13 Placebo: 6	1 dropout AEs: Active: 16% (2/12) (one with atopic dermatitis flare and one with loose stools) Placebo: 17% (1/6) (vomiting)	18 patients successfully completed 7 d of treatment Active: 12 patients Placebo: 6 Significant reduction ($P < .010$) in basophil CD63 expression in response to <i>ex vivo</i> stimulation at month 6 Trend toward a reduction in eosinophil and basophil numbers after treatment
Wang et al., 2015 ¹² FAHF-2 (food allergy herbal formula 2, a mix of 9 herbs) Peanut, tree nut, sesame, fish, and/or shellfish	Randomized, double-blinded, placebo-controlled, dose escalation, phase 1 trial FAHF-2 or placebo (2:1), 10 tablets (each tablet: 0.5 g) 3 times a day, for 6 mo Duration: 6 mo Goal: 5 g of protein	Age range: 12-45 N = 68 Active: 47 Placebo: 22	9 dropout (8 in active and 9 in placebo) AEs: Active: 4 (median) per patient Placebo: 5 (median) per patient Severity: Mild or moderate No severe reaction Mostly GI symptoms (60% of the total reaction in both active and placebo)	86% (58/59) finished the study Active: 80% (37/46) Placebo: 95% (21/22) Intent-to-treat analysis, the placebo group had a higher eliciting dose and cumulative dose compared with the active group ($P = .05$) Main cumulative dose tolerated: <i>Placebo</i> Baseline: 352.5 mg protein At 6 mo: 1022.1 mg protein <i>Active</i> Baseline: 266.2 mg protein At 6 mo: 369.2 mg protein
Wood et al., 2013 ¹⁵ Heat-killed <i>E. coli</i> expressing modified recombinant Ara h 1, 2, and 3 Peanut	Pilot study phase I Rectal administration of Ara h 1, 2, and 3 encapsulated in heat/phenol-killed <i>E. Coli</i> MD: 3093 mcg biweekly for 3 wk (during escalation phase, received weekly dose over 10 wk) Duration: 16 wk	Age range: 15-50 N = 5 Active: 10 Control: 5	AEs: <i>Active</i> 20% of anaphylaxis (3/10 patients experienced it) <i>Control</i> 0 severe reaction 1/5: diarrhea	Active: 40% (4/10) desensitized to 3093 mg peanut protein
Animal studies				
Author/year/food	Summary			
Srivastava et al, 2013 ¹⁰⁰ Peanut	Peanut oral immunotherapy with CpG/peanut nanoparticles in a murine model of peanut anaphylaxis. When CpG are administered together with peanut, mice are better protected against anaphylaxis.			
Li et al, 2003 ⁹⁶ Peanut	Heat-killed <i>Listeria monocytogenes</i> together with native or modified peanut protein has shown to suppress peanut anaphylaxis in mice.			
Smarr et al, 2011 ¹⁰⁰ Peanut	Administration of syngeneic apoptotic cells coated with peanut allergen. Peanut-allergic mice were tested with intravenous syngeneic spleen cells that have been conjugated with peanut. The conjugation induced apoptosis of the donor cells, which may contribute to the recipient antigen presenting cells that engulf the cell allergen conjugate.			
Liu et al, 2013 ⁹⁷ Peanut	Fusion proteins of allergen and human Fcγ chains that bind FcγRIIb and inhibit basophils and mast cells.			

AE, Adverse event; GI, gastrointestinal.

TABLE VII. Key points of novel therapies for food allergy

- (1) Most of the patients treated with OIT achieve desensitization; however, only a minority achieves sustained unresponsiveness.
- (2) The safety and efficacy outcomes of peanut OIT appear to be superior in infants and young children compared with older patients suggesting a distinct advantage to initiating immunomodulatory treatment early in life.
- (3) The long-term adherence to OIT is negatively affected by the chronic gastrointestinal symptoms, and there is a small risk of treatment-emergent eosinophilic esophagitis.
- (4) OIT affords better efficacy but is associated with higher frequency of systemic side effects compared with SLIT and EPIT.
- (5) Combination of OIT and omalizumab enhances safety of OIT but appears to have no significant effect on efficacy. Additional strategies including combining OIT with probiotics or Chinese herbal medicine are currently being investigated.
- (6) Efficacy of SLIT is limited by the low dose of allergen delivered sublingually; SLIT is generally well tolerated with majority of adverse reactions being mild oral pharyngeal pruritus.
- (7) EPIT appears to be safe and well tolerated with majority of adverse reactions being local skin rashes and pruritus; human efficacy data have not been published yet.

EPIT, Epicutaneous immunotherapy; OIT, oral immunotherapy; SLIT, sublingual immunotherapy.

SUMMARY

There are no currently approved therapies for FA, although 2 commercial products (peanut AR101 by Aimmune Therapeutics [Brisbane, Calif] and Viaskin Peanut by DBV Technologies [Montrouge, France]) are in the phase III clinical trials. FDA has granted Breakthrough Therapy Designation status for both products, and they are anticipated to be approved in a couple of years, pending favorable clinical trials results. Specific-food OIT has superior efficacy but causes more AEs, imposes more life-style restrictions, and is more labor-intensive compared with EPIT and SLIT. SLIT is safe but its efficacy is limited by the low dose of the allergen delivered sublingually. EPIT is safe; preliminary efficacy data suggest that EPIT has a modest treatment effect that is greater when initiated in children younger than 12 years. None of these immunotherapeutic approaches have been proven to deliver a permanent cure of food allergy (Table VII). Improvements in safety allowing for the inclusion of patients with severe phenotypes of food allergy and asthma, refinements in dose and duration of treatment to enhance efficacy, and understanding of the mechanisms underlying desensitization and tolerance are desirable. Emerging evidence suggests that early initiation of peanut OIT in infants and young children may offer superior efficacy and safety due to lower OIT doses used and more favorable response to immunomodulation in a developing immune system. Large clinical trials of rigorous design and adequate sample sizes are necessary to fully evaluate the effects of food immunotherapy. Alternative approaches utilizing the combination of several synergistic treatments (eg, OIT and omalizumab or EPIT followed by OIT) or modified hypoallergenic molecules combined with adjuvants may be necessary for patients with the most severe phenotypes of FA.

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