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Allergen-Specific Immunotherapies for Food Allergy

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With rising prevalence of food allergy (FA), allergen-specific immunotherapy (AIT) for FA has become an active area of research in recent years. In AIT, incrementally increasing doses of inciting allergen are given with the goal to increase tolerance, initially through desensitization, which relies on regular exposure to allergen. With prolonged therapy in some subjects, AIT may induce sustained unresponsiveness, in which tolerance is retained after a period of allergen avoidance. Methods of AIT currently under study in humans include oral, sublingual, epicutaneous, and subcutaneous delivery of modified allergenic protein, as well as via DNA-based vaccines encoding allergen with lysosomal-associated membrane protein I. The balance of safety and efficacy varies by type of AIT, as well as by targeted allergen. Age, degree of sensitization, and other comorbidities may affect this balance within an individual patient. More recently, AIT with modified proteins or combined with immunomodulatory therapies has shown promise in making AIT safer and/or more effective. Though methods of AIT are neither currently advised by experts (oral immunotherapy [OIT]) nor widely available, AIT is likely to become a part of recommended management of FA in the coming years. Here, we review and compare methods of AIT currently under study in humans to prepare the practitioner for an exciting new phase in the care of food allergic patients in which improved tolerance to inciting foods will be a real possibility.

Key Words: Food allergy; subcutaneous immunotherapy; sublingual immunotherapy; oral immunotherapy; epicutaneous immunotherapy

INTRODUCTION

Food allergy (FA) affects 6% of adults[1] and up to 8% of children. The prevalence of allergy and anaphylaxis is increasing.[2,3] Standard management has been strict food avoidance and preparedness with an epinephrine auto-injector (EAI) in the event of a reaction.[4] Despite efforts at avoidance, severe reactions may occur in up to a third of food allergic children.[5] Given risk for accidental reactions and persistence of FA beyond childhood, there is an unmet need for therapies for FA. A number of allergen-specific methods are being studied, and may become commercially available in the coming years. In this review, we will discuss food allergen-specific immunotherapies (AITs) that are being evaluated in humans.

SECTION 1: WHAT ARE THE METHODS OF AIT FOR FA?

AIT utilize frequent delivery of allergen via various routes to induce tolerance. Food AITs currently under study include oral immunotherapy (OIT), sublingual immunotherapy (SLIT), epicutaneous immunotherapy (EPIT), and subcutaneous immunotherapy (SCIT) with modified allergen, as well as lysosomal-associated membrane protein (LAMP)-DNA based vaccines. An overview of these AIT modalities is provided below and compared in Table 1.

OIT and SLIT

In OIT, native or modified food allergen is ingested; whereas in SLIT, liquid allergen extract is applied under the tongue. SLIT and OIT respectively start with sub-threshold doses in 0.0001 μg- and 0.1 mg-range, which are increased under physician supervision during an initial rapid dose-escalation day up to 0.01 μg-range and mg-range. The highest tolerated dose after initial dose-escalation may be repeated on the following day to confirm it will be safely tolerated during daily doses at home. This

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Table 1. Comparison of allergen-specific immunotherapies for food allergy currently under study in human subjects

Features	OIT	SLIT	EPIT	SCIT with hypoallergen*	LAMP-DNA vaccine*
Food allergens	Peanut, cow's milk, egg, wheat, multi-food	Peanut, cow's milk, hazelnut, peach	Peanut, cow's milk	Peanut, fish	Peanut
Stage of study	Phase I-IV	Phase I-III	Phase I-III	Phase I-II	Phase I
Typical protocol	Initial dose-escalation day; doses administered daily throughout protocol, with bi-weekly dose increases during build-up phase (months), followed by maintenance (months-years)		Daily patch application for increasing intervals until 24 hour per day maintenance (years)	Weekly incrementally increasing doses	Current trial: 4 doses every 2 weeks
Maintenance dose	Daily; 300 mg to 4 g	Daily; 2 to 7 mg	Daily; 50 to 500 μg	Weekly 60 ng	Unknown
Observed doses	Initial dose escalation; up-dosing every 1 to 2 weeks	Up-dosing every 1 to 2 weeks	Initiation and periodic observation	All; typically weekly for build-up and monthly for maintenance	All are observed
Dosing restrictions	Take with food; avoid physical activity 2 hours after; withhold during illness	Avoid eating 30 minutes following dose	none	Period of in-office observation following each dose	Under observation in the office
Notable advantages	Improved efficacy compared to SLIT and EPIT; Cost efficient	Improved safety profile compared to OIT	Best safety profile of AIT for food allergy under study in humans; Ease of administration	Dosing only once per week; Observed dosing may improve compliance	Potential to induce tolerance with limited number of doses
Notable disadvantages	Frequent office visits during up-dosing; frequent AE which may include anaphylaxis; risk of EoE	Frequent AE; theoretical risk of EoE	Limited data: appears to have reduced efficacy compared to other modalities	Frequent office visits during up-dosing; administered by injection	Administered by injection

AE, adverse event; AIT, allergen-specific immunotherapy; EoE, eosinophilic esophagitis; EPIT, epicutaneous immunotherapy; LAMP, lysosomal-associated membrane protein; OIT, oral immunotherapy; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.
*Very limited data in humans.

is followed by a build-up phase during which daily doses are increased every 2 weeks under physician supervision up to maintenance doses in mg-range for SLIT and gram-range for OIT. Daily maintenance dosing is continued for months to years.

EPIT

In EPIT, 50-500 μg (usually 250 μg) of food protein electrosprayed onto a patch is applied to the upper arm or interscapular space. EPIT protocols typically start with 2 hours of patch application under clinician supervision in the office. Thereafter, daily patch application continues at home, with duration of application increased incrementally up to 24 hours per day. During maintenance, a new patch is applied daily and worn 24 hours per day for 1 or more years.[6,7]

SCIT

In SCIT, allergen is administered by subcutaneous injection in incrementally increasing doses under clinical supervision. Current SCIT trials utilize alum-adsorbed hypoallergen which has been modified chemically or with site-directed mutagenesis to reduce immunoglobulin (Ig) E-binding capacity.[8]

LAMP-DNA vaccines

In LAMP-DNA vaccines, DNA encoding allergen is administered in bacterial plasmid vectors, which express both the allergen epitope and LAMP-I for enhanced immunogenicity. They are administered by intramuscular or intradermal injection, every 2 weeks for a limited number of doses.

SECTION 2: IMMUNE MECHANISMS

Immune mechanisms by which AIT may induce tolerance are not fully elucidated. The observed changes in immune function (Table 2) appear to hinge on altered allergen-specific T-cells responses, with induction of T-regulatory cells (Tregs) and suppression of T_H2 immunity. Mechanisms of alteration in T-cell phenotype through AIT are discussed below and summarized in Fig. 1.

Natural tolerance acquisition and that conferred by AIT with native allergen appear to occur through induction of $Foxp3^+$ Tregs. Antigen uptake by immature tissue-resident dendritic cells (DC) in the absence of costimulatory signals results in DC-mediated Treg induction, through secretion of immunosuppressive cytokines and other mechanisms.[9,10] These induced-Tregs suppress allergic responses through secretion of inhibito-

Table 2. Immunomodulation in allergen-specific immunotherapy

Immune parameter	Functional correlate
↓SPT wheal diameter	Decreased mast cell reactivity
↓CD63 expression in basophil activation test	Decreased basophil reactivity
Initial ↑sIgE, followed by sustained ↓sIgE ↑sIgG, particularly ↑sIgG4 ↑sIgA (limited to OIT and SLIT)	Altered antibody isotype production by B cells
↓IL-4 and IL-13 production by PBMCs	Suppression of T_H2 immunity
↑IFN-γ production by production by PBMCs	Induction of T_H1 $CD4^+$ T cells
↑IL-10, TGF-β production by PBMCs ↑$FoxP3^+CD25^+CD4^+$ T cells	Induction of T-regulatory cells

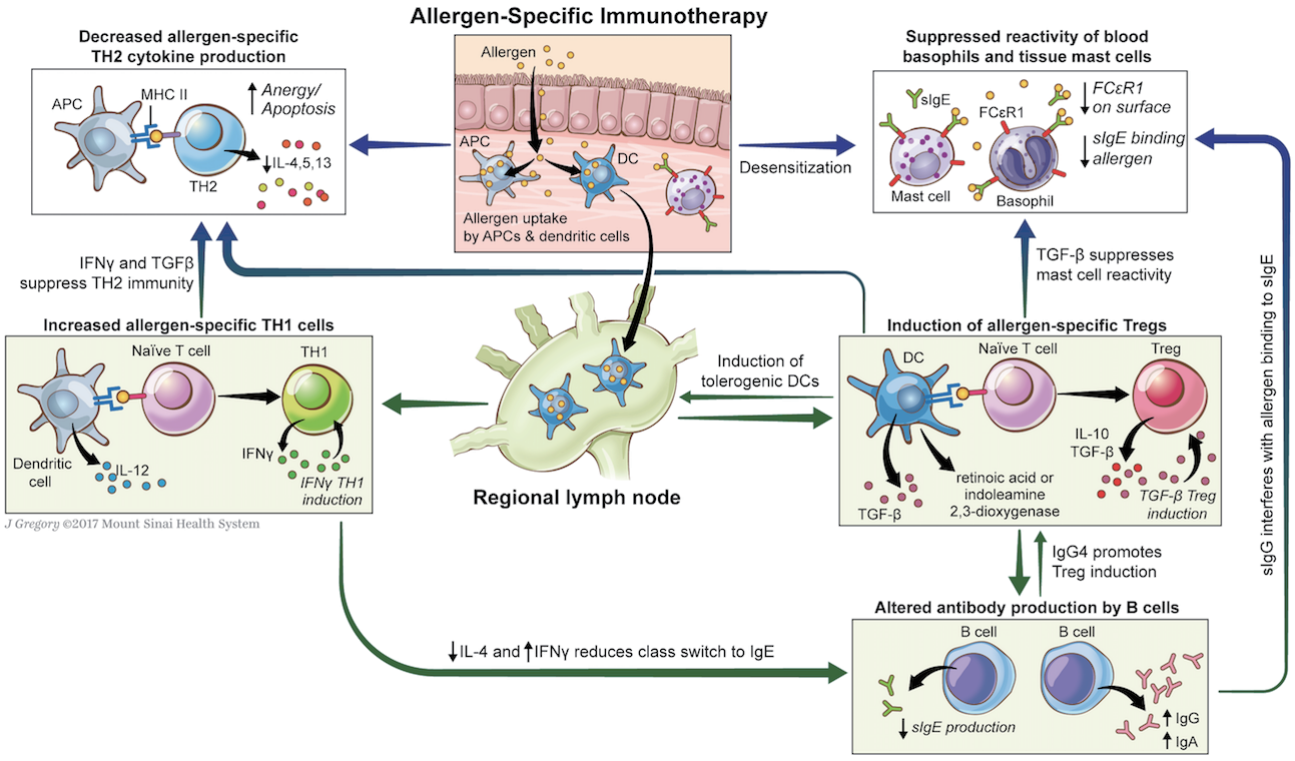

Fig. 1. Putative mechanisms of tolerance induction in allergen-specific immunotherapy. In allergen-specific immunotherapy (AIT), native or modified allergen is taken up by dendritic cells which migrate to regional lymph nodes, where they induce naïve T cells to regulatory T cell phenotype, through presentation of the allergen in context of MHC, secretion of cytokines such as TGF-β, generation of retinoic acid and indoleamine 2,3-dioxygenase, and other mechanisms. Secretion of cytokines IL-10 and TGF-β suppress T_H2 immunity and mast cell reactivity, reduce sIgE synthesis, and may increase sIgG and sIgA synthesis. AIT, particularly with LAMP-DNA vaccines, may also enhance tolerance through increased T_H1 immunity: presentation of allergen by dendritic cells in context of MHC to naïve T cell may induce T_H1 commitment particularly in presence of costimulators; production of IFN-γ by T_H1 cells suppresses T_H2 responses and reduces class switch to IgE. Other mechanisms of AIT may include increased anergy and apoptosis of T_H2 cells through persistent antigenic stimulation.

ry cytokines (interleukin [IL]-10, IL-35, and transforming growth factor [TGF]-β), which further amplifies Treg induction. Tregs also express surface receptors which alter DC function and induce target cell senescence.[11]

Immunotherapy appears to induce a shift away from T_H2-predominant immune responses, with reduced allergen-specific production of T_H2 cytokines.[6,12-16] This may occur not only through the immunosuppressive effects of Tregs as elaborated above, but also through a shift towards T_H1 immunity.[6,17,18] T_H1 cytokines such as interferon (IFN)-γ specifically inhibit T_H2 immunity and IgE production. Alternative mechanisms include anergy and deletion of allergen-specific T_H2 cells through repeated and frequent exposure to high doses of allergen.[19]

OIT

OIT utilizes the mechanisms underlying oral tolerance, result-

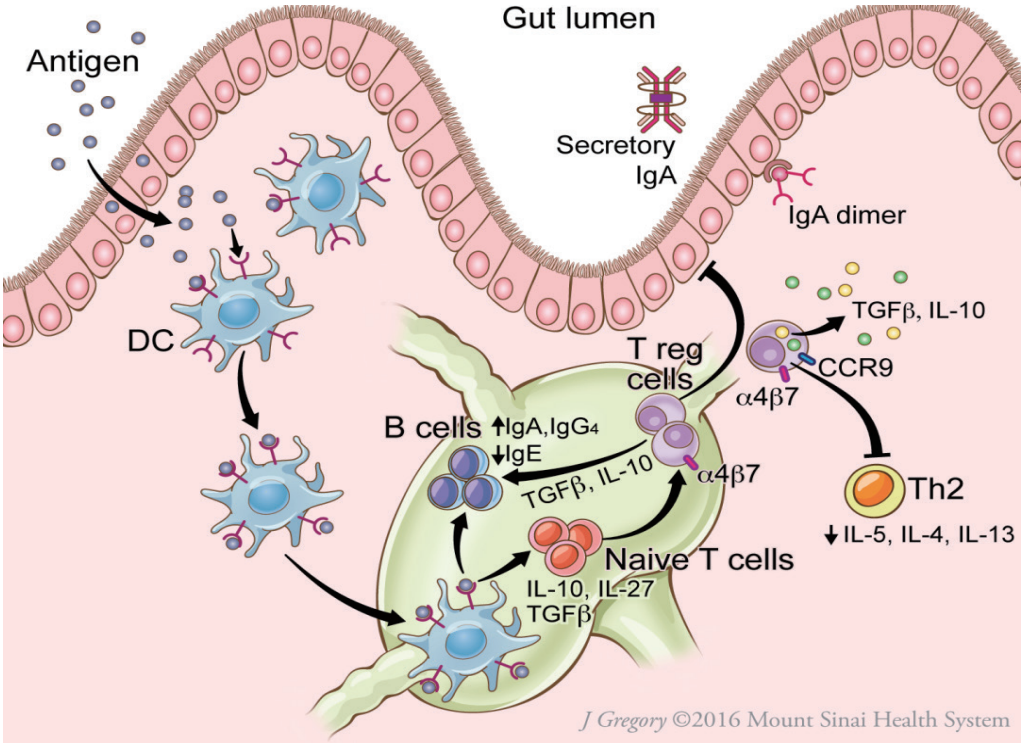

Fig. 2. Putative mechanisms of oral tolerance induction in the gut. On passage through the epithelial barrier, food protein allergen is captured by the dendritic cell (DC). The DC migrates to the nearby mesenteric lymph nodes and produces TGF-β, IL-10, and IL-27, which induce T regulatory cells (Tregs) and promote secretion of IgA and IgG4 by B cells. Tregs express surface receptors CCR9 and α4β7 integrin, which direct migration to the gut. Tregs secrete immunosuppressive cytokines IL-10 and TGF-β, which reinforce tolerance. Reprinted from Journal of Allergy and Clinical Immunology: In Practice (Volume 5), Gernez Y and Nowak-Wegrzyn A, "Immunotherapy for Food Allergy: Are we there yet?", Page 253, 2017, with permission from Elsevier.

ing in suppression of allergic responses (Fig. 2). Oral tolerance is likely dependent on induction of Tregs within gut-associated lymphoid tissue.[9,20] The steps through which this occurs include delivery of antigen to lamina propria DC by goblet cells (or other mechanisms); antigen uptake by $CD103^+$DC in the intestinal lamina propria; CCR7-directed migration of DC to mesenteric lymph nodes (MLNs); and interaction between DC and T-lymphocytes within MLNs.[9,20] B-regulatory cells may also play a role in tolerance induction.[21] The role of Tregs, B-regulatory cells, and DCs in oral tolerance has recently been reviewed in detail.[20]

OIT is associated with reduced skin prick test (SPT) wheal diameter and reduced basophil reactivity, initial increase followed by a gradual decrease in antigen-specific IgE, sustained increase in antigen-specific IgG_4 and antigen-specific IgA, decreased allergen-specific production of T_H2 cytokines (IL-4, IL-13), increased allergen-specific production of T_H1 (IFN-γ) and Treg cytokines (TGF-β), and Treg induction.[6,17,22-28] It appears however that some of these immunologic changes may be transient, with reversal on withdrawal of therapy and sometimes during maintenance.[23,27]

SLIT

SLIT utilizes the tolerogenic environment of the oral mucosa. Langerhans cells (LC; skin- and mucosa-homing DC) rapidly take up antigen, which has been transported across sublingual ductal epithelial cells.[29] LC migrate to local lymph nodes, where they present allergen to naïve T cells, inducing Tregs through secretion of immunosuppressive cytokines IL-10 and TGF-β.[30]

SLIT trials for FA provide evidence of Treg induction, and reduced T_H2 cytokine production, that may reverse on cessation or during maintenance.[27] SLIT trials report reduced basophil reactivity, reduced SPT wheal diameter, and increased antigen-specific IgA and IgG_4/IgE ratio.[26,27,31]

EPIT

EPIT is purported to induce tolerance through prolonged application of antigen to intact, non-inflamed skin. In mice, antigen applied to skin is taken up by LC in the *stratum corneum* and transported to draining lymph nodes, where these LC induce $Foxp3^+$ Tregs locally.[32] Treg induction also appears to occur distally with generation of gut-homing LAP^+Foxp3^- Treg cells, which provide sustained protection against anaphylaxis through direct TGF-β-dependent Treg suppression of mast cell activation.[33]

In the first clinical trials of EPIT for FA, treated subjects had increased IgG_4/IgE ratios, with trends towards decreased basophil reactivity and decreased T_H2 cytokine responses. Unlike OIT and SLIT, allergen-specific IgE did not change significantly with EPIT compared to controls.[6,34]

SCIT

The mechanisms underlying tolerance induction for SCIT with alum-adsorbed hypoallergen may differ from those for SCIT with native allergen. In SCIT with native allergen, immune tolerance is induced by similar mechanisms described above, with antigen-uptake by immature subcutaneous DC, migration of DC to local lymph nodes, Treg induction by tolerogenic DC, and Treg-mediated suppression of T_H2 immune responses.[35] In SCIT using hypoallergen, alum-adsorption provides a costimulatory signal that promotes a T_H1 response, which also serves to inhibit T_H2 immunity. In murine and rabbit studies, subcutaneous immunization with hypoallergenic carp parvalbumin (Cyp c 1) resulted in increased sIgG and decreased sIgE antibodies; and inhibition of IgE-binding, basophil degranulation, and allergic symptoms on challenge.[36,37]

In the only published results of SCIT with hypoallergen for FA in humans, a 2017 abstract reported evidence of immunomodulation with increased peanut-specific IgG_4 in subjects treated with subcutaneous injection of chemically modified alum-adsorbed peanut (HAL-MPE1) compared to controls.[38]

LAMP-DNA vaccines

LAMP-Vax is a next-generation DNA vaccine platform designed to stimulate an immune response against a particular protein, by injecting the DNA encoding the protein. After vaccine administration, antigen-presenting cells (APCs) take up the vector, which translates DNA into allergen associated with LAMP-I.[39] LAMP-Vax DNA immunization contrasts with the immune response to conventional DNA vaccines, which are processed and primarily presented through major histocompatibility complex (MHC)-I and elicit a cytotoxic T response. LAMP-Vax DNA immunization initiates a more complete immune response, including antibody production, cytokine release, and critical immunological memory. In the C3H/HeJ peanut allergic mice (sensitized via oral ingestion of peanut and cholera toxin), intradermal injection of 50 μg ASP0892 attenuated allergic symptoms during peanut challenge as indicated by lower disease scores and higher body temperature compared to vector control, reduced peanut-specific IgE levels and increased peanut-specific IgG2a levels.[39,40]

There is currently an ongoing phase I, randomized, placebo-controlled study to evaluate safety, tolerability, and immune response in adults allergic to peanut after receiving intradermal or intramuscular injection of ASP0892 (ARA LAMP-Vax), a single multivalent peanut (Ara h1, h2, h3) LAMP-DNA Plasmid Vaccine (NCT02851277).

SECTION 3: DESIGN OF AIT CLINICAL TRIALS

With OIT, SLIT, and EPIT being the focus of most published AIT clinical trials, much of the below discussion is based on published data evaluating these therapies. A general schematic of OIT and SLIT is provided in Fig. 3.

Goals of therapy

While the most desired outcome of AIT would be permanent tolerance, clinical trials investigating immunotherapies for FA typically use practical endpoints of desensitization and sustained unresponsiveness (SU). Desensitization is a temporary state of hyporesponsiveness, which is induced and maintained by frequent (daily) exposure to the offending antigen. Immune reactivity may return upon withdrawal of antigen exposure for a sufficient period of time. SU is a prolonged antigen hyporesponsiveness which persists after a period (typically 2-12 weeks) of cessation of therapy and avoidance of allergen.

Design of AIT clinical trials

Shared features of AIT clinical trials

Clinical trials share a number of features. For recruitment, entry criteria typically include a history of reaction to the food or physician-diagnosed FA, with evidence of IgE-sensitization. Typical exclusion criteria include history of life-threatening anaphylaxis, poorly controlled asthma, other form of concomitant immunotherapy, medications that either suppress immune response or increase risk of reactions, and certain chronic conditions. Most of the rigorous studies will require a double-blind placebo-controlled oral food challenge (DBPCFC) to determine the threshold prior to initiation of therapy, to confirm presence of the FA, and to eliminate subjects who are tolerant of the food or reactive to placebo.

For randomized, controlled trials (RCT), subjects are then randomized to AIT or to the control group (placebo and/or strict avoidance of allergen). To evaluate immunomodulation on AIT (Section 3), clinical trials may perform allergen-specific evaluation prior to AIT initiation, at various time-points during the study and at the conclusion of therapy. Therapy protocols are undertaken for various forms of AIT as described in Section 1. Adverse events (AEs) are monitored through out the trial. Subjects may withdraw for any reason. Common reasons include persistent and/or severe AE, anxiety related to doses or oral food challenge (OFC), inability to comply with protocols, or new medical problems or medications.

At the conclusion of therapy, desensitization is typically evaluated with DBPCFC, and reported as the portion of subjects tolerating standardized dose of food or as the increase in the maximum tolerated dose of allergen compared to prior to IT. For those trials also evaluating SU, subjects avoid therapy as well as native food for a period (typically 2-12 weeks) after which DBPCFC is again undertaken. Some trials may report

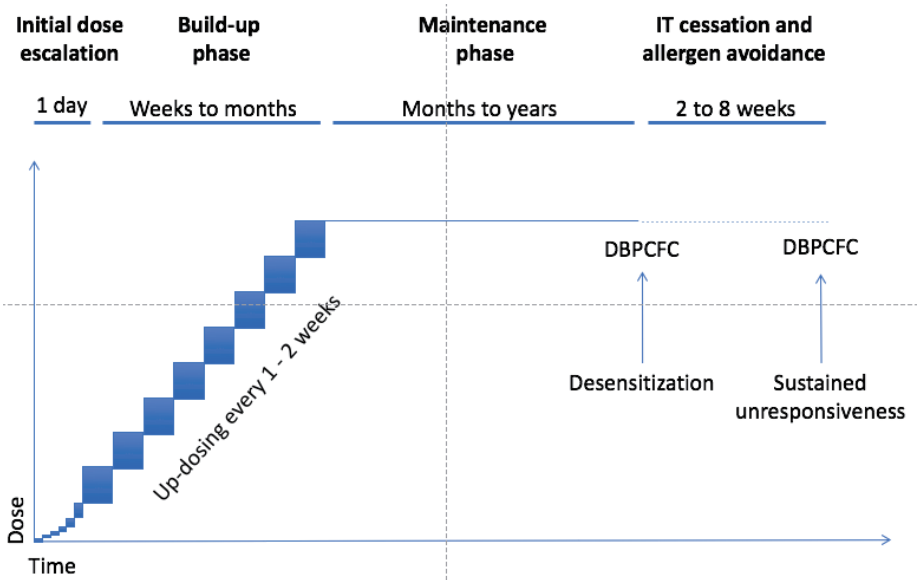

Fig. 3. Typical protocol for oral and sublingual immunotherapy. Initial doses of OIT and SLIT are generally given under medical supervision. Initial dose escalation day(s) starting at subthreshold dose with increasing doses given every 30 minutes over several hours is more common for OIT than for SLIT. Highest tolerated dose given under observation is then continued daily at home, and increased every 1 to 2 weeks under supervision during the build-up phase. The dose achieved at the end of the build-up is continued daily during a maintenance phase. After a few months or years of maintenance, double-blind placebo-controlled food challenge (DBPCFC) to the food is performed to assess for desensitization. Daily dosing may then be discontinued for a period of 4-12 weeks and reintroduced during DBPCFC, to assess sustained tolerance (SU). Reprinted from Journal of Allergy and Clinical Immunology: In Practice (Volume 5), Gernez Y and Nowak-Wegrzyn A, "Immunotherapy for Food Allergy: Are we there yet?", Page 253, 2017, with permission from Elsevier.

consumption of the food years out from therapy, to evaluate long-term success with AIT.

Divergent features of AIT trials

Direct comparison of results of various studies is hampered by variation in trial design. The following frequently differ between trials: allergic profile of individuals enrolled in the trial; duration of initial dose-escalation, build-up, and maintenance phases as well as avoidance period prior to SU-OFC; daily maintenance dose; and dose administered during OFCs to define desensitization and SU. Though all trials report moderate or severe AE as well as administration of epinephrine, reporting of minor AE may differ, with some trials reporting only what are deemed clinically-relevant dose-related AE, and others with a lower threshold to report minor AE.

SECTION 4: ORAL IMMUNOTHERAPY TRIALS

Overview of OIT trials

OIT remains a subject of active investigation, with most trials demonstrating efficacy limited by safety and compliance. Published studies have evaluated OIT with major food allergens, including milk, egg, peanut, and wheat, with safety and efficacy varying by food allergen. In recent years, investigators have evaluated OIT with modified proteins, with multiple foods, and/or combined with immunomodulatory agents.

Efficacy

Oral administration of gradually increasing quantities of food protein during OIT effectively induces desensitization in a majority of food allergic subjects, provided they can tolerate and comply with therapy. A portion of those achieving desensitization go on to demonstrate SU 2-12 weeks post-OIT.[12,24,41] For those achieving SU, long-term follow-up studies demonstrate continued consumption of offending food months to years after OIT completion.[42, 43]

Safety

The use of OIT in routine clinical practice has been limited by its AE, which are most often mild, but can include anaphylaxis, chronic gastrointestinal (GI) discomfort, and eosinophilic esophagitis (EoE). Safety varies by allergen, with milk carrying increased risk of AE compared to peanut, egg, and perhaps wheat. The majority of subjects experience some symptoms with OIT, including oropharyngeal pruritus, rhinitis, abdominal discomfort, vomiting, urticaria, angioedema, atopic dermatitis flare, cough, and wheeze. Most of the time, these are non-severe and self-resolving; sometimes administration of antihistamine, short-acting beta agonists, or systemic steroids is required. Though uncommon, most OIT trials are accompanied by a few severe reactions requiring administrations of epinephrine. Persistent, frequent, or severe symptoms often interfere with adherence and result in drop-outs accompanying virtually

every OIT trial. While severe reactions occur most often during initial dose escalation and build-up, they can occur with home administration of previously tolerated doses. A major development in reducing IgE mediated AE with OIT has been concomitant administration of omalizumab, discussed in section "OIT with omalizumab."[44]

Cofactors

Adverse reactions occurring with previously tolerated doses often occur in the setting of cofactors which lower allergic threshold, such as viral infection, febrile illness, active allergic rhinitis in the pollen season, physical exertion, or administration on an empty stomach.[45-47] To address cofactors, most OIT protocols advise dose adjustments in the setting of viral infection, avoidance of exertion in the hours following a dose, and administration after a full meal.

EoE

A meta-analysis by Lucendo and colleagues[48] concluded that EoE may develop in up to 2.7% of OIT subjects, and often resolves on withdrawal of OIT. It is possible that more subjects develop OIT-related EoE than is reported, as some discontinuing OIT for GI symptoms suspicious for EoE are not evaluated with endoscopy.[47] It is not clear whether OIT unmasks EoE to the culprit food or increases the likelihood of EoE.

Adherence

OIT requires significant commitment from families and patients in order to adhere to therapy. Families and patients need the flexibility in their schedules and access to transportation to return many times during the protocol. Initial dose escalation may require a full day (or several days depending on the protocol) in an inpatient setting. For build-up phases (which may take weeks to months), patients must return every 1 to 2 weeks for observed dosing. Finally, subjects must take their dose every day for months to years; for patients with taste aversion, parents and patients with anxiety, and families with significant life events, this may prove challenging. As a consequence, most OIT studies report withdrawals from the protocol for issues not specifically related to AE.

Quality of life (QoL)

Despite its risks and frequent adverse effects, OIT appears to improve QoL,[49] alleviating risk with accidental exposure, food-related anxiety, and social and dietary limitations.

Cost-effectiveness

Peanut-OIT with probiotic was found to be cost efficient compared to avoidance in a long-term economic model, with an incremental cost-effectiveness ratio of $2,142 per quality-adjusted life year. However, peanut-OIT subjects were more likely to experience peanut-related allergic reactions and anaphylaxis; this appeared to be of particular relevance to subjects who experience a low rate (<25%) of allergic reactions related to accidental exposure, or when probability of SU was less than 68%.[50]

Details of the specific OIT-studies are presented in the tables; cow's milk (CM; Tables 3 and 5), egg (Tables 4 and 5), peanut (Table 6), and wheat (Table 7).

OIT with omalizumab

A major development in improving safety of OIT has been the use of omalizumab (Table 8). Its use as pretreatment and continued administration through build-up offers significant protection from IgE-mediated reactions, allowing for more rapid and safe dose escalation, with less withdrawals due to dose-related AE. However, reactions to previously tolerated doses may occur after cessation of omalizumab.[44,51,52]

CM-OIT with omalizumab

In 2011, Nadeau and colleagues[44] published results of a 24-week protocol with 9 weeks of omalizumab pretreatment and 16 weeks of CM-OIT with omalizumab, followed by a maintenance phase without omalizumab. In this uncontrolled pilot study, 82% of 11 enrolled subjects reached goal daily maintenance dose, demonstrated desensitization to 7.25 g of milk protein, and subsequently continued home ingestion of >8 g milk protein daily. Though all patients experienced some AE, only 1.6% of doses elicited any reaction, significantly less than 35%-50% observed in some of the first milk OIT trials.[45,53] However, after cessation of omalizumab during maintenance therapy, 2 of 9 subjects administered EAI for moderate reactions after home doses.

Wood and colleagues[54] published results of a 30-month CM-OIT protocol in which participants were randomized to OIT with or without omalizumab until month 28. For omalizumab and placebo groups (respectively), efficacy in achieving desensitization to 10 g CM protein OFC (89% and 71%) and 8 week-SU (48% and 36%) were similar. AEs to CM-OIT were significantly reduced in the group on omalizumab: the median percent of doses with symptoms per subject were 2.1% and 16.1%, and dose-related withdrawals were 0 and 4, respectively.

Peanut-OIT with omalizumab

Schneider and colleagues recruited highly sensitized peanut allergic subjects for open-label study of peanut-OIT with omalizumab, which was given for 12 weeks preceding OIT and continued through 2 months of OIT build-up.[55] Twelve of 13 subjects reached 4 g maintenance, continued with 8 months OIT, and subsequently demonstrated desensitization to 8 g peanut protein (PP) during OFC. The most severe AEs were 2 grade 3 reactions, both of which occurred during maintenance.[55] In 2016, MacGinnitie and colleagues[47] conducted a study randomizing peanut-OIT subjects to omalizumab or placebo as pretreatment and during build-up phase to daily maintenance

Table 3. Representative milk oral immunotherapy clinical trials

Design & reference	Sample: size & age	Protocol: duration & daily maintenance dose	Outcome (by ITT) and other significant findings	Notable adverse events
Milk OIT, open-label in highly sensitized Meglio *et al.* 2004	21 subjects 5-10 years	6 months 200 mL	Milk OIT induced desensitization to daily 200 ml dose in 71% of subjects considered to have severe cow milk allergy	No reported EAI 14% developed moderate symptoms on first dose 14% had dose-limiting symptoms during build-up
Milk and egg OIT vs avoidance in young children, RCT Staden *et al.* 2007	14 milk 11 egg 20 avoidance Median 2.5 years (range 1-12 years)	Mean 21 months 100 mL cow milk 1.6 g egg	64% of OIT subjects were able to integrate allergenic food into the diet, compared to 35% of avoidance group (P=0.05); 36% of OIT group demonstrated 2-month SU	No severe AE. No EAI 9 AE-related withdrawals All active had AE, 4 with moderate AE. Among controls, 5 had moderate symptoms on accidental exposures
Milk OIT vs placebo, RCT Skripak *et al.* 2008	12 active 7 placebo 6-17 years	6 months 15 mL	Milk OIT induced desensitization, with median eliciting dose in active subject 5,140 mg compared to 40 mg in placebo (P<0.001)	1% of active doses elicited multi-system AE, vs 0 in placebo (P=0.01); 1 of 12 active withdrew due to AE
Milk OIT, Open-label follow up of Skripak 2008. Narisety *et al.* 2009	15 subjects, tolerant of 75 mL after above OIT	Median 4 months open-label following 6 months blinded 15 mL	Milk OIT induced desensitization to between 90 and 480 mL in 87%, with safety concerns	EoE in 1 subject. 6 EAI in 4 subjects. Multi-system reaction decreased from 11% in first 3 months to 4.8% in subsequent month
Milk OIT with gradual build-up vs placebo, RCT Pajno *et al.* 2010	15 active 15 placebo 4-10 years	4.5 mo 200 mL	Milk OIT with gradual outpatient build-up induced desensitization in 66% of active, vs 0 in placebo, with safety concerns	Among active group, 3 patients experienced severe AE with 2 EAI; 7 mild AE; 3 had no AE
Milk OIT vs placebo, RCT in young children Martorell *et al.* 2011	30 active 30 placebo 2-3 years	1 year 200 mL	Among young subjects, milk OIT induced 200 mL-desensitization in 90% on active, vs 23% in placebo, with safety concerns	2 EAI. 37% of subjects experienced multi-system reaction. 2 AE-related withdrawals
Low-dose OIT vs avoidance, in highly sensitized Yanagida *et al.* 2015	12 active 25 avoidance 6-13 years	1 year, with 5-day inpatient build-up 3 mL	In a highly sensitized group, low-dose OIT protocol induced 3 mL-desensitization in 58% of active and 14% of controls (P=0.018); and 25 mL-desensitization in 33% of active vs 0 of controls (P=0.007), with good safety profile	1 EAI after home dose, given for cough; no AE-related withdrawals

AE, adverse event; EoE, eosinophilic esophagitis; EAI, epinephrine auto-injector; ITT, intention to treat; OIT, oral immunotherapy; RCT, randomized controlled trial; SU, sustained unresponsiveness.

dose of 2 g. Though reaction rates were similar for omalizumab and placebo, omalizumab subjects tolerated therapy at higher doses and significantly more omalizumab subjects (79% of 29) tolerated the 4 g PP challenge 12 weeks after omalizumab cessation compared to placebo (1 of 8).

Multifood-OIT with omalizumab

Multifood-OIT addressing up to 5 foods was the subject of an open-label study, in which 25 subjects received omalizumab as pretreatment and during 8 weeks of build-up therapy to attain daily maintenance dose of 4 g food protein. All participants reached doses equivalent to a 10-fold increase in allergen tolerance by 2 months of therapy, and mean time to maintenance was just 4.5 months. Regarding safety, initial dose escalation and build-up phases were limited to mild reactions; the most severe reactions occurred during maintenance, with 0.06% of doses causing moderate chest symptoms and 0.02% moderate abdominal symptoms. One severe reaction after a home maintenance dose was treated with EAI.[52]

Recurrence of symptoms after cessation of omalizumab

Significant adverse reactions have been reported with continued OIT in the weeks following omalizumab cessation: Nadeau and colleagues[44] reported 2 moderate AE (treated with EAI) among 11 subjects; Schneider and colleagues[55] reported 2 grade 3 reactions among 13 subjects. In Begin *et al.*'s study with

Table 4. Representative egg oral immunotherapy clinical trials

Design & reference	Sample: size & age	Protocol: duration & daily maintenance dose	Outcome (by ITT) and other significant findings	Notable adverse events
Egg OIT, open-label Buchanan *et al.* 2007	7 subjects 1-7 years	24 months 0.3 g/day	Among subjects without history of anaphylaxis, 24-month egg OIT induced 8 g-desensitization in 4 of 7, with good safety profile	No severe AE. No EAI. Mild AE during initial dose escalation; 1 reaction during build-up; none during maintenance
Egg OIT in young children: see Staden *et al.* 2007 in Table 3				
Egg OIT, open-label Vickery *et al.* 2010	8 subjects 3-13 years	18-40 months maximum 3.6 g/day	Using a modified build-up protocol with IgE-dependent up-dosing, 75% achieved 3.9 g-desensitization achieved, with good safety profile	No severe AE. No EAI. Symptoms in 83% on initial dose escalation; 1 required SABA. No reactions on maintenance
Egg OIT vs placebo, RCT Burks *et al.* 2012	40 active 15 placebo 5-11 years	22 months 2 g/day	55% on active vs 0 on placebo achieved 5 g-desensitization after 10 months OIT; After 22 months OIT, 75% achieved 10 g-desensitization; 28% achieved 2 month-SU	No severe AE. No EAI. Symptoms with 25% of active vs 4% placebo. 5 AE-related withdrawals in active, vs 0 in placebo
Egg OIT, long-term follow-up of Burks *et al.* 2012 Jones *et al.* 2016	as above	Up to 4 years As above	With prolonged OIT, 50% of active subjects achieved 4 to 6-week SU to 10 g. 1 year after study conclusion, 64% of active and 25% of placebo were consuming egg (P=0.04)	No severe AE. No EAI. 12 of 22 active still reporting mild symptoms with egg at years 3 to 4
Short-course open-label egg OIT vs placebo, RCT Caminiti *et al.* 2015	17 active 14 placebo 4-10 years	4-month OIT with 5 months egg-containing diet 4 g	Abbreviated OIT protocol induced 4-g desensitization in 94% (compared to 1 of 14 in placebo), with 29% achieving 3-month SU	1 EAI during desensitization phase. 1 reaction requiring SABA and steroid during maintenance
Short-course open-label egg OIT, vs avoidance, Escudero *et al.* 2015	30 active 31 avoidance 5-17 years	3-month OIT 1 undercooked egg (3.6 g)	Abbreviated OIT protocol induced 2.8 g desensitization in 93%, with 1 month-SU in 37% (vs 1 of 31 placebo), with acceptable safety profile. All with SU were consuming at 36 months post-OIT	Symptoms with 5.9% of active doses. 5 episodes respiratory distress with 1 EAI in active group
Highly sensitized subjects, low-dose egg OIT vs avoidance, RCT Yanagida *et al.* 2016	21 active 12 avoidance 6-19 years	12 months, with 5-day inpatient dose escalation 0.1-0.2 g scrambled egg	Among subjects with history of anaphylaxis or sIgE >30 kIU/L, a modified, low-dose protocol induced 2 week-SU to 0.2 g in 71% (vs 0 of 12 controls); and SU to 1.8 g in 33%, with acceptable safety profile	No severe AE. No EAI. Symptoms with 6.5% of home doses. 2 AE-related withdrawals
High dose egg OIT vs placebo, RCT Perez-Rangel *et al.* 2017	19 active 14 placebo Mean 10.4 years	5 months; with 5-day build-up 1 undercooked egg (=3.6 g powder)/ 48 hours	A high-dose, abbreviated protocol with inpatient build-up induced desensitization to 1 undercooked egg in 89% of active subjects, vs 0 of placebo	During build-up, 2 episodes of anaphylaxis and 2 EAI. No severe AE during maintenance

AE, adverse event; EAI, epinephrine auto-injector; ITT, intention to treat; OIT, oral immunotherapy; RCT, randomized controlled trial; SU, sustained unresponsiveness.

25 subjects, all moderate reactions (with 0.06% of doses) and one severe reaction (treated with EAI) occurred during maintenance after omalizumab cessation.[52]

OIT with other immunomodulatory agents

OIT with probiotic

An Australian study has evaluated peanut-OIT combined with probiotic (PPOIT). Tang and colleagues[56] reported that 31 PPOIT subjects, who were treated with active OIT and *Lactobacillus rhamnosus* CGMCC 1.3724 (NCC4007; Nestlé Health Science, Konolfingen, Switzerland) at a fixed dose of 2×10^{10} colony-forming units (freeze-dried powder) once daily for 18 months, had higher rates of desensitization (90% vs 7%) and 2-5 week-SU (82% vs 4%) compared to 28 placebo (placebo PPOIT and placebo probiotic) subjects. Regarding safety on home dosing, the PPOIT group had 6 severe AE with 3 EAI administrations compared to 4 severe AE with 2 EAI administrations on placebo. A follow-up study published in 2017 found that after a mean of 4.2 years from cessation of PPIOT, 67% of 24 PPOIT subjects were consuming peanut on a regular basis; and 58% of 12 PPOIT

Table 5. Oral immunotherapy with modified egg and milk proteins

Design & reference	Sample: size & age	Protocol: duration & daily maintenance dose	Outcome (by ITT) and other significant findings	Notable adverse events
Baked milk OIT, open-label, in highly sensitized subjects Goldberg *et al.* 2015	15 milk OIT failures reactive to 30 mg milk 6-12 years	12 months 1.3 g baked milk/day	Among highly reactive subjects, only 20% tolerated 1.3 g/day of baked milk; those completing 12 months did have increase in challenge threshold to unheated milk	2 EAI for 2 episodes of anaphylaxis after home dosing. AE occurred at doses previously tolerated >1 mo. 53% withdrew due to IgE-mediated reactions
Hydrolyzed egg OIT, vs placebo, RCT Giavi *et al.* 2016	15 active 14 placebo No entry OFC 1-5 years	6 months 9 g hydrolyzed egg	OIT with hydrolyzed egg not effective over placebo in inducing desensitization	7 dose-related AE in active vs 2 in placebo. No severe AE or EAI
Baked egg OIT, open-label Bravin *et al.* 2016	15 subjects 5-17 years	2-9 months 6.25 g baked egg	Only 53% were able to complete the protocol. All who completed protocol subsequently tolerated boiled egg	No moderate or severe AE. No EAI. 7 were intolerant of first dose and 5 tolerated partial doses
Ultra-high temperature treated milk OIT, open-label Perezábad *et al.* 2017	20 subjects 1-11 years	18-36 months 25 g goat and sheep milk sheep (30% protein)	70% achieved desensitization to 200 mL cow milk within 24 months	57% among the 14 achieving desensitization had mild reactions. Among the 6 who did not, there were more severe reactions (including anaphylaxis) and 2 AE-related withdrawals

AE, adverse event; EAI, epinephrine auto-injector; ITT, intention to treat; OFC, oral food challenge; OIT, oral immunotherapy; RCT, randomized controlled trial.

subjects demonstrated 8-week SU, compared to 1 of 12 placebo.[43] The impact of this RCT is significantly limited by the lack of a proper control for the effect of peanut-OIT alone as well as the lack of blinding and no DBPCFC to confirm peanut allergy at baseline.

OIT with Chinese herbs

FAHF-2 is a 9-herb formula based on traditional Chinese medicine that blocks peanut-induced anaphylaxis in a murine model. In phase I studies, FAHF-2 was found to be safe and well tolerated; there was laboratory evidence of immunomodulation without appreciable clinical benefit. No significant differences in allergen-specific IgE and IgG_4 levels, cytokine production by peripheral blood mononuclear cells (PBMCs), or basophil activation between the active and placebo groups were detected. *In vitro* studies reported that subjects' baseline PBMCs incubated with FAHF-2 and food allergen produced significantly less IL-5, greater IL-10 levels, and increased numbers of Treg than untreated cells.[57] A clinical trial is underway evaluating combination of FAHF-2, multi-food-OIT, and omalizumab (NCT 02879006).

SECTION 5: SLIT TRIALS

Overview of SLIT trials

SLIT trials have evaluated utility in treatment of hazelnut, peanut, and CM allergy (Table 9).[13,31,58,59] SLIT significantly increases threshold for reactivity in subjects who comply with therapy, though with reduced efficacy compared to OIT.[24,26] AE, which are typically mild and limited to oropharyngeal pruritus, are common in SLIT. Moderate and severe AE occur with less frequency in SLIT compared to OIT.[13] Cofactors, as described with OIT, appear to lower threshold for reactivity to SLIT.[58] Occurrence of EoE in association with aeroallergen SLIT[60,61] suggests a theoretic risk for EoE with food SLIT.

SLIT trials

Hazelnut-SLIT

The first SLIT trial published in 2005 reported desensitization to 20 g hazelnut (approximately 14 hazelnuts) in 50% of 12 SLIT subjects compared to 9% of 11 placebo subjects, after 8-12 weeks of therapy. Mean eliciting dose increased significantly from 2.3 to 11.6 g in SLIT subjects ($P=0.02$). Regarding safety, there were 3 systemic reactions, all of which occurred during build-up and responded to antihistamine. Mild reactions accompanied 7.4% of doses.[58]

Peanut-SLIT

Using a 12-18 month peanut-SLIT protocol enrolling subjects aged 12-37 years, Kim and colleagues[13] reported that 11 active younger SLIT subjects (1-11 years) consumed 20 times more peanut than 7 subjects randomized to placebo. Compliance was similar on SLIT and placebo. Symptoms accompanied 11.5% of active and 8.6% of placebo doses; 0.26% of home SLIT doses were treated with antihistamine, 1 with albuterol; none with EAI. Using a 44-week SLIT protocol among older SLIT

Table 6. Representative peanut oral immunotherapy clinical trials

Design & reference	Sample: size & age	Protocol: duration & daily maintenance dose	Outcome (by ITT) and other significant findings	Notable adverse events
Peanut OIT open-label Jones *et al.* 2009	39 subjects 1-16 years	36 months 1.8 g	Peanut OIT induced 3.9 g-desensitization in 74% of subjects with acceptable safety	3.7% of home doses were accompanied by symptoms; 0.8% requiring treatment, with 2 EAI 4 AE-related withdrawals
Peanut OIT open-label Blumchen *et al.* 2010	23 subjects 3-14 years	Median 9 months, with 7-day rush 0.5 g minimum	Using a shorter protocol, 61% reached target daily dose of 500 mg. At 1-wk SU OFC, median highest tolerated dose was 1 g. Safety concerns persist despite lower target maintenance, primarily among asthmatics	0.3% of doses accompanied by AE. 4 AE-related withdrawals all due to asthma exacerbations, with one hospitalization
Peanut OIT vs placebo, RCT Varshney *et al.* 2011	19 OIT 9 placebo 1-16 years	12 months 5 g	Peanut OIT induced 5-g desensitization in 84% of active subjects, vs 0 on placebo ($P<0.001$), with acceptable safety profile	2 EAI with initial dose escalation; no EAI after home dose (except in placebo arm) 3 AE-related withdrawals
Peanut OIT open-label Anagnostou *et al.* 2011	22 subjects 4-18 years	9-17 months 0.8 g	Peanut OIT with lower maintenance dose of 800 mg induced 6.6 g-desensitization in 64% of subjects, with acceptable safety profile	No EAI. 0 AE-related withdrawals. 86% experienced some AE with doses. 0.4% of build-up & 0.3% of maintenance doses required SABA
Peanut OIT vs avoidance, RCT Anagnostou *et al.* 2014	49 OIT 46 avoidance 7-16 years	6 months 0.8 g	In a study inclusive of subjects with life-threatening anaphylaxis to peanut, peanut OIT induced 1.4 g-desensitization in 50% of active subjects, compared to 0 on avoidance, with acceptable safety profile	2 home EAI in 1 participant Wheeze after 0.41% of doses in 22% of participants; 4 AE-related withdrawals
Follow up of Jones 2009; Peanut OIT open-label Vickery *et al.* 2014	39 subjects 1-16 years	22 months 4 g max	4 week SU to 5 g achieved in 31% of enrolled subjects and 50% of subjects completing the protocol. All subjects with SU were consuming peanut 40 months post-OIT	6 AE-related withdrawals
Low vs high dose Peanut OIT in young subjects Vickery *et al.* 2017	20 low dose 17 high dose 9-36 months	29 months 0.3 g or 3 g	Among younger subjects, low and high dose OIT had similar outcomes, inducing 5 g-desensitization in 81% of subjects and 1 month-SU in 78%, with good safety profile	No severe AE; no EAI. 95% of subjects had some dose-related AE, mostly mild, 15% moderate. 2 AE-related withdrawals
Standardized peanut OIT product vs placebo, multicenter RCT Bird *et al.* 2017	29 OIT 26 placebo 4-26 years	5-9 months 0.3 g	With active OIT, 79% and 62% tolerated 0.443 g and 1.043 g with minimal or no symptoms, respectively; compared to 19% and 0% on placebo ($P<0.0001$), with good safety profile	93% of active and 46% of placebo groups experienced dose-related AE. Mostly mild, 4-6% moderate, none severe. 6 AE-related withdrawals, 4 due to GI symptoms

AE, adverse event; EoE, eosinophilic esophagitis; EAI, epinephrine auto-injector; GI, gastrointestinal; ITT, intention to treat; OFC, oral food challenge; OIT, oral immunotherapy; RCT, randomized controlled trial; SU, sustained unresponsiveness.

Table 7. Wheat oral immunotherapy clinical trials

Design & reference	Sample: size & age	Protocol: duration & daily maintenance dose	Outcome (by ITT) and other significant findings	Notable adverse events
Wheat OIT, Open-label Rodriguez del Rio *et al.* 2014	6 subjects 5-11 years	6-7 months 10.6 g	OIT with wheat induces desensitization in most subjects (5 of 6), with acceptable safety profile	Symptoms with 6.25% of up-doses 2 urticarial reactions during maintenance
Wheat OIT open-label, in highly sensitized subjects Sato *et al.* 2015	18 active; 11 historical controls 5-14 years	2 years 5.2 g	Among highly-sensitized subjects, wheat OIT induces 2-week SU to 5.2 g in 61%, compared to 9% of historical controls avoiding wheat	Symptoms with 6.8% of outpatient doses, with 1 EAI administration

EAI, epinephrine auto-injector; ITT, intention to treat; OIT, oral immunotherapy.

Table 8. Oral immunotherapy with omalizumab

Design & reference	Sample: size & age	Protocol: duration & daily maintenance dose	Outcome (by ITT) and other significant findings	Notable adverse events
Milk OIT with omalizumab Nadeau *et al.* 2011	11 subjects 7-17 years	6 months, first 4 months with omalizumab 2 g	With concomitant administration of milk OIT and omalizumab, 82% achieve DS to 2 g 8 weeks post-omalizumab; and subsequently ingested >8 g milk protein at home.	Just 1.6% of doses elicited any reaction; After omalizumab cessation, 2 had moderate AE for which EAI given
Milk OIT with or without omalizumab, RCT Wood *et al.* 2016	27 omalizumab 18 placebo 7-32 years	28 months, all with omalizumab 520 mg	While efficacy in achieving DS to 10 g and 8-wk SU were not different with and without omalizumab, AEs were significantly reduced in active group.	Omalizumab group had reduced reactions (2% vs 16%) and reduced drop-out (2 vs 5) EoE reported in placebo
Milk or egg OIT with omalizumab Martorell-Calatayud *et al.* 2016	14 subjects, 5 cow milk allergic, 9 egg allergic 3-11 years	14 months, first 2 months with omalizumab 200 mL milk 1.8 g egg	In a group of 14 subjects unable to tolerate conventional OIT, all were able to achieve maintenance dose while on omalizumab, though some relapsed after omalizumab cessation	60% of cow milk allergic and 33% of egg allergic developed anaphylaxis between 2.5 and 4 months after cessation of omalizumab
Peanut OIT with omalizumab Schneider *et al.* 2013	13 subjects, highly sensitized 7-15 years	8 months, with omalizumab for first 2 4 g	Even among highly sensitized, omalizumab allows for safe and effective DS, with 92% completing protocol and achieving DS to 8 g	2 grade 3 reactions during maintenance
Peanut OIT, with or without omalizumab, RCT MacGinnitie *et al.* 2017	29 omalizumab 8 placebo 6-19 years	4 months, 1st month with omalizumab 2 g	Omalizumab-treated subjects tolerated OIT at higher doses, with 79% of active achieving DS (to 2 g), vs 1 of 8 placebo. These 79% went on to demonstrate DS to 4 g 12 weeks post-omalizumab	Reactions after 7.8% active vs 16.8% placebo (P=0.15) EAI admin: Active 4, placebo 3 EoE: active 1, placebo 1
Multi-food OIT with omalizumab Begin *et al.* 2014	25 subjects 4-15 years	6 months, first 4 months with omalizumab 4 g per protein	OIT with omalizumab enabled all participants on OIT with up to 5 foods to achieve doses 10-fold higher than eliciting dose at enrollment	All moderate (at least 0.06% of doses) and severe (1 EAI admin) reactions, occurred during maintenance

AE, adverse event; DS, desensitization; EAI, epinephrine auto-injector; EoE, eosinophilic esophagitis; ITT, intention to treat; OFC, oral food challenge; OIT, oral immunotherapy; RCT, randomized controlled trial; SU, sustained unresponsiveness.

subjects (12-37 years), Fleischer and colleagues[59] reported that 70% of 20 SLIT subjects were considered responders (ingested 5 g PP or 10-fold more than baseline), compared to 15% of 20 on placebo (P<0.001). Symptoms accompanied 37% of doses; 2.9% required treatment, with 1 administration of albuterol and 1 of EAI (during build-up). In open-label follow-up study of the same subjects, 11% of 37 subjects continuing with SLIT were desensitized to 10 g PP, with all 4 subsequently demonstrating 8-week SU. There were no EAI administrations. Twenty-five withdrew for various reasons, including 2 for dose-related AE.[31]

SLIT vs OIT trials

Trials compareing SLIT and OIT are presented in Table 10.

Peanut-SLIT vs OIT

Peanut-OIT subjects experienced a 141-fold mean increase in the highest tolerated dose compared to a 22-fold mean increase among SLIT-subjects after 1 year of therapy. One-month SU was achieved by 3 of 10 OIT-subjects compared to 1 of 10 SLIT. SLIT-subjects experienced less severe AE, with 5 EAI administrations related to OIT vs none with SLIT.[26]

CM-SLIT vs OIT

In a study comparing CM-SLIT alone to therapy with SLIT for initial up-dosing followed by CM-OIT, SLIT/OIT subjects were significantly more likely to demonstrate desensitization (70% of 20) and 6-week SU (40% of 20) compared to subjects receiving SLIT alone (1 of 10). Multisystem reactions and medical intervention (antihistamine, albuterol, and EAI) were more frequent with OIT.[24]

SECTION 6: EPIT TRIALS

Overview of EPIT

Peanut and CM-EPIT have been shown to increase threshold for reactivity in 3 published trials.[6] Though efficacy is more modest compared to OIT and SLIT, EPIT appears to have a more favorable side effect profile. Most AEs are limited to local cutaneous symptoms at the patch application site; occasional systemic reactions have been non-severe and resolved with an-

Table 9. Clinical trials of sublingual immunotherapy

Design & reference	Sample: size & age	Protocol: duration & daily maintenance dose	Outcome (by ITT) and other significant findings	Notable adverse events
Hazelnut SLIT vs placebo, RCT Enrique *et al.* 2005	12 active 11 placebo 18-60 years	8 to 12 weeks 13 mg	Hazelnut SLIT induced desensitization in 50% of active subjects tolerating 20 g hazelnut after therapy, vs 9% placebo, with good safety profile	Mild reactions in 7.4% of doses; systemic reactions in 0.2% (N=3), all during build-up. No EAI
Peanut SLIT vs placebo, RCT Kim *et al.* 2011	11 active 7 placebo 1-11 years	12 to 18 months 2 mg	Peanut SLIT induces desensitization, with active group ingesting 20-fold more protein than placebo (P=0.011), with good safety profile	Symptoms with 11.5% of active doses, vs 8.6% placebo. 1 home dose required albuterol. No EAI
Peanut SLIT vs placebo, RCT Fleischer *et al.* 2013	20 active 20 placebo 12-37 years	11 months 165 to 1,385 μg	Peanut SLIT induces desensitization in a majority: 70% of active tolerated 5 g or ingested 10-fold more than at baseline, vs 15% of placebo (P<0.001), with good safety profile	Symptoms with 37% of doses; 2.9% of doses require treatment, with 1 administration of albuterol and 1 EAI, during build-up
Peanut SLIT, long-term follow-up of Fleisher *et al.* 2013 Burks *et al.* 2015	37 active	3 years dose as above	With 3 years peanut SLIT, only a portion (11%) of subjects achieved desensitization and 8-wk SU to 10 g, with good safety profile, but high (>50%) drop-out rate	2% of doses with symptoms; no severe AE, no EAI. 2 AE-related withdrawals

AE, adverse event; EAI, epinephrine auto-injector; ITT, intention to treat; OFC, oral food challenge; OIT, oral immunotherapy; RCT, randomized controlled trial; SLIT, sublingual immunotherapy.

Table 10. Clinical trials comparing oral and sublingual immunotherapy

Design & reference	Sample: size & age	Protocol: duration & daily maintenance dose	Outcome (by ITT) and other significant findings	Notable adverse events
Milk SLIT followed by OIT, vs milk SLIT alone, RCT Keet *et al.* 2012	20 SLIT/OIT 10 SLIT 6-17 years	15 months OIT 1 g or 2 g; SLIT 7 mg	SLIT/OIT therapy was more effective than SLIT alone in inducing desensitization (70% vs 10%) and SU (40% vs 10%); though safety profile was better in SLIT. Some lost clinical desensitization 1 week off OIT	Multisystem AE and β-agonist therapy for AE were higher on SLIT/OIT than SLIT alone (IRR 11.5 and 8.6, P<0.001). 4 EAI in SLIT/OIT; 2 in SLIT alone
Peanut OIT vs SLIT, RCT Narisety *et al.* 2015	11 OIT 10 SLIT 7-13 years	12 to 18 months OIT 2 g SLIT 3.7	OIT was more effective than SLIT in inducing desensitization, with 141- vs 22-fold increase in highest tolerated dose (P=0.01), with SLIT having the better safety profile	AE more common with OIT doses (43% vs 9%, P<0.001), including moderate AE (3.4% vs 1.3%, P<0.001). 5 EAI on OIT vs 0 on SLIT

AE, adverse event; EAI, epinephrine auto-injector; ITT-intention to treat; OFC, oral food challenge; OIT, oral immunotherapy; RCT, randomized controlled trial; SLIT, sublingual immunotherapy; SU, sustained unresponsiveness.

tihistamine. With reduced AE and fewer visits at a medical facility for up-dosing, adherence might be better with EPIT compared to OIT and SLIT.

EPIT trials

EPIT clinical trials are summarized in Table 11. The randomized, double-blind, placebo-controlled phase 1b trial of peanut-EPIT conducted in 5 centers in the US included 100 subjects, aged 6-50 years, randomized 4:1 (peanut/placebo) to receive Viaskin Peanut (VP) treatment in dosing cohorts at doses of 20, 100, 250, and 500 μg or placebo. This trial reported an overall acceptable safety and tolerability after 2 weeks of therapy. There were no severe AE and no EAI administrations; 2 systemic reactions were thought to be related to protein transfer to mucosal surface. Three of 49 active subjects withdrew due to treatment-related symptoms.[7]

In the multicenter-RCT conducted by the Consortium for Food Allergy Research, 74 peanut allergic individuals (ages 4-25 years) were treated with placebo (n=25), VP 100 μg (n=24) or VP 250 μg (n=25), for 52 weeks. The primary outcome was defined as passing a 5,044-mg PP DBPCFC or achieving at least 10-fold increase in successfully consumed dose from baseline. Treatment success was seen in 3 (12%) placebo-treated participants, 11 (46%) VP100-participants, and 12 (48%) VP250-participants (P=0.005 and P=0.003, respectively, compared with placebo; VP100 vs VP250, P=0.48). Median changes in success-

Table 11. Clinical trials of epicutaneous immunotherapy

Design & reference	Sample: size & age	Protocol: duration & daily maintenance dose	Outcome (by ITT) and other significant findings	Notable adverse events
Milk EPIT vs placebo, RCT Dupont *et al.* 2010	10 active 9 placebo 10 months-8 years	3 months of 3 48-hour applications per week, 1 mg	Milk EPIT resulted in a non-significant increase in mean maximum tolerated dose from 1.8 mL to 28 mL (P=0.18), with good safety profile	Local AE in 4 active subjects vs 2 placebo; 24 systemic AE in active group, vs 8 in placebo No anaphylaxis or EAI
Peanut EPIT vs placebo, RCT Jones *et al.* 2016	49 active 20 placebo 5-50 years	2 weeks with 4 different patch doses, 20-500 μg	2 weeks peanut EPIT was safe and well tolerated	2 systemic reactions; no severe AE and no EAI
Peanut EPIT vs placebo, RCT Jones *et al.* 2017	49 active 25 placebo 4-25 years	52 weeks, 100 or 250 μg	47% of active tolerated 5 g OFC or had 10-fold increase in successfully consumed dose, vs 15% in placebo. Treatment success more likely in <11 years	Reactions extending beyond patch site occurred in 0.1% active, one with systemic hives
Peanut EPIT vs placebo, RCT Preliminary results released Oct 2017	10 active 6 placebo 4-11 years	52 weeks, 250 μg	35.3% of active vs 13.6% of placebo demonstrated significant response. Mean cumulative reactive dose of 44 mg in active vs 144 mg placebo, with significant increase from baseline (P<0.001)	4 treatment-related serious AE in 3 active subjects; no severe anaphylaxis. 1.1% drop-out rate due to treatment-emergent AE

AE, adverse event; EAI, epinephrine auto-injector; EPIT, epicutaneous immunotherapy; ITT, intention to treat; OFC, oral food challenge; RCT, randomized controlled trial; SU, sustained unresponsiveness.

fully consumed doses were 0, 43, and 130 mg PP in the placebo, VP100-, and VP250-groups, respectively (placebo vs VP100, P=0.014; placebo vs VP250, P=0.003). Treatment success was higher among younger children (P=0.03; age 4-11 vs >11 years). Regarding AE, 80% of EPIT doses had local reactions vs 14.4% placebo. Non-patch site reactions were reported at similar frequency in EPIT and placebo-groups (0.1% and 0.2%, respectively); no EAI or albuterol was required. There were 3 withdrawals from each group, one for treatment-related symptoms in the EPIT group.[6]

In October 2017, preliminary results of Peanut EPIT Efficacy and Safety (PEPITES) phase III trial evaluating the safety and efficacy of VP in children 4-11 years of age were released (https://globenewswire.com/news-release/2017/10/20/1151107/0/en/DBV-Technologies-Announces-Topline-Results-of-Phase-III-Clinical-Trial-in-Peanut-Allergic-Patients-Four-to-11-Years-of-Age.html). PEPITES reported a statistically significant response, with 35.3% of patients responding to VP 250 μg after 12-months, compared to 13.6% of placebo-patients (difference in response rates=21.7%; P<0.001; 95% confidence interval [CI], 12.4%-29.8%). The primary endpoint, defined as the 95% CI in the difference in response rates between the active and placebo arms, did not reach the 15% lower bound of the CI that was proposed in the study's Statistical Analysis Plan (SAP).

Regarding the Cumulative Reactive Dose (CRD), a key secondary endpoint measuring threshold reactivity during DBPCFC at month-12, patients treated with VP 250 μg and placebo reached a median CRD 444 mg and 144 mg PP, respectively. Median CRD at baseline was 144 mg in both groups. This increase from baseline was statistically significant compared to placebo (P<0.001). PEPITES reported 12 serious adverse events (SAEs) in 10 active-subjects (4.2%), and 6 SAEs in 6 placebo-subjects (5.1%); 4 SAEs in 3 active-subjects (1.3%) were possibly related to treatment; no SAE qualified as severe anaphylaxis. The most commonly reported AEs were mild-moderate patch application site reactions. The discontinuation rate was 10.1%, comparable between the active- and placebo-arms, with a 1.1% dropout rate due to treatment emergent AEs. Mean patient adherence exceeded 95%.

SECTION 7: CLINICAL TRIALS OF ADDITIONAL FORMS OF AIT

Other forms of AIT include SCIT with alum-adsorbed hypoallergen and LAMP-DNA vaccine, both of which are being actively investigated in human subjects. A phase IIb clinical trial evaluating safety and efficacy of SCIT with alum-adsorbed, recombinant fish allergen parvalbumin (NCT02382718) is completed but not as yet published. Preliminary results of a phase I clinical trial evaluating safety and immunomodulation with alum-adsorbed chemically modified peanut extract (NCT02851277)[38] have been presented in an abstract form. Subjects were randomized to receive 15-20 incrementally increasing weekly doses of study product (HAL-MPE, n=17) or placebo (n=6). Local and systemic reactions were observed more often in the active group; no late (>4 hours after therapy) systemic reactions were

observed. Authors concluded that the therapy was safe and well tolerated.[38]

Two additional forms of AIT, including SCIT with native peanut allergen and rectally-administered modified PP, were previously studied in humans and abandoned due to unacceptable safety profile.[62-64]

SECTION 8: AIT IN CLINICAL PRACTICE

AIT in today's clinical practice

Currently available AIT

Of various modalities of AIT, OIT is the only therapy currently accessible to physicians and patients, as food may be delivered in native form and may be purchased and/or prepared at home. While some physicians have begun offering OIT to families who are eager for therapy, OIT in the clinical setting continues to carry risks observed in research studies: in a retrospective chart review of 352 patients undergoing peanut-OIT in clinical practice, patients did experience 95 severe reactions requiring epinephrine.[65]

Current recommendations for OIT in clinical practice

Experts have yet to recommend that OIT be part of routine clinical practice, due to safety concerns and uncertainty regarding duration of tolerance, even following prolonged therapy. One exception to this is regular ingestion of baked goods among milk- and egg-allergic children, which appears to safely hasten tolerance acquisition to unheated milk and egg.[66,67] OIT with native food proteins remains a risky endeavor; and protocols for subject selection and administration of OIT in clinical practice are lacking.

Subject-selection for OIT

When guidelines for OIT in clinical practice become available, selecting appropriate subjects for therapy will be as important as protocol design. There are currently no strict criteria to assist practitioners in choosing subjects for OIT. Patients who are highly sensitized or at high risk for severe anaphylaxis may not be appropriate candidates for OIT. Lower threshold dose at entry challenge, higher sIgE, increased sIgE: total IgE ratio, larger SPT wheal diameter, and personal history of asthma or allergic rhinitis were associated with worse outcomes, as measured by frequency of severe AE, adherence to treatment, and demonstration of desensitization and SU.[12,68,69] Virtually every OIT trial excludes subjects with history of severe anaphylaxis, uncontrolled asthma, or other chronic conditions and medications which may put subjects at higher risk for more severe reactions; OIT has thus not been studied in and would not be appropriate for patients with these characteristics.

Most food-allergic patients may be of milder phenotype than those included in OIT trials: while entry OFC for clinical trials requires reactivity at doses <100-300 mg, most reactions (55%) during OFC in practice occur at doses >250 mg.[70] Therefore, OFC outcomes among the majority of food-allergic subjects will be better than reported in clinical trials.

Factors unrelated to reactivity will also be important in providing safe and effective OIT. Risks of OIT may be unacceptable among patients and families who express hesitance in administering epinephrine, or who do not understand the importance of dose adjustments for and avoidance of cofactors, which lower threshold for reactivity. Compliance with therapy is likely to be hampered by anxiety surrounding dose administration, taste aversions, and insufficient resources to ensure daily dose administration and regular follow-up.

Discussion of OIT should take place in the context of a growing body of evidence on OIT as well as changing landscape of AIT for FA. With SLIT and EPIT likely to become available in the next few years, it may be that waiting for a safer option is a better strategy. Alternatively, it may become clear that immunotherapies are more effective and/or safer in younger children, and should be started sooner rather than waiting for another therapy to become available. Evidence on the safe and effective use of OIT will continue to accumulate in the coming years, with guidelines from experts likely to follow.

Selecting among AIT options in clinical practice in the future

OIT, SLIT, and EPIT for major food allergens are likely to be part of FA-management in the coming years. Depending on outcomes of other clinical trials for LAMP-DNA peanut vaccines and SCIT with hypoallergens, these too may be options. With availability of multiple options, sufficient understanding of AIT will be necessary to evaluate appropriateness of therapy for individual patients. Clinicians will need to engage patients and families in a discussion of realistic outcomes and adverse effects. This discussion will not only be guided by clinical history and allergy testing, but also by assessment of the patient's and family's goals and ability to adhere to protocols.

Combination therapy may prove to be a helpful strategy if and when multiple therapies are available. As has already been done in some clinical trials, a subject may initiate therapy with SLIT, and then transition to OIT. Sufficient desensitization with a few years of EPIT might make more effective therapies such as OIT a safer option in the future. Immunomodulatory therapies such as omalizumab, dupilumab, probiotic bacteria, and/or Chinese herbs may be combined with AIT to improve safety and efficacy.

SECTION 9: FUTURE DIRECTIONS

There is a race to develop commercial treatment for FA fueled by increasing prevalence and severity of food allergies in children, particularly peanut allergy. The multi-center phase III clinical trials of peanut-OIT and EPIT are ongoing. Approved, standardized protocols for food immunotherapy that can be

safely and effectively implemented in clinical practice are needed. We also need to establish the minimum effective and safe maintenance dose, duration of AIT, and frequency of maintenance dosing for long-term therapy. Considering that at least 30% of those with persistent FA are allergic to multiple foods, treatments for milk, egg, wheat, tree nuts, seeds, fish, and shellfish allergy, as well as approaches for combining multiple foods, are desirable. Approaches to mitigating side effects of AIT, as well as mechanisms to enhance efficacy and development of permanent oral tolerance such as adjuvants, nanoparticles, DNA vaccines, or combined therapies, need to be explored. Biomarkers predictive of the favorable response to AIT are highly desirable. Patients with the most severe phenotype of life-threatening anaphylaxis are currently excluded from clinical trials, yet they are in the dire need of effective treatment that can be adhered to long-term as it is obvious that such patients will need most likely a life-long therapy. Tremendous progress has occurred in the past decade but the permanent cure for FA remains elusive and further research into tolerance development is necessary.

CONCLUSION

Emergence of FA as a global health problem underscores the importance of research to develop effective treatment strategies. A growing body of evidence supports the concept of AIT for subsets of food-allergic patients. Currently studied therapies have significant efficacy limitations and associated adverse effects, and do not offer reassurance regarding long-term protection following discontinuation of treatment. The equipoise between AIT vs food avoidance is reflected by the lack of official guidelines from the allergy societies and regulatory agencies and lack of standardized products. Hopefully within the next few years, clinicians will gain a better understanding of the utility of AIT, discover biomarkers predictive of favorable outcomes and develop strategies to enhance safety and efficacy of AIT.

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