

Food Allergy Immunotherapy with Adjuvants



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KEYWORDS

• Food allergy • OIT • SLIT • EPIT • Adjuvant therapy • Modified allergens

KEY POINTS

- Emerging forms of immunotherapy for food allergy (OIT, SLIT, and EPIT) have shown significant promise, but remain limited by concerns about efficacy, durability of effect, and/or safety.
- The next generation of treatments for food allergy will aim to improve the efficacy and/or safety of existing immunotherapy through immunomodulation.
- Future therapies will also aim to benefit patients suffering from multiple food allergies through effects that are not allergen-specific.

BACKGROUND/INTRODUCTION

Symptoms of food allergy typically develop in early childhood with approximately 8% of children believed to have a food allergy in the United States,¹ and recent

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research suggests as many as 10.8% of US adults may have a food allergy.² At the present time there is no Food and Drug Administration (FDA)-approved therapy for treatment of food allergies and affected individuals must strictly avoid allergens in their diet while carrying auto-injectable epinephrine at all times. The burden of disease of food allergy is impacted by the continuous vigilance required to avoid ubiquitous food allergens and the potentially life-threatening nature of an anaphylactic reaction. The most commonly studied interventional therapies (oral immunotherapy [OIT], sublingual immunotherapy [SLIT], and epicutaneous immunotherapy [EPIT]) fall short in providing a completely satisfactory treatment for all patients. These approaches require daily exposure to allergen, and the pros and cons of each therapy have prevented allergists and patients alike from universal enthusiastic acceptance of one modality as superior to avoidance for all food allergic patients. This review briefly reviews the aforementioned therapies and expands on investigative therapies with potential future benefit.

OVERVIEW OF ORAL, SUBCUTANEOUS, EPICUTANEOUS, SUBCUTANEOUS IMMUNOTHERAPY

OIT is performed by gradually increasing the amount of allergen ingested over a period of time until a “maintenance dose” of allergen is attained. The initial doses of allergen are less than the triggering threshold. After an initial escalation day, participants return biweekly for dose escalation until the therapeutic dose is achieved. Peanut OIT has been studied more rigorously than OIT with other foods, and a recent phase 3, international, placebo-controlled trial using a standardized, manufactured peanut OIT product (AR101, Aimmune Therapeutics) showed that 67.2% of participants by intention to treat (85% of completers) met the primary endpoint, the ability to ingest 600 mg of peanut protein or more, without dose-limiting symptoms, after approximately 6 months of daily ingestion of 300 mg of peanut protein, whereas only 4% of placebo participants achieved this endpoint.³

Other methods of desensitization under investigation have been less successful in ensuring a consistent level of protection. SLIT involves placing a small amount of solubilized allergen under the tongue. Top SLIT doses are typically at least 1/100th those of maintenance OIT doses. The largest peanut SLIT trial to date enrolled 40 peanut-allergic adolescents and adults, evenly assigning patients to treatment and placebo.⁴ A 10-fold or more increase in the reaction-triggering threshold was achieved by 70% of subjects assigned to treatment compared with 15% of placebo subjects. The median reactive dose increased from 3.5 mg to 496 mg after 44 weeks of therapy.

EPIT delivers allergen via an adhesive patch. Natural water loss from the skin displaces allergen from the patch and resident Langerhans cells (LC) selectively deliver antigen to local lymph nodes, initiating an immunologic response. EPIT patches contain 250 µg of peanut allergen, at least 1/100th that of typical SLIT doses and at least 1/1000th that of OIT doses. A recent phase 3 trial enrolled 356 participants and demonstrated a responder rate of 35.3% in peanut-patch-treated subjects versus 13.5% of placebo-treated subjects.⁵

Subcutaneous immunotherapy (SCIT) has been used for more than 100 years for treatment of environmental allergen sensitivities. SCIT for peanut allergy using intact allergen without modification or adjuvant has been studied in few subjects and abandoned as a therapeutic option because of frequent anaphylaxis and a high dropout rate.^{6,7}

The balance between efficacy and safety is not perfectly met with any of the preceding therapeutic options. Although adverse effects (AEs) from peanut OIT are generally

mild, they certainly exceed those of standard allergen avoidance or of patients receiving placebo, and use of auto-injectable epinephrine in treatment subjects significantly exceeds that of placebo-treated subjects.⁸ Patients receiving SLIT and EPIT do not typically experience AEs on the same scale as patients receiving OIT; however, the safety benefit is met with a sacrifice in margin of efficacy for some patients, and at the present time serum biomarkers are not available to predict which patients will benefit most from which therapy. Each of the therapies, when effective, is believed to most often induce a transient state of benefit that diminishes with removal of the therapy or abstinence from the allergen for most allergic individuals. With these facts in mind, it is important to consider alternative approaches with adjuvants that would both augment the allergic response and protect the allergic individual from potential AEs.

IMMUNE MECHANISMS OF FOOD IMMUNOTHERAPY

Regardless of approach, the end-effect of immunotherapy is to increase the regulatory T-cell response and downregulate the manifestation of allergic symptoms associated with IgE cross-linking on mast cells and basophils. Allergen is initially taken up by dendritic cells and antigen-presenting cells (APCs). Dendritic cells migrate to local lymph nodes and induce production of allergen-specific regulatory T cells characterized by increased production of interleukin (IL)-10 and transforming growth factor (TGF)-beta.⁹ TGF-beta suppresses mast cell reactivity, primarily through downregulation of FCεR1 on the cell surface of tissue mast cells and blood basophils. Concomitantly, Th1 production of interferon (IFN)-γ induces class-switch to immunoglobulin (Ig)E and increases specific IgG and IgA production. Allergen-specific IgG plays a crucial role by both binding and neutralizing allergen and through the induction of inhibitory signaling via FCγRIIB on mast cells and basophils. Prolonged exposure to allergen may lead to additional changes, including anergy and deletion of allergen-specific Th2 cells through repeated and frequent exposure to high doses of allergen, as has been demonstrated in patients receiving timothy grass pollen SCIT.⁹ Additional changes specific to the type of therapy being used are outlined as follows.

OIT takes advantage of T regulatory cell (Treg) induction within gut-associated lymphoid tissue. In the initial stages of OIT, an increase in allergen-specific IgE is noted along with stimulation of resident Th2A cells and initial differentiation of naïve T cells into allergen-specific Th2 cells, increasing the proinflammatory response.¹⁰ Repeated exposure to allergen leads to IgE endocytosis and actin rearrangement on mast cells and basophils, making these cells hyporesponsive. Over time, the Th2 cellular response decreases and allergen-specific IgG4 increases with a concomitant decrease in allergen-specific IgE. The Treg response strengthens with enhanced epigenetic modifications at the Foxp3 locus.

SLIT allows for allergen uptake through LCs in the sublingual ductal epithelial cells.⁹ The safety of SLIT is associated with the relative paucity of mast cells and eosinophils in oral tissues.¹¹ Oral APCs exhibit a tolerogenic phenotype with LCs producing IL-10 and TGF-beta and expressing indoleamine 2,3-dioxygenase and macrophages producing IL-10, IL-12 and expressing retinaldehyde dehydrogenase 2 (RALDH-2). The default response of oral LCs, in the absence of allergen stimulation, is tolerance rather than inflammation. SLIT adjuvants take advantage of the default response and are primarily aimed at enhancing the induction of allergen-specific Th1 and/or Treg-cell responses via directed signaling to oral LCs and macrophages.

EPIT presents antigen to local LCs found in intact, noninflamed skin and allergen is undetectable in the peripheral circulation.¹² It has been theorized that EPIT may induce longer lasting protection than OIT or SLIT through the generation of

gut-homing LAP + Foxp3- Tregs, which suppress mast cell activation via TGF- β -dependent mechanisms.¹³ OIT also induces gut-homing Tregs; however, EPIT-induced Tregs have been shown to retain suppressive activities longer than those induced by OIT.¹⁴

LIMITATIONS OF FOOD IMMUNOTHERAPY

Immunotherapy for foods has shown promise but significant limitations in both efficacy and safety have prevented widespread clinical implementation. EPIT is limited mainly by its lower rate of efficacy.⁵ Although rates of successful desensitization are generally much higher for SLIT and especially OIT, the effects are commonly lost after treatment cessation, as illustrated by low rates of sustained unresponsiveness.¹⁵ In practical terms, this means that patients need to continue immunotherapy indefinitely to ensure ongoing protection. Significant modifications to lifestyle may be needed to accommodate dosing (eg, avoiding exercise for 2 hours after dosing, not dosing on an empty stomach) and this may create a substantial treatment burden over time. Furthermore, immunotherapy for foods is allergen-specific. Although studies of OIT with multiple foods have shown promise, the need to treat each individual food further increases the burden of treatment for the individual.

Safety concerns for food immunotherapy are related to allergic AEs. For EPIT and SLIT, AEs are generally limited and typically involve symptoms at the treatment site (skin and oral mucosa, respectively), whereas OIT presents more significant safety concerns. Systemic reactions, including anaphylaxis requiring epinephrine use, occur with OIT. A recent analysis estimated that peanut OIT implemented broadly would likely cause more anaphylaxis than it would prevent.¹⁶ A systematic review and meta-analysis of peanut OIT safety and efficacy concluded with high certainty that current regimens increase allergic reactions and anaphylaxis when compared with placebo or avoidance.⁸ Although no deaths have been attributed to OIT, a child in Japan was left ventilator dependent after a severe reaction during milk OIT (Motohiro Ebisawa, MD, PhD, personal correspondence, April 2018).

However, most reactions during OIT occur after intentional ingestion of an OIT dose, not on accidental ingestion. This arguably may lead to better preparedness and treatment of reactions when they do occur. Although exact rates of reactions due to accidental ingestion are not clear, they do commonly occur despite parental vigilance and label-reading.¹⁷ Baumert and colleagues¹⁸ estimated that an increase in peanut threshold of reactivity from ≤ 100 mg to 300 mg would reduce the risk of reaction due to peanut contamination of cookies, ice cream, doughnuts/snack cakes, and snack cake mixes by more than 95%. Although the phase 3 AR101 results did not report on rates of reactions due to accidental ingestion, at exit double-blind placebo-controlled food challenge (DBPCFC), 76.6% of subjects were able to tolerate a single dose of 300 mg,⁹ indicating their threshold was higher than that identified by Baumert and colleagues¹⁸ as clinically relevant for reduction of accidental reactions. This suggests that immunotherapy should drastically reduce rates of accidental reactions.

Gastrointestinal AEs from OIT are also frequent and are the most common cause of treatment discontinuation. Biopsy-proven eosinophilic esophagitis (EoE) has been documented in OIT subjects as well. A meta-analysis estimated the rate of EoE in those undergoing OIT at 2.7%.¹⁹ A more recent analysis estimated the rate of EoE in subjects undergoing OIT at 5.1% based on confirmed cases, with up to 34.1% having symptoms possibly related to EoE.²⁰ However, asymptomatic mild gastrointestinal eosinophilia (involving the esophagus, gastric antrum, and/or duodenum) may be common at baseline in peanut-allergic adults before undergoing OIT.²¹ Certain

comorbidities (severe or uncontrolled asthma, severe atopic dermatitis, EoE) are generally considered contraindications to OIT, preventing treatment of many patients who potentially could benefit the most from therapy. Together these limitations in efficacy and safety illustrate an unmet need for alternative or adjunctive therapies to improve efficacy, safety, or both.

ORAL IMMUNOTHERAPY ADJUVANTS

Omalizumab

Omalizumab, a monoclonal antibody targeting the Fc portion of IgE antibodies, has been FDA-approved for allergic asthma and has shown promise in the treatment of food allergy as well, both as monotherapy and as an adjunct to OIT. Anti-IgE monotherapy with TNX-901 raised the threshold of reactivity for peanut,²² whereas a phase II study with omalizumab was halted prematurely due to severe reactions during the entry oral food challenges (OFCs) (before drug administration) but the limited data before cessation suggested a similar effect.²³ Two studies showed an increase in threshold dose for various food allergens after omalizumab treatment.^{24,25} Logically, these effects of omalizumab on food allergen thresholds should allow for more rapid escalation of OIT dosing and limit AEs such as urticaria and anaphylaxis. Thus, studies of omalizumab-facilitated OIT to date ([Table 1](#)) seem to confirm that omalizumab allows safer, more rapid desensitization but does not affect sustained unresponsiveness (SU) and additionally does not protect against EoE.

Milk

The first study of omalizumab as an adjunct to OIT was an open-label pilot study of 11 children with severe milk allergy.²⁶ After 9 weeks of pretreatment with omalizumab followed by 7 to 11 weeks of omalizumab-facilitated milk OIT, 9 of 10 passed a DBPCFC 8 weeks after omalizumab discontinuation and were able to incorporate >8 g/d (>240 mL milk) in their diet thereafter. Adverse reactions were mostly mild (1.8%), and epinephrine was used at a rate similar to previous OIT studies. In an open-label case series of 14 subjects with milk or egg allergy, all 5 milk-allergic subjects reached a maintenance dose of 6.6 g after 9 weeks of pretreatment with omalizumab²⁷; however, 3 (60%) of 5 of the milk-allergic subjects relapsed with grade 3 or 4 anaphylaxis (Clark and Ewan grading²⁸) within 4 months of omalizumab cessation. The only randomized, placebo-controlled trial to date demonstrated marked improvements in safety outcomes (fewer adverse reactions, fewer reactions requiring treatment). There was no statistically significant benefit on rates of passing a 10-g desensitization OFC and SU rates were low for both groups.²⁹

Peanut

In 2013, Schneider and colleagues³⁰ published the first open-label pilot study of omalizumab-facilitated peanut OIT in 13 highly allergic children. After 12 weeks of omalizumab pretreatment, 12 (92%) of 13 reached a maintenance dose of 2 g peanut protein after 8 weeks of OIT. Twelve weeks after omalizumab was discontinued, 85% passed a 4 g peanut protein DBPCFC and 92% tolerated an open 4-g challenge. Reactions were minimal (2% of doses) and mostly mild. MacGinnitie and colleagues³¹ then demonstrated that omalizumab was superior to placebo in facilitating rapid peanut desensitization and 79% tolerating 2 g peanut protein 6 weeks after drug discontinuation. This number increased to a total of 31 (94%) of 33 subjects after treatment failures were offered open-label omalizumab. Despite the omalizumab arm receiving much higher doses of peanut protein, the overall rate of adverse reactions did not significantly differ. Yee and colleagues³² subsequently reported on long-term

Table 1
Summary of food immunotherapy with adjuvants

Method of AIT + Adjuvants	Specific Adjuvants	Murine or Human	Reference	Condition or Disease	Study Design, Number of Participants, Age Range	Protocol; Duration and Dosing	Outcome and Other Significant Findings	Adverse Events
OIT	Omalizumab	Human	Nadeau et al, ²⁶ 2011	Milk allergy	Phase I open label, 11 subjects, age 7–17 y (median 8 y)	Omalizumab monotherapy pretreatment × 9 wk → Omalizumab-facilitated OIT (rush to 1 g on day 1, weekly increase to 2 g) through wk 16 → OIT monotherapy through wk 24	Primary objective: 9 of 11 (82%) achieved 2000 mg/d dose within 7–11 wk of initial desensitization 9 passed DBPCFC (7250 mg) plus open challenge (4000 mg or 8000 mg), all 9 then tolerated >8000 mg/d (>240 mL) SU: not assessed	1 dropout (abdominal pain, EoE ruled out) Reactions with 1.8% of doses (0.3% moderate, 0.1% severe)
		Human	Wood et al, ²⁹ 2016	Milk allergy	DBPCRT, 57 subjects, age 7–32 y	Omalizumab (n = 28) or placebo (n = 29) → at mo 4 open-label milk OIT- 22–40 wk to reach maintenance (min 520 mg goal 3.8 g/d) → Unblinded at mo 16 → Desensitization OFC and omalizumab discontinuation at mo 28 → Milk OIT discontinued at mo 30 (strict avoidance) → SU OFC at mo 32	No benefit in efficacy (desensitization or SU) • Desensitization OFC (10 g) at wk 28 passed: 24/27 (88.9%) Omalizumab vs 20/28 (71.4%) placebo (P = .18) • SU OFC (10 g) at wk 32 passed: 13/27 (48.1%) Omalizumab vs 10/28 (35.7%) placebo (P = .42)	Significant improvement in safety in omalizumab group: • Doses per subject provoking symptoms (2.1% vs 16.1% P = .0005) • Dose-related reactions requiring treatment (0.0% vs 3.8%, P = .0008)
		Human	Martorell-Calatayud et al, ²⁷ 2016	Milk or egg allergy	Open-label case series, 14 subjects (5 milk-allergic, 9 egg-allergic), age 3–13 y with prior failure of OIT	9 wk pretreatment with omalizumab → OIT to maintenance dose (6.6 g CM or 1.8 g EW) → omalizumab discontinued 2 mo after maintenance dose achieved	All patients (100%) achieved desensitization 8 of 14 (57.1%) continued maintenance OIT 6 of 14 (42.9%) patients relapsed with grade 3–4 anaphylaxis upon ingestion 2.5–4 mo after omalizumab discontinued (3 of 5 (60%) for CM; 3 of 9 (33%) for EW) SU: not assessed	Only 4 (28%) developed mild reactions during induction phase of OIT

Human	Schneider et al, ³⁰ 2013	Peanut allergy	Open-label, 13 subjects, median age 10 y, failed entry DBPCFC at 100 mg dose or lower, and median peanut-specific IgE level of 229 kUA/L	12-wk omalizumab pretreatment → Day 1 OIT to max 250 mg peanut protein (cumulative dose 490 mg) → ~8 wk peanut OIT up-dosing to maintenance (2 g peanut protein) → Omalizumab discontinued, maintenance OIT continued for 12 wk → 4 g peanut protein DBPCFC	OIT day 1: • 13 of 13 (100%) ingested max cumulative 490 mg peanut protein (7 without symptoms, 6 with minimal symptoms) After 8 wk OIT (20 wk omalizumab): • 12 of 13 (92%) reached 2 g peanut protein maintenance dose 12 wk after omalizumab discontinued (with OIT continued): 11 of 13 (85%) tolerated 4 g peanut protein DBPCFC	2.0% of doses associated with reactions (1.8% of doses with mild symptoms, 0.2% of doses with moderate symptoms, 0.06% with severe symptoms) 1 subject withdrew due to persistent nausea/vomiting after reaching 1250 mg dose No reactions to omalizumab
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Method of AIT + Adjuvants	Specific Adjuvants	Murine or Human	Reference	Condition or Disease	Study Design, Number of Participants, Age Range	Protocol; Duration and Dosing	Outcome and Other Significant Findings	Adverse Events
		Human	MacGinnitie et al, ³¹ 2017	Peanut allergy	DBPCRCT, 37 subjects, median age 10 y	Omalizumab (n = 29) vs placebo (n = 8) 12 wk pretreatment → Day 1 OIT to 250 mg peanut protein (CTD 490 mg) → Peanut OIT weekly up-dosing to 2 g → After week 19 study drug discontinued → 4 g OFC 12 wk later → 4 g or 2 g daily maintenance Treatment failures (unable to tolerate 250 mg peanut protein after 8 wk desensitization) → open-label omalizumab and peanut OIT	12 of 13 (92%) tolerated open 4 g peanut protein challenge SU: not assessed OIT day 1: • Omalizumab: 23 of 29 (79%) tolerated max 250 mg dose (490 mg CTD) • Placebo: 1 of 8 (13%) tolerated max 250 mg dose (490 mg CTD) Tolerance of 2 g peanut dose 6 wk after study drug withdrawal (primary endpoint): • Omalizumab: 23 of 29 (79%) • Placebo: 1 of 8 (13%) Treatment failures: • Omalizumab 2 of 27 (7.4%) • Placebo 6 of 8 (75%) • All tolerated 2 g while on open-label omalizumab In total 31 of 33 (94%) of subjects who received omalizumab and peanut OIT tolerated 2 g peanut	2 of 33 (6%) who received both omalizumab (blinded or open-label) and peanut OIT had symptoms suggestive of EoE (1 [3%] biopsy-proven) 1 of 8 (13%) of placebo patients had biopsy-proven EoE while on OIT 6 of 22 (27%) who passed 4 g open challenge had allergic reactions to 4 g maintenance dose (4 [18%] required epinephrine) but tolerated decreased dose of 2 g thereafter No statistically significant difference in rate of reactions in omalizumab (7.8% of doses) vs placebo (16.8% of doses) arms (P = .15) despite omalizumab group

					6 wk after omalizumab stopped 4 g open challenge 12 wk after omalizumab stopped:	receiving much higher doses
					• Omalizumab: 22 of 27 (81%) passed • Placebo: 1 of 8 (13%) passed	
Human	Yee et al, ³² 2019	Peanut allergy	LTFU of the 13 subjects from Scheider et al 2013 study	LTFU visits every ~6 mo up to 72 mo Allowed to change peanut dose formulations; optional spacing of dosing from daily to every-other-day to twice weekly to weekly Dose adjusted if symptoms occurred (ranged from 500 mg to 3500 mg)	SU: not assessed 7 of 13 (54%) continued peanut OIT through mo 72 QoL improved from baseline in all subjects SU: not assessed	6 of 13 (46%) discontinued due to adverse reactions Higher peanut IgE and Ara h2 IgE associated with discontinuation 1 of 13 (7.7%) developed EoE
Human	Bégin et al, ³⁴ 2014	Multiple food allergy	Open label, 25 subjects, median age 7 y Up to 5 foods (mean 3.6 foods): peanut (all), milk, egg, tree nuts, wheat, sesame.	8-wk omalizumab pretreatment → rapid desensitization Omalizumab discontinued at week 16 Maintenance OIT dose 4 g/food daily	OIT day 1: • 19 of 25 (76%) reached max first day dose (250 mg protein per food) with minimal or no symptoms All patents reached dose of 1 g/food by 3 mo of OIT 88% reached max dose 4 g/food by 9 mo of OIT SU: not assessed	5.3% of home doses triggered reactions 94% of reactions were mild Reaction rates dropped by 70% after 6 mo of therapy 1 severe reaction after reaching 4 g/food maintenance, treated with epinephrine
Human	Andorf et al, ³⁵ 2017	Multiple food allergy	Observational LTFU of Bégin 2014 with additional subjects without peanut allergy (total 34)	Same as Bégin 2014 except maintenance dose of 2 g to 4 g (high dose) vs 300 mg (low dose) LTFU visits every 6–12 mo	All passed 2 g OFC to each of their food allergens at the end of LTFU Choice of low vs high maintenance dose: • All 6 almond subject and all 8 pecan chose low dose	No change in maintenance dose due to safety concerns Reactions occurred with 3.5% of maintenance doses (95.6% mild)

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Table 1
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		Human	Andorf et al, ⁷⁸ 2018	Multiple food allergy	DBPCRCT, 48 subjects, median age 8 y (2–5 foods, mean 3.3 foods)	Followed median 53 mo (32–62 mo) 8-wk pretreatment omalizumab (n = 36) vs placebo (n = 12) → rapid desensitization Study drug discontinued at week 16	73% of egg and 80% of milk chose high dose Week 30 2 g protein/food DBPCFC: 30 of 36 (83%) omalizumab passed vs 4 of 12 (33%) placebo	No severe adverse events Lower rates of AEs in omalizumab group
		Human	Andorf et al, ³⁶ 2019	Multiple food allergy	RCT, 70 subjects (age 5–22 y), multiple food allergies (confirmed by DBPCFC)	Exit DBPCFC at week 36 16 wk of open-label omalizumab (weeks 0–16) 22 wk of multifoood OIT (weeks 8–30) If 1 g/food maintenance dose reached by week 28–29, then randomized 1:1:1 to 1 g, 300 mg, or 0 mg for 6 wk (weeks 30–36) DBPCFC at wk 36	10 dropouts (5 failed desensitization) 34 of 40 (85%) on active treatment (1 g or 300 mg) vs 11 of 20 (55%) on 0 g tolerated 2 g of each food allergen Highest failure rates with cashew and peanut Threshold of reactivity increased even for 9 failures (CTD increased from 15 mg to 750 mg) 6-wk SU (0 g arm): 55% passed 2 g DBPCFC	No clinically significant difference in rates of AEs among groups BUT higher 4 doses of epinephrine given in 1 g arm vs 1 in 0 g arm and 0 in 300 mg arm
	Probiotics	Human	Tang et al, ⁴³ 2015	Peanut allergy	DBPCRCT, 62 subjects, 1–10 y	Peanut OIT (peanut flour, 50% peanut protein) combined with probiotic <i>Lactobacillus rhamnosus</i> CGMCC (1.3724 at a fixed dose of 2×10^{10} CFU) (PPOIT), or placebo OIT without	Possible SU achieved in 82.1% with PPOIT & 3.6% with placebo ($P < .001$) Desensitization with DBPCFC (cumulative dose 4 g peanut protein) achieved in 89.7% receiving PPOIT and 7.1% receiving placebo ($P \leq .001$)	PPOIT was well tolerated with no participants withdrawing because of AE. Number needed to treat of 9 to produce clinical benefit in 7 children

	Human	Hsiao et al, ⁷⁹ 2017	Peanut allergy	4-y follow-up on previously reported cohort	probiotic, once daily for 18 mo	58% of PPOIT vs 7% of placebo subjects demonstrated 8-wk SU ($P<.012$)	
Dupilumab	Human	NCT03682770; recruiting	Peanut allergy	Phase 2, Multicenter, DBPCRT; 156 subjects; 6–17 y	dupilumab + AR101 (peanut OIT) or placebo; every 2 wk	Desensitization with DBPCFC at wk 28	
FAHF	Murine	Srivastava et al, ⁴⁸ 2017	Peanut and tree nut allergy	Placebo-controlled RCT; 3 groups: sham treatment (water), OIT alone, OIT + 3-wk prior and 3-wk BF2 cotreatment (dose 12 mg/d)	Mice were sensitized with, then underwent, 1 d peanut (PN), walnut (WN) and cashew (CSH) rush OIT plus 3 wk of maintenance dosing of 6.25 mg PN/WN/CSH cocktail; OFC at 1, 2, 5, 6 wk after therapy	1-wk after OFC: BF2 treatment significantly enhanced OIT desensitization (37.5% OIT mice reacted vs 18% BF2+OIT mice, $P<.01$). BF2+OIT produced more sustained protection than OIT alone at 5–6 wk after OFC with all 3 foods (100% sham, 91% OIT only, 23% BF2+OIT mice reacted with median score lower vs sham $P<.05$). BF2+OIT prevented OIT increase of antigen specific IgE, and pro-tolerogenic IFN- γ /IL4 and IL10/IL4 ratios ($P<.05$ –.01 vs OIT alone), associated with more persistent protection	BF2 reduced rush OIT build-up dose phase AE: 43% of OIT- only mice had moderate to severe reactions vs 12% of BF2+OIT with mild reactions and lower median symptom scores ($P<.001$)
	Human	Wang et al, ⁴⁹ 2015	Peanut, tree nut, sesame, fish, and/or shellfish allergy	DBPCRT; 68 subjects; 12–45 y	FAHF-2 tablets 15 g/d or placebo, with DBPCFC to a max 5 g protein after 6 mo	By ITT, placebo group had higher eliciting and cumulative dose ($P = .05$) at final DBPCFC; no difference in requiring epinephrine to treat reactions ($P = .55$); no significant difference in immunologic parameters (allergen-specific IgE, IgG4, cytokine production, or BAT)	Total 387 AE, none severe, no difference in the number reported per subject between groups. GI complaints most common. Notably, 44% subject has poor drug adherence for at least 1/3 of study period

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	E-B-FAHF-2 + Omalizumab	Human	NCT02879006; recruiting	Milk, egg, peanut, almond, cashew, hazelnut, walnut, sesame, and/or wheat allergy	DBPCRT, phase 2; 34 subjects, 6–40 y	All subjects = multiallergen OIT + omalizumab × 4 mo (2 mo pre-OIT + 2 mo build-up phase). Then randomized to E-B-FAHF-2 or placebo, OIT therapy (1 gm each food allergen) × 2 years, with post OFC	Primary outcome: SUs evaluated by the absence of dose-limiting symptoms to a cumulative dose of 4444 protein; secondary outcome of desensitizing to 4444 mg and/or 7444 mg or higher	
	Interferon-gamma	Human	Noh & Lee, ⁵⁴ 2009	Egg, milk, or wheat allergy	Case control; 25 subjects (IFN-γ + OIT n = 10, OIT alone n = 5, IFN-γ alone n = 5, no treatment n = 5), children	SC IFN-γ given 10–20 min before each dose of OIT, then OFC done at therapy completion and 3 mo post; duration was dependent on food	10 subjects who received IFN-γ + OIT achieved SU. No subjects achieved SU or desensitization with OIT alone, IFN-γ alone, or no treatment. IFN-γ + OIT associated with increased food-specific IgE, but reduced SPT wheal	All OIT participants failed to complete OIT protocol and withdrew because of frequent and severe reactions
		Human	Noh & Jang, ⁵⁵ 2014	Milk, egg, wheat, soy	Case control; 25 subjects (IFN-γ + dual OIT ^a n = 10, IFN-γ + classic OIT ^b n = 5, OIT alone n = 5, no treatment n = 5), children	SC IFN-γ (3 × 10 ⁶ IU/m ²) given 10–20 min before doses of OIT per protocol; duration was dependent on food. No assessment of SU	Desensitization achieved in 10/10 and 5/5 subjects who received dual OIT and classic OIT, respectively. No subjects desensitized who received OIT alone or no treatment	

SLIT	CpG-nanoparticles	Murine	Srivastava et al, ⁶⁰ 2016	Peanut allergy	Total 90 mice in 7 groups (n = 10–22/group)	4 weekly gavages with either CpG/PN-NPs, individual vehicle components (5 groups), or no treatment; then 5 monthly peanut OFCs	Mice treated with CpG/PN-NPs, compared with none of the vehicle components or control mice, were significantly protected from anaphylaxis in all OFCs (lower median symptom scores $P < .01$ vs .001 vs sham, higher post-challenge body temperatures $P < .05$ –.001 for CpG/PN-NPs vs sham treatment, lower 30 min post-OCF blood histamine levels $P < .05$ –.001 between the treatment and vehicle control groups), and had decreased splgE/IgG1 (observed at all challenges except the first challenge at week 14, $P < .05$ –.001), and increase in peanut-specific IgG2a (TH1-associated immunoglobulin) levels ($P < .05$ –.01) at all 5 OFCs
		Murine	Kulis et al, ⁵⁹ 2013	Peanut allergy	Prophylactic model (a) and therapeutic model (b)	a. 0.5 mg peanut protein $\pm$ 30 μ g of 3 types of CpG molecules (ODNs) on days 1, 8, and 22 via intraperitoneal (i.p.) injection; day 36, 1 mg protein i.p. injection challenge. b. 3 groups, placebo, peanut alone, or peanut plus type A, B, or C CpG. IT on days 36, 39, 43, 46, 50, and 53; i.p. challenge on day 63	a. Type B ODNs inhibited anaphylaxis in the sensitization protocol (lower symptom scores $P < .01$, body temperature $P < .001$, and mouse mast cell protease 1 release $P < .05$ vs sham) compared with sham treatment. b. Co-administration of type B ODN + peanut protein reduced anaphylactic reactions $P < .01$, increased IFN- γ $P < .001$ and peanut-IgG2a $P < .01$ –.001, without a significant decrease in peanut IgE or IL-4 responses

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Table 1
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Method of AIT + Adjuvants	Specific Adjuvants	Murine or Human	Reference	Condition or Disease	Study Design, Number of Participants, Age Range	Protocol; Duration and Dosing	Outcome and Other Significant Findings	Adverse Events
		Murine	Zhu et al, ⁵⁸ 2007	Peanut allergy	Prevention model (a) and therapeutic model (b); 5 mice per group	a. Sensitization 3 times with oral peanut $\pm$ IMO; 1 mg peanut challenge day 28 b. Sensitization and days 0 & 14, starting on day 21 treated 4 times every 4 d with oral IMO; challenge day 34	a. Combination of IMO/peanut vs peanut only decreased IgE, IL-5, IL-13, and increased IgG2a and IFN- γ levels (all $P < .05$) b. IM vs PBS-treated treated mice showed decreased IgE, IL-5, and IL-13 levels, and increased IgG2a and IFN- γ levels in the serum, intestines, and spleen cells (all $P < .05$)	
SCIT	LAMP-vax DNA	Human	NCT03755713, recruiting	Peanut allergy	Phase 1, Randomized, Placebo-Controlled, 3 cohorts with 10 subjects each, ages 12–17 y	ID administration of ASP0892 (ARA-LAMP-vax) in 3 cohorts: ASP8062 low-dose, high-dose, placebo	Evaluate safety, tolerability and immune responses	
		Human	NCT02851277, recruitment completed	Peanut allergy	Phase 1, randomized, placebo-controlled, 30 subjects, 18–55 y	ID administration: ASP8062 low dose, high dose, placebo. IM administration: high dose and placebo; once every 2 wk for 4 doses	Evaluate safety, tolerability and immune responses	
	HAL-MPE1	Human	Bindslev-Jensen et al, ⁶⁷ 2017	Peanut allergy	DBPCRT, treatment group with HAL-MPE1 (11 subjects) or placebo (6 subjects)	Randomized to receive 15–20 weekly incremental doses of subcutaneous HAL-MPE1 or placebo	After HAL-MPE1, there were more frequent but generally mild (redness and no wheal sizes exceeding 5 cm) local reactions, and no late systemic reactions	

	Human	NCT02991885	Peanut allergy	DBPCRT, 42 participants, 5–50 y	Weekly subcutaneous HAL-MPE1 or placebo	Assessing safety, tolerability and immunologic effects	
	Murine	Van der Kleij et al, ⁶⁶ 2019	Peanut allergy	n = 6 sensitized mice per group	Day 42- SC treatment with 200 µL of the different test preparations (PE or MPE ± Al(OH) ₃) or PBS ± Al(OH) ₃ , 2×/wk for 6 wk. Challenges: 12 mg PE IG day 91, IP 0.1 mg PE days 98 and 112	HAL-MPE1 reduces allergenicity while still retaining immunogenicity of peanut extract (did not affect peanut-specific human T-cell proliferation in vitro (<i>P</i> = .23), induced IgG responses cross-reactive with native PE, reduced IgE binding to Ara h 2 and Ara h 6, and reduced basophil activation (<i>P</i> < .01) and mediator release)	
	Human	NCT02382718	Fish allergy	DBPCRT, 45 participants, 18–65 y	SC injections of mCyp c 1 (or placebo) in an up-dosing phase (build up from 6ng- 60 µg over 10 injections in an 8 week period), followed by maintenance phase (60 µg once at 2 wk, then 4 monthly injections ×4 mo)	Assessing efficacy and safety	
PVX-108	Human	Prickett et al, ⁷² 2019 AAAAI abstract, ACTRN1 2617000692336	Peanut allergy	DBPCRT, 66 subjects (Stage 1: 48 subjects, stage 2: 18 subjects), 18–65 y	8 cohorts received either ID PVX108 or placebo in increasing doses; final cohort-6 IDs of 150 nmol × 16 wk	Serum from peanut-allergic demonstrated a lack of basophil reactivity to PVX108 vs peanut extract	No participants experienced any serious AE, only mild to moderate and mostly related to injection site reactions
CpG-nano-particles	Murine	Pali-Scholl et al, ⁷³ 2013	Peanut allergy	Murine model	SC injection of protamine nanoparticles complexed with Ara h 2	Favorable increase in Ara h 2-specific IgG2a without detectable Ara h 2-specific IgE	

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Method of AIT + Adjuvants	Specific Adjuvants	Murine or Human	Reference	Condition or Disease	Study Design, Number of Participants, Age Range	Protocol; Duration and Dosing	Outcome and Other Significant Findings	Adverse Events
Mucosal		Human	Wood et al, ⁷⁵ 2013	Peanut allergy	Controls: 5 healthy adults, Subjects: 10 peanut-allergic adults, ages 18–50 y	Rectal administration of EMPT-123. Controls: 4 weekly escalating doses to max study dose 3063 µg. Subjects: 10 weekly escalating doses from 10 µg to 3063 µg, then 3 biweekly doses of 3063 µg	Significant reduction in SPT titration (10.0 within-subject change; $P = .02$) and basophil activation; no significant changes for total IgE, peanut IgE, or peanut IgG4	50% of participants unable to complete the dosing regimen (2 mild & 1 moderate reaction) and 20% experiencing severe allergic reactions (anaphylaxis)

Abbreviations: AE, adverse event; AIT, allergen-specific immunotherapy; ARA-LAMP-vax, a multivalent peanut (Ara h1, h2, h3) LAMP-DNA plasmid vaccine; BAT, basophil activation test; DBPCFC, double-blind placebo-controlled food challenge; DBPCRT, double-blind placebo-controlled randomized trial; EoE, eosinophilic esophagitis; HAL-MPE1, aluminum hydroxide adsorbed modified peanut extract; ID, intradermal; Ig, immunoglobulin; IM, intramuscular; IMO, immune modulatory oligonucleotide; ITT, intention to treat; LAMP-vax, lysosomal associated membrane protein vaccine; LTFU, long-term follow-up; ODNs, oligodeoxynucleotide molecules; OFC, oral food challenge; OIT, oral immunotherapy; PPOIT, peanut OIT combined with probiotic; RCT, randomized control trial; SC, subcutaneous; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SPT, skin prick test; SU, sustained unresponsiveness.

^a Dual OIT: a dose of interferon-gamma with OIT in the morning and a dose of OIT alone in the evening.

^b Classic OIT: single daily dose of interferon-gamma with OIT.

follow-up from the pilot study by Schneider and colleagues³⁰ that 6 (46%) of 13 subjects discontinued OIT due to adverse reactions, indicating that omalizumab did not alter the need for nor increase the tolerability of long-term ongoing therapy.

Multifood oral immunotherapy

Thirty percent of children with food allergy react to multiple foods.³³ As such, the ability to simultaneously treat all of an individual's food allergies is highly desirable. Although the benefits of immunotherapy are allergen-specific, omalizumab's effects are not. Thus, omalizumab has potential to be used to treat children with multiple food allergies. Bégin and colleagues³⁴ treated 25 subjects with omalizumab (8 weeks pretreatment and 8 additional weeks during OIT) and multifood OIT for up to 5 allergens. Nineteen (76%) of 25 tolerated the maximum day 1 initial dose escalation, all patients reached a maintenance dose of 1 g/food by 3 months of OIT, and reactions occurred with 5.3% of doses and were mostly mild. Long-term follow-up of these subjects plus 9 additional (34 total) revealed that all subjects passed 2 g OFC to each food after a median of 53 months.³⁵

Another study by Andorf and colleagues³⁶ examined the durability of 30 weeks of omalizumab-facilitated multifood desensitization by comparing various maintenance doses of each food beginning 14 weeks after omalizumab discontinuation. Thirty-four (85%) of 40 randomized to continued active OIT (1 g or 300 mg) passed a DBPCFC after 6 weeks on the assigned dose, versus 20 (55%) among those who discontinued OIT. Durability of effect varied by food. Threshold of reactivity was increased even among those who failed the challenge. SU was not examined. A large upcoming multicenter phase 3 trial aims to provide deeper insight into omalizumab as monotherapy and as an adjunct to multifood OIT and whether subjects can maintain dietary consumption of the foods after omalizumab cessation over longer follow-up (NCT03881696).

Probiotics and Oral Immunotherapy

The increase in both prevalence and severity of food allergy has occurred simultaneously with global changes in environment and lifestyle. Some of these factors have been associated with gut microbiome dysbiosis and proposed to correlate with the development of food allergy, leading to recent investigations into the role of probiotics on immune tolerance mechanisms in food allergy.^{37–40} Early studies demonstrated that cow's milk formula containing the probiotic *Lactobacillus rhamnosus* GG accelerated immune tolerance acquisition in cow's milk-allergic children, confirmed on 3-year follow-up.^{41,42} The efficacy of probiotics as an adjuvant for OIT has been recently studied in an Australian cohort of peanut-allergic children. Subjects were randomized to receive 18 months of either peanut OIT combined with probiotic (PPOIT) or placebo OIT without probiotic.⁴³ Desensitization was achieved in 89.7% receiving PPOIT and 7.1% receiving placebo, and possible SU in 82.1% with PPOIT and 3.6% with placebo. Four-year follow-up showed that 58% of PPOIT compared with 7% of placebo subjects demonstrated 8-week SU,⁴⁴ suggesting long-lasting clinical benefit of this combined therapy. An additional benefit to PPOIT is that it was well tolerated with no participants withdrawing because of adverse events, in contrast to reported rates of OIT withdrawal ranging from 10% to 30%. Subjects participating in the trial did not all undergo entry food challenges to verify allergic status, and the length of time abstaining from therapy to measure SU varied among participants, with some abstaining for only 2 weeks before the SU challenge. Future studies into the efficacy of PPOIT will better elucidate its potential superiority to OIT without a probiotic supplement.

Dupilumab and Oral Immunotherapy

Dupilumab is a monoclonal antibody that targets the IL-4-receptor-alpha, effectively inhibiting both IL-4 and IL-13. It is currently being studied in combination with AR101 for peanut allergy (NCT03682770).⁴⁵ It is already FDA-approved for moderate to severe asthma and eczema, and investigation is ongoing for its use in eosinophilic esophagitis (NCT02379052).⁴⁶ Although the ultimate benefit of dupilumab for facilitating OIT and improving the safety of OIT remains to be seen, the potential of dupilumab to improve control of severe comorbidities may theoretically expand the use of OIT to subjects in whom OIT otherwise may be contraindicated.

Food Allergy Herbal Formula and Oral Immunotherapy

It has been suggested that Chinese herbal medicines can be of value in treating a myriad of diseases, including allergies. Initial murine model studies demonstrated that treatment with FAHF-2 (food allergy herbal formula 2) eliminated anaphylaxis and downregulated Th2 responses in peanut-allergic mice.⁴⁷ More recent studies by this group using B-FAHF-2 (BF2) with peanut and tree nut OIT in sensitized mice demonstrated an advantage to adjuvant therapy.⁴⁸ Benefits included reduced frequency of and less severe adverse reactions during OIT build-up, enhanced OIT desensitization, more sustained protection, and pro-tolerogenic cytokine profile. The only human study to date was disappointing, with no clinical benefit and none of the expected immunomodulatory effects versus placebo, possibly due in part to poor adherence.⁴⁹ Ongoing areas of investigation include a DBPCRT using multiallergen OIT with omalizumab, followed by OIT with B-FAHF-2 for 2 years (NCT02879006).⁵⁰

Interferon- γ

The role of IFN- γ in food allergy has been explored in murine models as well as in patients with cow's milk allergy, both demonstrating allergy resolution.^{51–53} Its role in combination with OIT has been investigated in 2 case control studies. The first involved 25 children with egg, milk, or wheat allergy.⁵⁴ All 10 subjects who received IFN- γ with OIT achieved SU at 3 months, in contrast to no subjects achieving SU or desensitization with either treatment independently. Of note, all patients who received OIT alone failed to complete the OIT protocol and withdrew because of frequent and severe reactions. A later case control study of a similar pediatric cohort examined the use of IFN- γ with either classic or dual OIT.⁵⁵ Classic OIT involved a single daily dose of IFN- γ with OIT, compared with dual OIT with a dose of IFN- γ with OIT in the morning followed by a dose of OIT alone in the evening. All patients who received dual OIT and classic OIT achieved desensitization, compared with no patients who received OIT alone or no treatment. Although studies are limited, this suggests the addition of IFN- γ improved OIT tolerability and achieving desensitization.

SUBLINGUAL IMMUNOTHERAPY ADJUVANTS

Sublingual Immunotherapy cytosine-phosphate-guanine (CpG)-Nanoparticles

Although there has been great interest in adjuvant therapies using probiotics and other whole-cell bacteria, it has also been suggested that microbial macromolecules expressing toll-like receptor (TLR) ligands may provide similar adjuvant activity to activate the host immune system. CpG oligodeoxynucleotides (ODNs) are TLR9 ligands that induce Th1⁵⁶ and Treg⁵⁷ immunity, as demonstrated by the differentiation of T cells stimulated by CpG-activated dendritic cells into Tregs that suppress effector T-cell responses. Two studies demonstrated a reduction in peanut-induced

anaphylaxis in hypersensitive mice when treated with orally administered or injected peanut combined with CpG both prophylactically and therapeutically.^{58,59} In a mouse model of peanut immunotherapy, OIT with CpG-coated poly(lactic-co-glycolic-acid) nanoparticles containing peanut extract (CpG/PN-NPs) improved allergic disease in peanut-sensitive mice.⁶⁰ Only the mice treated with CpG/PN-NPs were significantly protected from anaphylaxis in all OFCs, developed a sustained and significant decrease in both peanut-specific IgE and IgG1 (TH2-associated immunoglobulin), as well as an increase in peanut-specific IgG2a (TH1-associated immunoglobulin). Overall, CpG/PN-NPs peanut OIT in a mouse model was found to be well tolerated, induced persistent protection from anaphylaxis, and conferred beneficial regulation of peanut-specific immune responses with favorable alteration in cytokine profiles. Further studies are needed to elucidate whether the same CpG sequences are immunostimulatory in mice and humans.

SUBCUTANEOUS IMMUNOTHERAPY

Lysosomal Associated Membrane Protein-vax DNA

DNA vaccines have been studied in a variety of diseases. Of particular interest in allergy is the use of LAMP (lysosomal associated membrane protein) technology to treat pollen allergies, and in novel therapeutic approaches in peanut allergy. This approach involves inserting DNA encoding the allergen in a plasmid containing the coding sequence for LAMP, such that when APCs take up the plasmid it induces synthesis of an allergen-LAMP fusion protein hypothesized to elicit Th1 responses.⁶¹ Studies by Su and colleagues⁶² using this approach with Japanese red cedar allergy in murine models showed it was not only effective in eliciting Th1-type immune responses, but also has a favorable safety profile and produces active immunologic effects.⁶³ Current investigations include phase I, randomized controlled studies evaluating the safety, tolerability and immune responses in peanut-allergic adolescents (NCT03755713⁶⁴) and adults (NCT02851277⁶⁵) receiving varying doses of intradermal or intramuscular injections of ASP0892 (ARA-LAMP-vax), a multivalent peanut (Ara h1, h2, h3) LAMP-DNA plasmid vaccine.

Subcutaneous Immunotherapy (Modified Allergen) (Aluminum Hydroxide Adsorbed Modified Peanut Extract)

The need for the development of a modified peanut extract to facilitate the clinical application SCIT for peanut allergy was recognized after early attempts with peanut extract resulted in many severe systemic reactions.⁶ Subsequent studies demonstrated that aluminum hydroxide adsorbed modified peanut extract (HAL-MPE1) reduces allergenicity while still retaining immunogenicity of peanut extract (PE).⁶⁶ In their in vivo mouse model, immunotherapy with Ara h 2 and 6 chemically modified (MPE) was capable of reducing allergic responses while maintaining immunologic potency. This data suggest greater safety in the preparation of MPE compared with PE potentially enabling higher and clinically effective dosing and supports further development of MPEs for SCIT. Human trials have examined the use of incremental escalating doses weekly with either HAL-MPE1 or placebo in peanut-allergic subjects.⁶⁷ Although early and late local reactions were more frequently observed after HAL-MPE1 compared with placebo, they were generally of mild intensity with no late systemic reactions exceeding grade I. The investigators suggested that this incidence and intensity of early and late local and systemic reactions supported the safety and tolerability of treatment with HAL-MPE1, and that 4 to 5 months of weekly dose escalations effectively induced immunologic changes. A similar but larger study with

42 participants ages 5 to 50 years is ongoing ([NCT02991885](#)).⁶⁸ This approach is also being investigated beyond peanut allergy using a novel biotechnological product, the recombinant hypoallergenic parvalbumin mCyp c 1, for SCIT in the treatment of fish allergy. This molecule has proven to be safe, hypoallergenic and immunogenic in a phase I/IIa study,⁶⁹ and is now being investigated in a multinational phase IIb study ([NCT02382718](#)).⁷⁰

Peptide-Based Vaccines (PVX-108)

Furthering the concept of using modified allergens is an approach using synthetic peptides representing T-cell epitope sequences of the major peanut allergens Ara h 1 and Ara h 2. This is theorized to target allergen-specific T cells without causing IgE-mediated inflammatory cell activation.⁷¹ A novel therapeutic product, PVX108, for intradermal immunotherapy demonstrated a favorable safety profile in a phase 1 trial (ACTRN12617000692336).⁷² No participants experienced any serious adverse events, and immunologic assays confirmed lack of basophil reactivity to PVX108 in contrast to peanut extract. A phase 2 clinical trial is planned in children.

Subcutaneous Immunotherapy + CpG

Another approach for allergen-specific immunotherapy is to use protamines, arginine-rich proteins that spontaneously assemble into nanoparticles with CpG-ODNs, which drive the immune response toward Th1. A murine model using subcutaneous administration of protamine nanoparticles complexed with Ara h 2 observed a favorable increase in Ara h 2-specific IgG2a without detectable Ara h 2-specific IgE.⁷³ Findings suggest that protamine-based nanoparticles with CpG-ODN counteract the allergen induced Th2-dominated immune response and may be considered a novel allergen immunotherapy delivery system.

MUCOSAL IMMUNOTHERAPY

The use of heat-killed (HK) bacterial adjuvants is another variation on recombinant proteins in immunotherapy to reduce clinical reactivity while maintain tolerogenic immune responses. The safety and potential efficacy of this approach at inducing long-term downregulation of peanut hypersensitivity was observed in a murine model of rectally administered HK *Escherichia coli* producing engineered (mutated) Ara h1, 2, and 3 (HKE-MP123).⁷⁴ Despite these promising preclinical studies, a later phase 1 study conducted to assess the safety of this vaccine had rather unexpected results as rectal administration of EMP-123 resulted in frequent adverse reactions, with 50% of participants unable to complete the dosing regimen and 20% experiencing severe allergic reactions.⁷⁵ Thus, although it was hypothesized that rectal administration would capitalize on the rich immunologic colonic environment to enhance tolerance development and allow safe administration of larger antigen doses, it is unknown whether the highly absorptive nature of the colonic mucosa potentially enhanced the observed risk of AEs. The investigators suggest that a more conservative approach using slower escalation and daily dosing may have minimized these reactions.

FUTURE AREAS OF INVESTIGATION

Ibrutinib

Ibrutinib is a Bruton tyrosine kinase (BTK) inhibitor that has been hypothesized to be useful in preventing allergic reactions, as BTK is a key component of not only B-cell receptor signaling but also plays a role in activation of mast cells and basophils via FcεRI signaling. A pilot study in 2 patients with chronic lymphocytic leukemia

demonstrated that ibrutinib completely eliminated skin test reactivity and IgE-mediated basophil activation test (BAT) responses to aeroallergens within 1 week of starting treatment.⁷⁶ This same group expanded on this work in a study of peanut and tree nut allergic patients who were given a standard FDA-approved dose of 420 mg of ibrutinib daily for 1 week.⁷⁷ Skin prick test analysis after 2 doses showed a sustained significant decrease in wheal and flare in all subjects for all allergens tested (average reduction 76.6% for wheal and 86.0% for flare, both $P < .0001$), as well as suppression of IgE-mediated BAT responses ($P = .0002$ at days 2 and 4, $P < .0001$ on day 7); however, serum-specific IgE to foods were unchanged at follow-up and responses were not sustained. After cessation of ibrutinib treatment, approximately 80% of SPT areas returned to within 80% of baseline diameter within 1 week, and IgE-mediated BAT responses recovered within days. Ibrutinib was considered safe and well tolerated with no serious adverse reaction; however, the study was limited by a small sample size ($n = 6$). Further investigation is necessary to evaluate potential use in preventing allergic reactions.

SUMMARY

Although there are currently no FDA-approved therapies for treatment of life-threatening food allergies, it is expected that the treatment landscape will change dramatically in the coming years. It is likely that physicians will have a choice of allergen-specific therapies in the near future; however, the treatment options most likely to appear on the market will not be tolerable for all food allergic patients, will not provide significant benefit for all patients, will not be sustainable long-term for all patients, and will not address the needs of patients with multiple food allergies. In an effort to improve safety and efficacy the next generation of investigative therapeutics will focus on targeted immune modulation and a decreased risk of anaphylaxis with therapy. Broader consideration will also be given to multifood allergic patients as non-allergen-specific therapies target prevention of anaphylaxis irrespective of the allergen. The treatment landscape for food allergy is changing quickly, and refined approaches to therapy will provide more comprehensive benefit to the most severely affected food allergic patients.

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