

Invited review article

Active treatment for food allergy

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OIT, oral immunotherapy; SLIT, sublingual immunotherapy; EPIT, epicutaneous immunotherapy; SCIT, subcutaneous immunotherapy; CM, cow's milk; OFC, oral food challenge; FAHF, food allergy herbal formula; RCT, randomized controlled trial; IT, immunotherapy; EoE, eosinophilic esophagitis

ABSTRACT

Food allergy has grown in rapidly in prevalence, currently affecting 5% of adults and 8% of children. Management strategy is currently limited to 1) food avoidance and 2) carrying and using rescue intramuscular epinephrine/adrenaline and oral antihistamines in the case of accidental ingestion; there is no FDA approved treatment. Recently, oral, sublingual and epicutaneous immunotherapy have been developed as active treatment of food allergy, though none have completed phase 3 study. Efficacy and safety studies of immunotherapy have been variable, though there is clearly signal that immunotherapy will be a viable option to desensitize patients. The use of bacterial adjuvants, anti-IgE monoclonal antibodies, and Chinese herbal formulations either alone or in addition to immunotherapy may hold promise as future options for active treatment. Active prevention of food allergy through early introduction of potentially offending foods in high-risk infants will be an important means to slow the rising incidence of sensitization.

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Background

An allergic reaction to food is defined as an IgE mediated reaction to ingestion of a specific food. Symptoms of food allergy may include abdominal pain, vomiting, urticaria and anaphylaxis. The prevalence of food allergy has risen considerably in recent years, now estimated to be 5% in adults and 8% in children, with some regional variability.^{1–5} Estimates of growth in incidence of food allergy range from 18% from 1997 to 2007, to a doubling over the past decade.^{3,6} With the incidence of food allergy rising so quickly, there has been an intensification of research efforts directed toward finding a treatment and eventually a cure.

Management of food allergy currently consists of strict and careful food avoidance, while keeping emergency treatment available at all times.⁷ If an allergenic food is ingested, this is treated

with intramuscular epinephrine/adrenaline or oral antihistamines (or occasionally systemic corticosteroids), depending on the age of the patient, severity of the reaction and the amount ingested. Without a pharmacologic option for active treatment, families are forced to remain ever-vigilant, closely monitoring food labels, taking caution with food at social gatherings and carrying an epinephrine/adrenaline auto-injector at all times. The stressful psychological effect that food allergy has on patients and their families is quite apparent, and quality of life is diminished.⁸ Families have reason to be stressed, as accidental ingestion occurs frequently⁹: one study reported that up to 75% of patients with peanut allergy will accidentally consume peanuts.¹⁰ Furthermore, treatment of accidental ingestions with an epinephrine/adrenaline auto-injector is anxiety provoking and perceived by patients and families as challenging.¹¹ The anxiety surrounding the potential for a severe reaction any time food is consumed significantly diminishes quality of life for patients and their families.

Food allergy is currently treated by a combination of specific food avoidance, provision of emergency treatment, and monitoring. Specifically, patients are told to specifically avoid the food to which they're allergic, which can be challenging given the

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large number of ingredients in commonly consumed foods. If a patient is accidentally exposed to an offending food, they are treated emergently with intramuscular epinephrine/adrenaline and oral antihistamines, as described above. Monitoring involves frequent food-specific IgE and skin prick testing. An oral food challenge (OFC) may be attempted as a patient develops a pattern that may be consistent with tolerance. The OFC represents the gold standard for diagnosis of food allergy, since some patients will spontaneously develop tolerance to previously offending foods over time.

Although food allergy is a commonly encountered problem, active treatment toward desensitization has been limited to the research setting. In this paper, we define desensitization as an increase in threshold reactivity for a particular subject, and sustained tolerance as retention of that increased reactivity threshold for months to years without further treatment. Subcutaneous immunotherapy (SCIT) for peanut allergy was studied in the 1990s, though in this trial, the rate of severe reactions was unacceptably high.¹² Since then, oral, sublingual, and epicutaneous immunotherapy, have been described in a number of trials, as have recombinant vaccines, immunobiologics, bacterial adjuvants and herbal therapeutics (Table 1).

The goal associated with food immunotherapy remains controversial. While some feel the goal should be to induce desensitization and sustained unresponsiveness, others feel that a small amount of tolerance – allowing a patient to tolerate an accidental bite of an offending food, for example – is clinically and emotionally significant. In this review, we highlight trials that look at both types of endpoints. Food allergy is a common problem resulting in significant physical, emotional and psychiatric morbidity and mortality; it is therefore necessary to find a safe, efficacious management strategy.

Allergen specific therapies

Subcutaneous immunotherapy

Subcutaneous immunotherapy was employed in 1992 for desensitization of peanut allergic subjects.¹³ Patients in this study completed an initial rush schedule followed by maintenance dosing. After promising initial results, the study was terminated early due to a fatal reaction. The fatality occurred following a formulation error in the pharmacy, wherein a placebo-treated patient received a maintenance dose of immunotherapy.

Since subcutaneous immunotherapy had been so successful in treating aeroallergy, the technique was reattempted for active treatment of food allergy, this time in an adult study.¹² Unfortunately, a very high rate of systemic reaction occurred: 23% of patients during rush buildup and 39% during maintenance dosing.

Recombinant proteins for use in SCIT, thought to potentially enhance safety, was reported by Zuidmeer-Jonghejan *et al.* in 2012.¹⁴ From this group, we can expect to see development of novel proteins representing the active allergens in peach and fish, which may be better tolerated than the unaltered food. Human studies in this arena have not been reported to date.

Table 1
Change in biomarkers after active treatment with immunotherapy.

Biomarker	Change after immunotherapy
Skin prick reactivity	↓
Allergen specific IgE	↓ (after initial increase)
Allergen specific IGG4	↑
Basophil activation	↓

Oral immunotherapy

Oral immunotherapy (OIT) involves exposing patients to escalating doses of the offending food with the goal of inducing desensitization or sustained unresponsiveness (Tables 1–4). OIT has primarily been attempted in the research setting and is not FDA approved. A typical OIT protocol involves an entry challenge to establish clinical reactivity, followed by escalating doses of the offending food until a pre-specified maintenance dose is achieved for a pre-specified amount of time. If this maintenance dose is successfully achieved, the patient is said to be *desensitized*. After that, the maintenance dose may be discontinued for a pre-specified amount of time and the patient rechallenged with the offending food. If the subject does not react, he or she has been said to have achieved *sustained tolerance*.

Side effects of OIT continue to be elucidated, and most commonly include abdominal pain and oral pruritus (75%, Table 3). More severe side effects such as eosinophilic esophagitis (2.7%) and severe reactions requiring intramuscular epinephrine/adrenaline (25% of patients, Table 3) are not uncommon.^{15–18}

The mechanism of action of OIT is postulated to involve modulation of the immune response (Table 1). Specifically, a decline in specific IgE and concomitant increase in protective IgG4, as well as induction of basophil activation energy and increased regulatory T-cells have been shown.^{19–21} Mast cells, basophils and neutrophils are all involved in the anaphylactic response, and are likely modified by OIT.²² B cell populations associated with food allergy have been described, along with changes in their IgG4 repertoire induced by OIT.²³

Oral immunotherapy for food allergy has been reported as early as 1998, though more recent trials have exhibited higher degrees of control and randomization; these will be reviewed below.²⁴

Peanut OIT

While advances in OIT continue rapidly, there is still no FDA-approved treatment available, and a recent Cochrane review reports uncertainty associated with this approach.²⁵ In a 2009 landmark peanut OIT randomized controlled trial (RCT), children with peanut allergy underwent an OIT protocol including initial day escalation, buildup and maintenance phases, and then OFC.²⁶ This systematic approach is typical of most RCTs for food allergy. Twenty-nine subjects completed the protocol, 27 of whom successfully ingested 3900 mg of peanut protein (equivalent to about 16 peanuts) following treatment. Mechanistic data reported included diminished skin prick test reactivity, peanut specific IgE, and basophil activation in the treatment group, with peanut-specific IgG4 significantly increasing.

In 2011, peanut OIT was further explored in another RCT, examining 28 subjects aged 1–16 years.²⁷ All 16 children in the treatment arm tolerated 5000 mg of peanut protein (roughly 20 peanuts) after OIT. Mechanistic data was of similar pattern to that

Table 2

Tolerance and sustained unresponsiveness induced by oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT).

Type of IT	Tolerance	Sustained unresponsiveness
OIT	>60%	10–50%
SLIT	10% (70% show modest level of tolerance)	Minimal
EPIT	Modestly induced in 28–50%	None demonstrated to date

Tolerance is defined by being able to tolerate the food in a typical diet. Sustained unresponsiveness is defined as being able to tolerate the food in a typical diet after immunotherapy has been terminated.

Table 3

Summary of adverse events reported in oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT).

Type of IT	Mild adverse events	Serious adverse events
OIT	2–5% of doses, mostly abdominal	Epinephrine/adrenaline required in less than 1% of doses, but up to 24% of patients. EoE association 2.7%.
SLIT	<2% of doses, mostly oropharyngeal	No severe or anaphylactic reactions reported.
EPIT	50% of patients, mostly skin	No severe or anaphylactic reactions reported.

Table 4

Factors which may improve efficacy and safety of food immunotherapy.

Efficacy: factors which may improve	Safety: factors which may improve
• Probiotic adjuvants • Younger age at initiation of IT	• Anti-IgE therapy (omalizumab) • Avoid dosing near exercise or URI • Lower maintenance dosing • Selection of patients with low specific IgE

described above, and additionally lower IL-5, IL-13 and an increased ratio of FOXP3-hi expression to FOXP3-intermediate expression CD4+ CD25+ T-cells was observed at the time of OFC in treated subjects.

A more recent RCT, the 2014 STOP II trial, was a crossover trial examining children 7–16 years of age.¹⁵ The primary outcome was desensitization, defined as tolerating 1400 mg of peanut protein, and this was recorded for 62% of subjects. Quality of life scores improved overall after OIT, although side effects including nausea and vomiting were reported in 31 of 39 patients. A systemic reaction requiring intramuscular epinephrine/adrenaline was reported after one dose in the trial (0.01%).

Desensitization to peanut protein using OIT is clearly possible. A remaining question is whether, after discontinuing OIT, desensitization persists. We define *sustained unresponsiveness* as persistent tolerance of the offending allergen after cessation of OIT. In 2014, Vickery *et al.* examined the phenotype of patients who exhibited sustained unresponsiveness after desensitization to peanut protein. In this protocol, subjects were desensitized to tolerate 4000 mg/day of peanut protein. OIT was then stopped, and one month later 12/24 subjects demonstrated sustained unresponsiveness to a 5000 mg open food challenge.²⁸ Subjects who exhibited sustained unresponsiveness had lower levels at baseline and at final OFC of skin prick test size, peanut-specific IgE, Ara h 1 IgE, and Ara h 2 IgE, along with reduced peanut-specific IgE to total IgE ratio. IgG4 was not significantly different among groups. In patients who exhibited sustained unresponsiveness, diet was liberalized to incorporate peanut.

Protocols have been modified to be shorter, including one in 2015 that reported faster time to maintenance dosing, lower maintenance dose (2 g peanut protein), and fewer side effects. Though this was a small study with limited generalizability, similar efficacy of desensitization was observed.²⁹

Peanut OIT with adjuvant

The use of adjuvants in OIT represents a promising area of exploration. A 2014 double blinded RCT, examining patients 1–10 years old, reported using peanut OIT combined with a bacterial adjuvant, the probiotic lactobacillus.³⁰ Among treated patients, desensitization occurred to 2 g of peanut protein in 89%. The authors examined possible sustained unresponsiveness, and reported success 2–5 weeks after discontinuation of treatment in 23 of 28

patients (82.1%), and in 1 of 28 patients receiving placebo. The number needed to treat was calculated to be 1.27, treat 9 patients, and 7 will show sustained unresponsiveness. This study was limited by the absence of an OIT-only group to show the effect of the probiotic, and the short time off of OIT until challenge.

A limitation of all OIT studies is a lack of long-term data. Whether sustained unresponsiveness exists at one or more years is currently unknown.

Future possibilities for peanut OIT

Use of peanut flour has been robustly studied in OIT, and now alternate formulations are now being examined. A peanut protein polyphenol edible matrix (to make peanut allergens less allergenic) for OIT was examined 2014.³¹ The study used an ex-vivo assay with human blood, and examined the effectiveness of the matrix protein. Compared to unmodified peanut flour, the edible matrix incorporating peanut protein was found to trigger less basophil degranulation. When examined using a mouse model, less mast cell degranulation was observed. Modification or alternate formulation of peanut protein remains an exciting possibility to increase tolerability of OIT.

Egg OIT

In a landmark 2012 study, the largest RCT for egg OIT to date was reported prospectively in children aged 5–11 years old by Burks *et al.*³² Forty children received egg OIT; 55% were desensitized to a maintenance dose of 2 g egg-white powder at 10 months, and 75% at 22 months. A 10 g oral food challenge confirmed desensitization. Of desensitized patients, 28% exhibited sustained unresponsiveness by completing a 10 g egg powder oral food challenge after discontinuing OIT for 2 months.

In 2015, an RCT was reported where a 4-month protocol desensitized 16 children aged 4–11 to a maintenance dose of 4 g of egg-white powder followed by egg avoidance to examine sustained unresponsiveness.³³ Among 16 kids aged 4–11 who achieved desensitization, 31% remained tolerant of egg-white powder after 3 months of avoidance.

Desensitization was reported using increasing home doses of a liquid hen's egg protein, with a success rate of 80% in achieving desensitization.³⁴ Modified protocols requiring OIT dosing as little as 2–3 times per week have been reported with similar efficacy.³⁵ Rush desensitization has induced tolerance in as little as 5 days.^{36,37}

An area of interest in egg allergy is why some patients react to food containing any egg, whereas others are able to tolerate egg in the extensively heated (baked) form. Current studies indicate that 64% of egg allergic patients tolerate extensively heated egg.³⁸ An area of research, then, is whether extensively heated egg may act as immunotherapy among patients who tolerate it. In 2012, this concept was examined in a study where patients tolerant of baked egg consumed it regularly (muffin or waffle), and 53% of those patients tolerated low-heat egg after a median of 37 months.³⁹ Only 26% of baked-egg restricted patients exhibited similar tolerance. This study had significant limitations, including absence of randomization, and further studies examining this question are warranted. Side effects are thought to be significant as well; it is reported that only two-thirds of baked-egg tolerant patients will regularly eat it due to abdominal pain.⁴⁰

The use of recombinant proteins such as Gal d 1, 2, 3, and 4 in egg OIT represents a novel therapeutic option. In a 2015 study, these proteins were found to react with egg-allergic patient's sera, though phase 1 human trials have not been reported.⁴¹

Quality of life appears to improve for patients on egg OIT,⁴² but side effects are common. These side effects include chronic abdominal pain and life threatening anaphylaxis.⁴³ Strategies to

minimize side effects include individualized dosing based on specific egg IgE, which may be a predictor of safety.^{44,45}

Milk OIT

Cow's milk (CM) OIT is thought to work by similar mechanism as other forms of OIT. It has been shown in infants that CM OIT increases protective protein-specific IgG4.⁴⁶ Successful desensitization using CM OIT was demonstrated in 2008, in a RCT of 60 children.⁴⁷ In this study, children were randomized to complete an in-hospital rush protocol followed by maintenance OIT to a maximum daily dose of 150 mL cow's milk. After one year of OIT, tolerance of 150 mL of CM was induced in 35% of treated children versus 5% of untreated. A 2010 study reported a desensitization protocol with weekly home up-dosing in 15 patients.⁴⁸ Adverse events were significant in one-third of those patients, with 2 of 15 in the treatment-group dropping out and 3 having immunotherapy stopped by the study staff.

While many studies have examined OIT in preschool to school aged children, some researchers believe that younger patients may be more amenable to desensitization. Martorell *et al.* studied CM OIT in 2011 among a population of 60 patients aged 24–36 months.⁴⁹ This study was an RCT where 30 children were treated with CM OIT. Among actively treated children, 90% became tolerant of CM, versus 23% of placebo-treated children. Adverse reactions were reported at a very high rate this young cohort: 80% of treated patients, most commonly urticaria-angioedema followed by cough.

Desensitization rates using CM OIT in smaller studies have ranged from 71 to 80%.^{50,51} Adverse reactions have been reported in up to 45.4%–95% of treatment doses, including mild reactions and local symptoms.^{51,52} Similar to other forms of OIT, CM IgG4 levels have been found to increase in patients actively treated.⁵²

Protocols examining SLIT induction followed by OIT have also been examined. In a study from Keet *et al.* in 2012, patients were randomized to receive either SLIT induction followed by OIT versus SLIT alone.¹⁷ While SLIT with OIT was found to be more effective, more adverse events were observed.

Long term effectiveness of CM OIT remains challenging. Five years after desensitization with OIT, only about half of patients successfully desensitized continued to tolerate one serving of milk per day.⁵³ The small number of patients that continue to consume and tolerate CM after OIT is thought to be due to abdominal pain.

Safety and tolerability of OIT has remained challenging. Changes in desensitization protocols based on individual patient characteristics were reported in 2013, where patients with lower CM specific IgE were desensitized faster.⁵⁴ Other patient characteristics that predict eventual tolerance include starting tolerant dose and whether epinephrine/adrenaline is required during initial challenge.^{55,56} Other predictors of clinical reactivity to CM include asthma, asthma requiring controller therapy, and allergy to more than 3 foods.⁵⁷ Laboratory characteristics that may predict safety and efficacy were reported by Martizez-Botas *et al.* in 2015.⁵⁸ In that study, a bioinformatics analysis selected two sets of 16 IgE binding peptides at baseline that predicted safety and efficacy. A similarly structured mechanistic study reported that levels of specific IgA, IgG, IgG1 and IgG4 to CM and casein, and cow's milk-specific IgE prior to OIT were higher in children who discontinued therapy due to adverse events than in those who achieved desensitization.⁵⁶

Many patients undergoing CM OIT have achieved desensitization, but clinical utility has been limited by adverse events.

Multifood OIT

For patients who have allergy to more than one food, multifood OIT has been attempted. In a small phase 1 trial, multifood OIT was comparable in safety to single food immunotherapy.⁵⁹ Among 25

patients, reaction rates of 3.3% and 3.7% were observed for multifood and peanut treated OIT patients respectively. Most reactions were mild, and epinephrine/adrenaline was used twice in each group. Efficacy was examined, though not the primary endpoint, and each group achieved target doses of foods in similar numbers, though the multifood group taking longer temporally to reach target dosing by design.

Multifood OIT has been examined using rush protocol with addition of anti-IgE monoclonal antibody, omalizumab.⁶⁰ Twenty five patients with multiple food allergies were treated with omalizumab for 8 weeks prior to and after rush desensitization in a phase 1 trial. The rush protocol allowed doses of 1250 mg of food protein on the initial day, which was successful in 19 of 25 subjects. At 18 weeks, subjects reached an average of 4 g food protein per allergen. Adverse reactions were comparable to other studies, occurring in 5.3% of home doses, and 94% of reactions were mild. For patients with allergy to multiple foods, these phase 1 studies show promise.

Anti-IgE adjunct therapy with OIT

Since food-specific IgE is largely responsible for allergic reactions to food, it follows that anti-IgE therapy may be a useful adjunct for OIT. Omalizumab was examined as a facilitator for rapid oral desensitization in peanut allergic patients in 2013.⁶¹ While there was no placebo arm, initial results were promising, with 12/13 patients achieving rapid oral desensitization. Ultimately, patients who achieved desensitization were able to tolerate 4 g of peanut flour in a median time of 8 weeks. Adjunctive therapy with omalizumab in children with multiple food allergies resulted in 16 week desensitization in 19/25 participants using multifood OIT, as discussed above.⁶⁰ Using omalizumab to facilitate rapid desensitization to cow's milk has also been reported.⁶² That pilot study reported 9 of 11 patients rapidly desensitized to 1000 mg in one day. Of note, one patient dropped out due to abdominal pain and the other required epinephrine/adrenaline to reverse a severe reaction.

Use of anti-IgE may facilitate rapid desensitization, although more rigorous placebo-controlled trials must be performed. While initial studies are small, rates of adverse events seem similar to conventional OIT.

Safety of OIT

The primary limitation of OIT is safety (Table 3). Adverse events requiring epinephrine/adrenaline administration are commonly reported. One retrospective review reported that among 395 patients and 240,351 doses, 95 doses required epinephrine/adrenaline administration due to a severe reaction.⁶³

Other adverse reactions during peanut OIT are not uncommon. Prospectively, one study reports that 3.5% of patients experience mild upper respiratory symptoms or skin symptoms.⁶⁴ It was reported in that trial that risk of adverse reactions climbs higher with several clinical predictors, including concurrent illness, poorly controlled asthma, timing of dose after consumption of food, physical exertion after dosing, and dosing during menses.⁶⁴

Abdominal symptoms and less severe side effects occur at a higher rate. Initial escalation of dosing was found to be associated with abdominal symptoms in 68% of subjects.⁶⁵ That trial also found other adverse events: an 18% risk of mild wheezing on the initial escalation day, and a 46% chance of having any symptoms after a buildup dose. A larger trial examining OIT found that nausea and vomiting occurred in 79.4% (31 of 39) of patients.¹⁵

Development of eosinophilic esophagitis (EoE) has been a feared complication of OIT. A meta-analysis performed in 2014 reported that EoE occurs in 2.7% of patients treated with OIT, although some feel this is under-diagnosed.¹⁸

In summary, adverse reactions during OIT are frequent, limiting clinical utility, and may include anaphylaxis, abdominal pain, wheeze or development of eosinophilic esophagitis. The gastrointestinal allergic side effects are the most limiting to the use of OIT presently.

Sublingual immunotherapy

As opposed to OIT, where patients consume the allergen of interest, sublingual immunotherapy (SLIT) employs the use of a liquid allergen extract, which patients place on the sublingual tissue. These extracts have been used in the research setting only, and are composed of the allergen suspended in a liquid or dissolving tablet. The sublingual formulation is held in place by the patient for up to several minutes before spitting out or swallowing the solution. SLIT has been FDA approved for pollen allergy (ragweed and grass), though SLIT remains investigational for foods. Indeed, no standardized products with known potency or shelf-life are available.

Peanut SLIT

The mechanism for inducing tolerance using SLIT has not been completely elucidated. Patients receiving SLIT have shown increased in salivary peanut-specific IgA compared to placebo.⁶⁶ Changes in peanut specific salivary IgA correlated to total peanut tolerated during DBPCFC, suggesting that IgA in saliva may have a role in modulating systemic response.

In a multicenter RCT of peanut SLIT, Burks *et al.* found that over 98% of doses were tolerated without adverse reactions beyond the oropharynx, and that epinephrine/adrenaline was not required for any reaction.⁶⁷ Desensitization to 10 g of peanut flour was achieved in 10.8% (4 of 37 patients), although 50% of subjects stopped therapy or dropped out by the 3-year follow up. Eight weeks after stopping SLIT, all 4 desensitized subjects achieved sustained unresponsiveness. Favorable response to SLIT was in part predicted by decreased peanut specific basophil activation and skin prick test titration.

In an RCT to examine the efficacy of 44-weeks of SLIT in peanut allergy, Fleisher *et al.* reported desensitization in 14 of 20 subjects (70%).⁶⁸ Desensitized subjects were able to consume either 5 g or at least a 10-fold increase in peanut powder during OFC, compared to 15% receiving placebo.

Comparison of OIT and SLIT has often come to similar conclusions: OIT is more effective in desensitization, but accompanied by more frequent and severe adverse events. In one retrospective comparison of SLIT to OIT for peanut-allergic children, the authors found OIT to have more significant mechanistic impact, as changes in peanut specific IgE and IgG4 were more pronounced.⁶⁹ OIT patients were noted to be three times more likely to pass desensitization OFC when compared to patients after SLIT. In a SLIT versus OIT prospective RCT, increased food challenge threshold was 141-fold for OIT and 22-fold for SLIT.⁷⁰ Adverse reactions were more commonly seen with OIT: 43% of doses versus 9% for SLIT.

Milk SLIT

Milk SLIT was first reported in 2006, where De Boissieu *et al.* reported 8 patients undergoing 6 months of therapy and a 70% desensitization rate, with 4 subjects eventually normalizing their diet.⁷¹ A larger RCT is reported by Keet *et al.*, with 30 children receiving either SLIT or SLIT followed by low- or high-dose OIT.¹⁷ In this trial, patients received 8 g milk protein challenges after 12 and 60 weeks of maintenance therapy. Of SLIT-only treated subjects, 1 of 10 passed the food challenge. Of subjects treated with SLIT followed by low dose OIT, 6 of 10 passed. Of subjects treated with SLIT followed by high dose OIT, 8 of 10 passed food challenges. After cessation of SLIT or OIT, 6 of the 15 desensitized patients regained

reactivity, and two of those patients became reactive after only 1 week. As expected, the addition of OIT to SLIT led to improved efficacy, but more systemic reactions were observed in OIT treated groups.

In summary, peanut and CM SLIT shows promise as a form of immunotherapy primarily for the safety profile when compared to OIT. Unfortunately, efficacy of SLIT compared to OIT remains limited. No trials regarding SLIT with egg allergy could be found.

One specific niche for SLIT may be for families or children whose goal is to avoid a life-ending reaction with very small, accidental ingestion, with minimal risk of side effects, though further study is warranted.

Epicutaneous immunotherapy

Epicutaneous, or patch immunotherapy (EPIT) studies are in preliminary phases of study and have shown some promise. Mechanistic mouse studies involving EPIT have shown induction of T-regulatory cells, down regulation of the allergic response, and prevention of new allergic sensitization.^{72–77} In 2010, ten CM allergic children were randomized to receive a 48-hour CM-patch three times per week for 3 months versus placebo in a pilot study.⁷⁸ An increasing trend in cumulative tolerated dose of cow's milk from a mean of 1.7 mL–23 mL was shown. Skin irritation was very common, reported in 50% of subjects. Severe reactions or anaphylaxis were not reported.

In 2012, the Efficacy and Safety of Several Doses of Viaskin Peanut in Adults and Children with Peanut Allergy (VIPES) study was initiated.⁷⁹ VIPES is a multicenter, double-blinded placebo controlled, phase IIb study of Viaskin peanut that has enrolled 221 peanut-allergic subjects in North America and Europe. Subjects aged 6–55 were randomized into four treatment arms: placebo, and one of three dosing groups (50, 100 and 250 µg peanut protein). Treatment success was defined as being able to tolerate at least 1 g of peanut protein or a 10 fold higher dose needed to elicit a reaction. Success was seen in all three treatment groups (45.3%, 41.1% and 50%, respectively). When treatment success was defined more strictly and perhaps more practically, as 10-fold improvement in tolerance and a minimum of 1 g tolerance, success occurred in 28.6%, 30.8% and 32.1% in each treatment group respectively, and in 6.5% of placebo treated patients. No systemic reactions requiring epinephrine/adrenaline were observed. This trial remains in progress to assess sustained unresponsiveness and is currently not in press. EPIT remains a subject of intense study, and given the safety profile, this strategy holds much promise.

Non allergen specific therapies

Recombinant vaccine

In the experimental setting, the use of peanut protein using an *Escherichia coli* capsule has been reported.⁸⁰ In this study, the EMP 123 bacterial shell was built around Ara h1, 2 and 3, and rectally administered to adult volunteers. Systemic reactions were observed in over 50% of patients. Another recombinant protein U-OMP16, using a *Brucella* species, was designed then studied in mice in 2014.⁸¹ In the murine model, the recombinant vaccine was found to abrogate IgE mediated milk allergy in mice. While recombinant vaccines certainly show promise, no acceptable safety or efficacy has been demonstrated in humans to date.

Chinese herbals

Food Allergy Herbal Formula 1 (FAHF-1), a Chinese herbal mixture, has generated interest for the potential to dampen the IgE

mediated response. In a model examining peanut-sensitized mice, FAHF-1 was found to prevent peanut anaphylaxis after 14 weeks of administration.^{82,83} The proposed mechanism of action of FAHF-1 is reduction of IL-4, IL-5 and IL-13 stimulation and reduction of allergic response, which was demonstrated *in vitro* in mice.⁸⁴

A more specific formulation, FAHF-2 underwent a phase 1 safety trial in 2010, and no adverse events were reported.⁸⁵ A 2010 follow up human study demonstrated suppression of basophil activation with FAHF-2.⁸⁶ More recently, FAHF-2 was used to treat three children with a history of food allergy.⁸⁷ After treatment for 1–2.5 years, all passed oral food challenge. The active ingredients berberine and limonin have been proposed, both found in FAHF-2.⁸⁸ Without phase 2 studies, this Chinese herbal therapy for food allergy, while fascinating, remains experimental.

On the horizon

A level of efficacy has been demonstrated for OIT, SLIT and EPIT, although an increase in adverse events has been associated with improved efficacy (Fig. 1). The future may incorporate different methodologies including immunotherapy, monoclonal antibodies, adjuvants and probiotics, as researchers fine-tune their approach. Animal models examining helminthes, DNA vaccines, and toll-like receptor agonists are currently underway.^{89,90}

Active prevention

With the startling growth in patients with food allergy, there has been a concerted effort to focus on prevention. A landmark trial reported in 2015 randomized 640 infants with severe eczema, egg allergy or both (high-risk for peanut allergy) to consume or avoid peanut until 60 months of age.⁹¹ Peanut allergy at 60 months was seen in 13.7% of avoidant infants, and 1.9% of actively treated infants (regularly consumed peanut). Early introduction of peanut dramatically reduced the incidence of peanut allergy. This strategy is further being explored, and active prevention with early introduction of peanut is now recommended and determined to be feasible.⁹²

Conclusions

Immunotherapy remains the most promising hope for patients with food allergy, who now rely on avoidance and carrying epinephrine/adrenaline auto injectors in case of accidental exposure (Table 5). Desensitization and sustained unresponsiveness after IT (immunotherapy) have been demonstrated, but at a cost, as

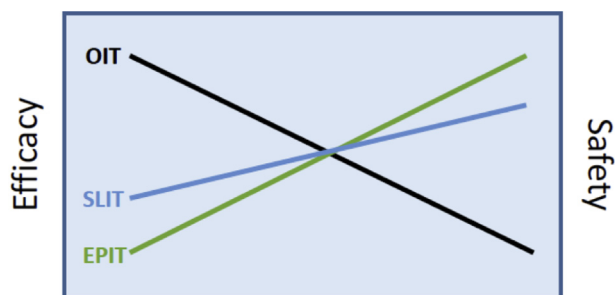


Fig. 1. Efficacy and safety have an inverse relationship as related to food immunotherapy. Oral immunotherapy (OIT) is most efficacious in inducing desensitization, while the highest rate of adverse reactions is observed, some of which are severe. Sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT) are generally less efficacious and associated with fewer total adverse events, none of which have been severe.

Table 5

Key issues in active treatment of food allergy.

- OIT is highly efficacious in achieving desensitization, but is limited by frequent adverse events such as anaphylaxis and EoE.
- SLIT is less efficacious than OIT, but more safely administered.
- EPIT is effective in inducing modest levels of tolerance with fewer adverse events, although further study is warranted.
- Anti-IgE therapy, using omalizumab, may be a useful adjunct in desensitization to have fewer allergic side effects.
- Probiotic adjunctive therapy with OIT has shown promise in an initial trial (though that trial was not placebo-controlled)
- Goals of active treatment of food allergy may shift in the future: from complete desensitization to providing modest levels of tolerance that would keep patients safe in a small, accidental ingestion.
- Active prevention of food allergy using early introduction of peanut in high risk infants will be an important strategy to reduce sensitization.

adverse events are common and can be severe. In the future, we may see more modest desensitization goals; perhaps enough protection to safely tolerate an accidental bite of an offending food. For families in whom the social/emotional impact is significant, this modest amount of desensitization may be dramatically relieving. As studies continue, we will certainly learn more about complications that are not completely understood, such as EoE. We can expect combinations of IT, monoclonal antibodies and adjuvants to further assist researchers find an efficacious, safe product. And while there currently exists no FDA-approved active treatment for food allergy, there continues to be a vigorous search for a cure.

Conflict of interest

AWB has consulting agreements with the following commercial entities: Allertein, Dynavax Technologies Corp., GLG Research, Mastcell Pharmaceuticals, Inc., Perrigo Company, Regeneron Pharmaceuticals, Inc., Perosphere, Inc., ActoGenix, Genetech, Valeant Pharmaceuticals, and Sanofi US Services. He serves on the boards of FARE, World Allergy Organization and Murdoch Children's Research Institute, and has research sponsored by Hycor Biomedical and Allergen Research Corporation. AKK has no conflict of interest to declare.

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