19 Emerging Food Allergy Therapies

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Introduction

IgE-mediated food allergy is a rapidly growing health problem affecting millions of individuals, both children and adults alike, worldwide. In the United States alone it is estimated that 15 million Americans, of which 5.9 million are children under 18 years of age, are affected by food allergy. Epidemiologic studies suggest that there has been an increase in prevalence over the past two decades that mirrors the increase in other atopic diseases like atopic dermatitis [1–5].

Food allergy is thought to be caused by a loss of oral tolerance or a delay in the development of oral tolerance, or both. There are likely genetic and environmental factors that play a role in the development of atopic disease [6, 7]. Current standard therapy for the management of IgE-mediated food allergies involves strict avoidance of the offending food(s) and immediate treatment of allergic reactions, including the use of epinephrine, due to accidental ingestion. This can be anxiety provoking to patients and their families and quality of life can be significantly affected [8, 9]. Prevention and treatment of allergic reactions can also place a financial burden on patients, families, and society (estimated at $24.8 billion per year) as the maintenance of strict avoidance can prove difficult [10]. Unfortunately, there are no FDA-approved treatments for food allergy to date and significant resources are being directed towards finding potential preemptive treatments and cure [11–13].

In this chapter, we first focus on reviewing food-allergen-specific treatment techniques that are under clinical investigation. Several types of immunotherapy are actively being studied for the treatment of food allergies, including oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT). As OIT and EPIT have been covered in depth in prior chapters, the current chapter will begin with a focus on SLIT. A number of other food-specific therapies will also be discussed including peptide-based vaccines, recombinant allergen vaccines, allergen DNA vaccinations, and transgenic plants, which have less supportive clinical study data available but which present exciting possible treatment modalities that warrant further investigation. Finally, non-allergen-specific therapies including anti-IgE treatment, traditional Chinese medicine, and probiotics will then be reviewed.

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Concepts of Desensitization, Sustained Unresponsiveness, and Tolerance in Immunotherapy

Although allergen avoidance is an effective form of management of food allergy, it is not equivalent to a true treatment or cure. To mitigate the risk of reacting to allergens, several investigational therapies are currently being studied. Currently, the most-studied form of disease-modifying treatment is allergen immunotherapy, which for the purposes of treatment in food allergies, is administered via three main routes: sublingual (SLIT), oral (OIT), and epicutaneous (EPIT) [12–15]. Treatment regimens consist of daily, incremental doses of whole-allergen extracts which are administered over the course of months to several years (Fig. 19.1). The over-arching goal of immunotherapy is to induce sustained immunologic and clinical tolerance to an allergen following cessation of therapy.

In order to evaluate immunotherapy and other emerging therapies for food allergy, it is important to understand the concepts of clinical desensitization, sustained unresponsiveness, and tolerance. *Desensitization* is defined as a temporary increase in the dose threshold required to trigger an allergic reaction while receiving active therapy. Desensitization may confer a level of protection in case of accidental ingestion but is usually achieved only after months of therapy and is dependent upon continued treatment. Loss of desensitization is not unusual, either in food allergy therapy or in the treatment of other allergic diseases, such as environmental allergies or hymenoptera venom allergy. The ideal therapy would, of course, be curative and allow an individual to ingest any amount of allergen without symptoms even in the presence of activating factors (such as acute illness or exercise). This is termed *tolerance*, which is not thought to depend upon continued allergen exposure. Clinical studies often assess whether an increased threshold of reactivity to an allergen is lost during a period off therapy or whether a temporary remission or *sustained unresponsiveness* (SU) can be maintained. Achieving SU appears to require years of therapy and has only been evaluated and identi-

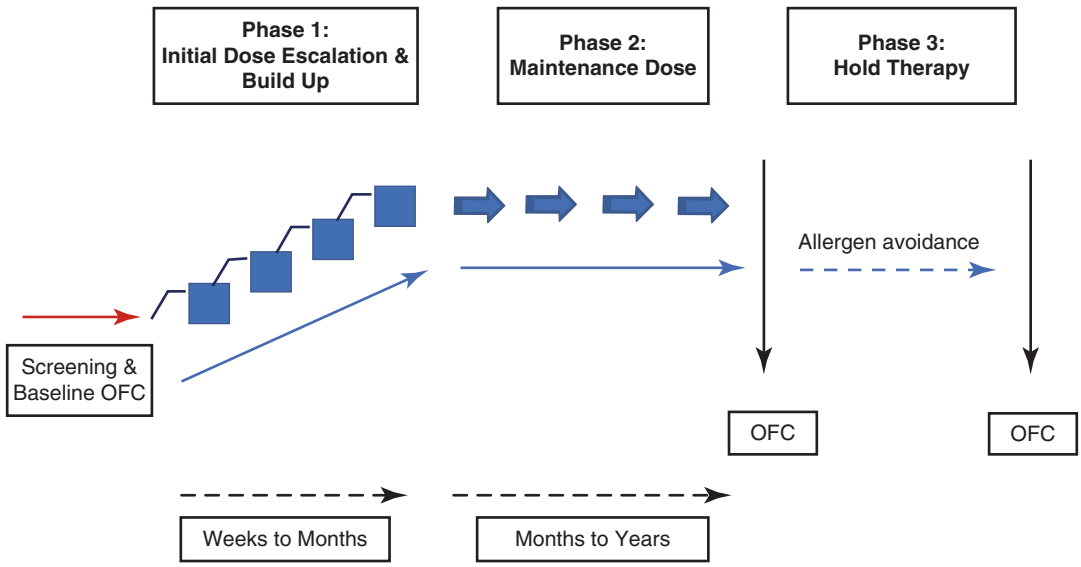

Fig. 19.1 General food immunotherapy administration protocol used in clinical studies. Subjects are first screened and have a baseline oral food challenge (OFC) performed to verify allergy and evaluate for threshold reactivity. Treatment begins with the build-up phase (+/− initial dose escalation with OIT) involving daily home dosing with observed dosage increases every 1–2 weeks. Once the maintenance dose is achieved, dosing continues for months to years and concludes with an OFC to evaluate for desensitization. Certain protocols then include a period of treatment avoidance lasting up to several months followed by an OFC to evaluate for sustained unresponsiveness

fied in subsets of treated individuals [16–19]. The biologic mechanisms underlying desensitization, sustained unresponsiveness, and tolerance are not well understood, and the achievement of true clinical and immunologic tolerance following active treatment of food allergy requires further investigation [12, 17, 20].

Allergen-Specific Immunotherapies

Sublingual Immunotherapy

The sublingual route of allergen administration is of significant interest given its success in achieving tolerance in individuals suffering from environmental allergies [21]. SLIT in food allergies involves administration of an allergen extract in liquid form to the sublingual space where it is held for 2–3 minutes to promote absorption and then swallowed. Dosing protocols for SLIT do not include the initial multi-dose escalation day commonly seen in OIT protocols. Rather, subjects begin treatment in the biweekly dose escalation phase receiving their first dilution of SLIT under clinical observation. If the dose is well tolerated, then subjects repeat the dose daily at home with dose escalations every 2 weeks until maintenance dosing is reached. Some SLIT protocols allow for weekly updosing and for some updosing to be performed at home, which offers a significant advantage over OIT in decreasing the time and cost associated with frequent clinic visits. This type of dosing schedule is in contrast to EPIT where only a single dose patch is required. The dose is instead controlled by a prescribed patch application time which is gradually increased over a few weeks until application for 24 hours/day is reached and only intermittent clinical monitoring is needed. Notably, dosing in SLIT is usually on the order of micrograms to milligrams, which is higher than with EPIT but much lower than with OIT dosed in milligrams to grams (Table 19.1). Maintenance SLIT therapy

Table 19.1 Comparison of food immunotherapies under current clinical investigation

	OIT	SLIT	EPIT
Allergens studied	Peanut, milk, egg, wheat, and multi-food regimens	Peanut, milk, hazelnut, peach	Peanut, milk
Observed dosing	Updosing under observation	Updosing under observation	Initiation and periodically afterwards
Typical maintenance dose	300–4000 mg	2–7 mg	50–500 μg
Typical protocol	Initial dose escalation over 1–2 days, then build-up with dose increases every 2 weeks until maintenance	Build-up with dose increases every 1–2 weeks until maintenance	Increasing patch application duration every 1–2 weeks until 24 hrs/day maintenance administration
Restrictions around dosing	Administer with food; avoid physical activity for 2 hours; do not take within 2 hours of bedtime; hold during acute illness	No eating for 30 minutes following dosing; hold during acute illness	Administer to intact skin; hold during acute illness
Immune modulation	↑ Food-specific IgG4 ↓ Food-specific IgE ↓ Skin testing and basophil reactivity	↑ Food-specific IgG4 ↓ Food-specific IgE ↓ Skin testing and basophil reactivity	↑ Food-specific IgG4 ↓ Food-specific IgE ↓ Skin testing
Common side effects	Gastrointestinal (abdominal pain, nausea), oral (local)	Oropharyngeal (local)	Skin (local)
Advantages	Higher reaction thresholds achieved compared to SLIT and EPIT	Moderate reaction thresholds, less frequent adverse effects	Simple administration, no taste aversion, strong safety profile
Disadvantages	Frequent office visits for updosing, common GI adverse events, risk of EoE, restrictions around dosing	Wider range of responses than OIT, medicinal taste, lack of phase III studies	Lower median reaction thresholds than OIT and SLIT after 12 months

then continues for a period of months to years and has been associated with clinical desensitization and changes in antigen-specific immune responses [15].

It is believed that SLIT works through allergenic interaction with Langerhans cells, which are the major dendritic cell population in oral mucosal tissues. Evidence suggests that allergen binding of oral Langerhans cells displays saturation kinetics that are dependent on both the allergen dose and exposure time, which is further supported by prior studies performed in mouse models and humans evaluating the safety and efficacy of sublingual immunotherapy in the treatment of allergic rhinitis [22–24]. Following antigen binding, Langerhans cells migrate to local lymph nodes where interactions with T-cells promote immune modulation through enhanced production of immunosuppressive cytokines, TGF-β and IL-10, and induction of Tregs [25].

The study of SLIT in clinical trials for the treatment of food allergy has primarily focused on peanut, although a few other foods including milk, hazelnut, peach, and kiwi have been evaluated with promising results [26–29]. In a multicenter, randomized, double-blind, placebo-controlled trial looking at the efficacy of 44 weeks of peanut SLIT, 14 of 20 subjects (70%) were able to consume either 5 g or had at least a tenfold increase in the amount of peanut powder they could consume compared to baseline [29]. Subjects were subsequently followed in a long-term extended maintenance phase where SLIT demonstrated a good safety profile. More than 98% of doses were administered without reported side effects aside from mild oropharyngeal tingling/itching. No doses of epinephrine were required. Immunological changes suggesting modulation of the allergic response including decreased peanut-specific basophil activation and skin prick testing persisted for the duration of study [14].

These results suggest that SLIT therapy may be an efficacious and safe treatment option for food allergy in the future, but larger clinical trials are still ongoing to try to answer additional questions regarding its use. For now, SLIT remains an investigational therapy and is not yet available to the public in the United States.

Sublingual Versus Oral Immunotherapy

Studies looking at direct comparisons of OIT versus SLIT in terms of efficacy and safety are limited. A retrospective comparison of SLIT versus OIT in peanut allergy in children found more significant changes in peanut-specific IgE and IgG4 levels in those treated with OIT. These patients were also three times more likely to pass a desensitization food challenge compared to those undergoing SLIT therapy [30].

A double-blind, placebo-controlled study evaluated 21 patients with confirmed peanut allergy who were randomized to either peanut SLIT with placebo OIT or peanut OIT with placebo SLIT. Following dose build-up, the daily maintenance dose (3.7 mg of peanut protein for SLIT and 2000 mg of peanut protein for OIT) was continued for 12 months. Oral food challenges were performed after 6 and 12 months of maintenance therapy at which time the subjects and investigators were unblinded. Those individuals that completed the 12-month challenge with mild or no symptoms discontinued therapy for 4 weeks and were then re-challenged. Subjects who were symptomatic at the 12-month challenge proceeded to an unblinded study phase where they were offered peanut OIT or SLIT for another 6 months. Subjects that were able to consume 5–10 grams of peanut protein prior to developing symptoms continued their prior therapy (either SLIT or OIT) for 6 more months. Those subjects that developed symptoms at less than 5 grams of peanut protein continued their prior treatment and had either active OIT or SLIT added on. At the end of this unblinded phase, a cumulative 10,000 mg oral food challenge was performed and those who successfully completed the challenge with minimal or no symptoms were taken off therapy for 4 weeks before being re-challenged.

Out of 21 enrolled subjects, 16 completed 12 months of therapy followed by an OFC. All subjects, regardless of treatment group, demonstrated increased challenge thresholds, and seven subjects (78%) of the active SLIT group and seven subjects (100%) of the active OIT group

exhibited at least a tenfold increase in the amount of peanut protein they could tolerate compared to baseline. However, the OIT group had a greater threshold increase compared to the SLIT group (141-fold versus 22-fold) after 12 months of therapy. Following unblinding, all nine patients on active SLIT continued on their therapy and had OIT added on, but two were unable to complete OIT build-up due to side effects. The other seven individuals completed 6 months of active OIT add-on treatment and were re-challenged, demonstrating a significantly increased tolerated dose (median OFC dose of 10,000 mg) compared to the amount tolerated following 12 months of SLIT alone. Out of the patients on active OIT, one individual passed the OFC at the end of 12 months and was taken off therapy, three individuals stayed on OIT alone for 6 more months, and three individuals continued OIT and had active SLIT added on for 6 months. All three patients that were on extended OIT therapy alone passed the 10,000 mg challenge at the end of treatment. For those on OIT with SLIT added on, a median tolerated OFC cumulative dose of 10,000 mg was achieved which was not significantly different compared to the amount tolerated following 12 months of OIT alone.

Although this study is limited in its sample size, the results suggest that both OIT and SLIT are effective at inducing desensitization with a greater level of desensitization achieved with OIT compared to SLIT. However, the potential advantage in efficacy afforded by OIT should be weighed against safety concerns. In this study, the proportion of doses administered that were associated with adverse reactions was significantly higher in the OIT versus the SLIT group (43% versus 9% of doses, respectively). A total of five doses of epinephrine were required to treat systemic reactions in four patients in the active OIT group while none were needed in the SLIT group [13, 31].

The dosing and efficacy of SLIT can be limited by the volume that can be held in the small sublingual space, but at the same time, lower dosing can confer the advantages of better tolerability and safety while still maintaining an acceptable level of desensitization [32]. These data support that SLIT, with its balance of safety and efficacy, may provide a viable alternative to OIT.

Peptide-Based Vaccines

One disadvantage of immunotherapy using whole native allergens in the treatment of food allergy (as is the case with OIT, SLIT, and EPIT) is the risk of anaphylaxis due to the food allergen binding and cross-linking IgE. By utilizing small peptide fragments containing short (usually ~8–16 amino acids in length), synthetic peptides made up of allergen-derived T-cell epitopes, one theoretically avoids the risk of cross-linking IgE on mast cells or basophils which can elicit immediate-type adverse reactions [33]. A T-cell epitope is the specific part of an antigen or allergen that is immunogenic and antigenic, so these peptides are still able to stimulate T-cell responses and lead to suppression and/or downregulation of the Th2 pathway, which is the primary goal of allergen immunotherapy. Peptide-based food allergy vaccination is a proposed method of treatment of food allergies that is still under early investigation but may offer an improved safety profile compared with classic immunotherapy techniques [34, 35].

In order to manufacture a peptide vaccine, all potential T-cell epitopes must first be identified. Epitope mapping requires the ability to sequence an allergen and to identify allergen-specific T-cell lines from large donor cohorts. These T-cell lines are screened for reactivity against synthetic peptides modeled after the target allergen. Once identified, precise epitope sequences are evaluated for their ability to stimulate T-cells, and those with the strongest immunogenicity are selected for immunotherapy. Peptide modification is sometimes required to improve solubility and stability in manufacturing of the final product. The efficacy of peptide immunotherapy has been demonstrated in studies of perennial and bee venom allergies, but its use in food allergy has not been widely explored [36–38].

Yang et al. investigated the therapeutic potential of peptide immunotherapy using synthetic peptides manufactured from three epitope

sequences that were identified in a previous study in a BALB/c mouse model of allergy to ovalbumin (Gal d2), which is one of the major allergens associated with egg allergy [39, 40]. In this study, mice were sensitized to ovalbumin with repeated oral feedings and then stratified into treatment or placebo groups. The treatment groups were given single synthetic peptide doses (AG-15, AI-15, or SL-15) or a mixture containing all three peptides. Following a three-week treatment period of subcutaneous immunotherapy where injections were administered three times a week, the mice were given oral challenges with high doses of ovalbumin to trigger anaphylaxis. Mice given multiple epitope-containing peptides achieved lower anaphylaxis scores and lower serum histamine and OVA-specific IgE levels compared to single-peptide treated or placebo-treated mice. The co-administration of three OVA T-cell epitopes also produced significantly higher mRNA expression of FOXP3 and TGF-beta in intestinal tissues compared to placebo or single-peptide treated mice. FOXP3 expressing T-cells are known for their inhibitory effects on Th2-allergic responses while TGF-beta inhibits effector T-cells and acts as a regulator in the induction of FOXP3 expression in regulatory T-cells. This suggests a potential modulatory effect of the T-cell response [40]. The authors concluded that ovalbumin peptide immunotherapy utilizing the administration of multiple T-cell epitopes led to suppressive effects in egg allergy in a mouse model that may be used to better understand mechanisms of peptide immunotherapy in food allergy in humans.

Similar research is being conducted in peanut allergy where Ara h 1, Ara h 2, and Ara h 3 are the major peanut allergens that have been identified as potential targets for peptide immunotherapy. Ongoing research into the identification of T-cell epitopes in these peanut allergens is crucial to isolating peptide targets for eventual use in peptide-based immunotherapy [41–44].

Recombinant Allergen Vaccines

The use of recombinant native allergens has also been considered for use in immunotherapy for food allergy, but the major concern in their use is the risk of inducing severe hypersensitivity reactions due to reactivity of the allergens with IgE. The best designed recombinant food allergens have a decreased or eliminated ability to bind IgE while retaining the ability to stimulate T-cell responses that is comparable to native proteins. The use of recombinant allergens in immunotherapy has the potential to induce desensitization with shorter courses of treatment as higher doses can be administered with little or no dose escalation required. In the production of recombinant allergens, IgE reactivity is mitigated through denaturation of the recombinant wild-type allergen, production of recombinant fragments, or formation of mosaics through reassembly of allergen fragments that leads to reduced IgE binding and decreased allergenic potential [45]. On the other hand, the allergen T-cell epitopes are preserved, which allows for IgG antibody production and promotion of regulatory and Th1 immunomodulatory effects. Support for the use of recombinant allergens in immunotherapy primarily stems from prior studies looking at the safety and efficacy of their use in treatment of environmental allergies to various allergens including Birch and Timothy grass pollens [46, 47].

Ara h 1, Ara h 2, and Ara h 3 are three major peanut allergens whose T-cell epitopes have been mapped out using synthetic peptides and sera from a large cohort of peanut-allergic individuals. Additionally, the amino acid sequences needed for IgE binding by these epitopes have been identified, allowing for the production of recombinant hypoallergenic variants of Ara h 1, Ara h 2, and Ara h 3 in *Escherichia coli*. In vitro studies have shown that modified peanut allergens exhibit decreased IgE binding compared to wild-type allergens while still retaining the ability to stimulate T-cell proliferation [48, 49].

Bacterial adjuvants are potent stimulators of the Th1 immune response and can be co-administered with hypoallergenic peanut proteins to help bolster the desensitization effect. The efficacy and safety of this technique has been explored in several studies. The effects of

three times weekly subcutaneous administration of heat-killed *Listeria monocytogenes* (HKLM) with a combination of three modified peanut allergens (mAra h 1, mAra h 2, and mAra h 3) over a period of 4 weeks was investigated by Li, et al. in a murine model of peanut allergy. Mice given the combination of modified allergens plus HKLM not only had reduced serum histamine and peanut-specific IgE levels, but when undergoing a peanut challenge, they had decreased incidence and severity of anaphylaxis compared to placebo mice. The incidence and severity of anaphylaxis in mice treated with mAra h 1–3 proteins alone were also reduced but to a lesser degree than the mAra h 1–3 plus HKLM group [50].

Another study utilized heat-killed *Escherichia coli* that produced engineered Ara h 1, 2, and 3 proteins (HKE-MP123) and administered this mixture rectally to mice and, following an intragastric peanut challenge, found that mice treated with HKE-MP123 exhibited significantly reduced plasma histamine levels and anaphylactic symptoms compared to sham-treated mice. This protective effect lasted up to 10 weeks after treatment was discontinued [51].

Given these encouraging results, a suspension comprised of three recombinant peanut allergens (Ara h 1, 2, and 3) encapsulated within inactivated *E. coli* was developed for human use and named EMP-123. Its safety and efficacy were assessed in a phase I non-randomized, open-label trial. EMP-123 was given rectally in weekly dose escalations from 10 to 3063 μg over 10 weeks in 10 peanut-allergic adults followed by three biweekly doses of 3063 μg. Of the 10 patients, 5 patients (50%) experienced adverse reactions severe enough to prevent them from completing the trial. The other five patients experienced mild or no symptoms. Assessing immunologic differences between the two patient groups revealed that that median baseline peanut-specific IgE and Ara h2-specific IgE levels were significantly higher in those individuals who were unable to complete the trial. Due to the high frequency of adverse reactions, the trial authors concluded that additional modifications to the allergens or dosing regimen would be needed [52].

DNA-Based Vaccines

Another distinct therapeutic approach is to completely discount the administration of protein altogether in favor of allergen exposure in the form of DNA. The concept of vaccinations using genetic material came about from studies showing that injections with a plasmid DNA (pDNA) vector could induce humoral and cellular responses to the encoded antigen. The pDNA sequence is taken up by antigen-presenting cells (APCs) which transcribes and translates the antigen-specific DNA into protein product and presents it on the cell surface to T-cells via MHC complexes [53, 54]. Since genetic vaccination preferentially induces a Th1 immune response, its use in allergic disease has been investigated in different mouse models since a weighted imbalance towards a Th2 immune response has been thought to be a major causative factor in the development of atopic disease [55, 56].

In a murine model, oral gene delivery using Ara h 2 pDNA complexed with chitosan, which is a nonimmunogenic polysaccharide that improves gene adhesion and transport in the gut, led to gene expression in intestinal epithelium. Immunized AKR mice showed a significant reduction in peanut-induced hypersensitivity symptoms following a period of sensitization and subsequent challenge with Ara h 2 protein compared to controls as observed using specific symptom measurements of anaphylaxis, serum peanut-specific IgE levels, and serum histamine levels. The study authors concluded that chitosan-pDNA nanoparticles could represent an oral option for the prevention of the development of food allergies [57]. In another study by Li et al., different mouse strains were administered intramuscular injections of plasmid DNA encoding Ara h 2. Following three weeks of immunization, injections of Ara h 2 elicited anaphylactic reactions in C3H/HeJ mice while immunized ARK/J and BALB/c mice remained asymptomatic. These studies highlight concerns that there is a strain-dependent response to pDNA-based immunizations which may translate to significant interindividual variations in efficacy in the treatment of food hypersensitivity in humans [58].

Additionally, results from human trials using DNA-based vaccines have suggested somewhat disappointing immunomodulatory effects [59].

In an attempt to enhance the efficacy of DNA vaccines, lysosomal-associated membrane protein-1 (LAMP-1) has been included in DNA plasmids to elicit enhanced immunomodulatory effects via greater production of antibodies and cytokines. In a study of Japanese Red Cedar (JRC) allergy, the DNA sequence of either CryJ1 or CryJ2, which are the immunodominant allergens to JRC, were fused to LAMP-1 and administered to BALB/c mice. Resulting data showed high IgG2a and low IgE titers as well as high IFN-gamma production, suggesting an enhanced Th1 response [60]. This suggests that LAMP-DNA vaccines may have therapeutic potential in the treatment of allergic disease. An ongoing phase 1 randomized, placebo-controlled trial is currently underway to assess the safety and efficacy of ASP892 (ARA LAMP Vax), a multivalent peanut (Ara h1, h2, h3) LAMP-DNA plasmid vaccine, in peanut-allergic adults (NCT02851277).

Transgenic Plants

One proposed method of combating the increasing incidence of food allergy is through reduction or abolishment of allergen expression in plants, which has been made possible with advances in biotechnology. In 1996, using antisense RNA technology, the expression of allergenic proteins found in seeds from several transgenic rice plants was found to be significantly lower than wild-type rice [61]. Herman et al. was able to completely suppress the accumulation of Gly m Bd 30 K, which is the major identified allergen in soybean, in soybean plants and their seeds through the use of transgene-induced gene silencing. There were no observed differences in composition, development, structure, or phenotype in the transgenic plants compared to controls [62]. In another study, RNA interference (RNAi) technology was used to decrease expression of the allergenic protein Lyc e 3 in tomatoes. There was decreased skin reactivity with prick-to-prick skin testing using fruits harvested from first- and second-generation transgenic plants compared to wild-type controls, suggesting decreased allergenic potential [63].

But the difficulty with attempts to produce hypoallergenic plants, even with utilization of the aforementioned approaches, lies in the fact that several allergenic proteins are oftentimes involved in IgE binding. Alteration in enough allergens to make the target food less likely to cause an allergic reaction may affect aspects of plant health and viability or even characteristics that would make the food less palatable, like taste and texture [64].

Nonspecific Allergen Immunotherapies

Anti-IgE

Non-allergen-specific approaches to the treatment of food allergy have been discussed, including the use of anti-human IgE IgG1 antibodies, which can be advantageous over traditional immunotherapies in being able to treat individuals who may be allergic to multiple foods or possess allergies to foods for which targeted immunotherapy has not yet been studied. Anti-IgE therapy is based on the concept that anti-IgE antibodies bind to the constant region of IgE molecules which prevents their binding to high-affinity FcεRI receptors on the surfaces of mast cells and basophils. This leads to a reduction in free IgE molecules and inhibition of IgE-mediated hypersensitivity reactions [12, 32, 46].

The first study looking at anti-IgE therapy in food allergy was a double-blind, placebo-controlled trial using TNX-901, a humanized IgG1 monoclonal antibody against IgE, performed by Leung, et al. in 2003. Results showed that subcutaneous administration of TNX-901 every 4 weeks for 4 doses in subjects with confirmed peanut allergy increased the mean reactivity threshold to peanut during oral challenge compared to placebo in a dose-dependent manner; however, the increase was only statistically significant in the group receiving the highest monthly dosing of 450 mg. Additionally, about 25% of treated subjects in the

450 mg monthly group showed no change in the threshold dose, suggesting that a subset of patients may not benefit from anti-IgE therapy or would require more frequent or higher doses to see a protective benefit [65].

Further studies using TNX-901 were discontinued following an agreement between pharmaceutical companies involved in developing anti-IgE therapies [66]. Subsequent studies utilized omalizumab (Xolair), a humanized monoclonal anti-IgE antibody that has shown promise in human studies of asthma and has been approved for treatment of severe, persistent allergic asthma. A phase II, double-blind, placebo-controlled trial performed in 2011 looked at the use of omalizumab in the treatment of peanut allergy. The study intended to randomize 150 subjects with confirmed peanut allergy and to compare changes in peanut tolerability thresholds before and after therapy. Unfortunately, the study was terminated early due to two severe anaphylactic reactions that occurred during the initial screening and enrollment process before omalizumab was actually initiated. Prior to trial discontinuation, 26 subjects had been randomized to omalizumab or placebo with 14 subjects completing 24 weeks of therapy followed by a double-blind, placebo-controlled oral peanut challenge. Four (44.4%) of omalizumab-treated subjects could tolerate at least 1 gram of peanut flour following completion of therapy compared to one (20%) placebo-treated subject. A large proportion of subjects did not achieve the primary endpoint, experiencing reactions at <1 gram of peanut flour; however, there was a shift towards greater peanut tolerability in omalizumab-treated subjects compared to those receiving placebo [67].

In addition to its limited clinical efficacy data as a monotherapy, anti-IgE therapy poses some significant disadvantages including the need for regular clinic administered injections and the high cost associated with treatment. Given the recent dramatic increase in studies examining immunotherapy protocols for food allergies, the use of anti-IgE therapy as an adjunct to other food-specific therapies has gained increasing attention [66]. In particular, administration of omalizumab with OIT may offer protective effects against IgE-mediated reactions, allowing for safer dose escalation and better treatment tolerability. In a randomized, placebo-controlled study, 37 peanut-allergic children were initially treated with either 12 weeks of omalizumab or placebo. They then underwent rapid one-day desensitization up to a cumulative dose of 490.5 mg of peanut protein, which represented a dramatic increase from the 6 mg maximum dose more typical of OIT protocols. The highest tolerated dose was administered daily at home followed by weekly updosing up to 2000 mg of peanut protein rather than the usual biweekly dosing schedule. The anti-IgE study drug was then discontinued and subjects continued on 2000 mg of peanut protein daily, if tolerated. An oral food challenge with a cumulative dose of 4000 mg peanut protein was performed 12 weeks following anti-IgE study drug discontinuation and, if tolerated, the 4000 mg daily dose was continued thereafter. The median peanut dose tolerated during rapid one-day desensitization was 250 mg for omalizumab-treated patients compared to 22.5 mg for placebo-treated patients. There were 23 out of 29 (79%) subjects in the omalizumab group that tolerated 2000 mg of peanut protein following omalizumab discontinuation compared to one out of eight subjects (12%) on placebo, which was a statistically significant difference. All 23 subjects on omalizumab passed the 4000 mg open challenge compared to only one subject on placebo. This suggests that the addition of omalizumab may allow for rapid OIT desensitization and offer protective benefits up to 6 weeks after the drug is discontinued [68]. Several other studies on the use of omalizumab with desensitization protocols to various foods have been performed with encouraging results [69–72], but one important question to consider is whether the rate of adverse reactions with continued OIT increases at some point after omalizumab has been discontinued. In a study by Nadeau et al., there were two reported adverse reactions graded "moderate" in severity and treated with epinephrine autoinjectors following omalizumab cessation in two patients (out of a total of 11) who were receiving cow's milk maintenance OIT [70]. This is a concern that requires further investigation.

Traditional Chinese Medicine

Herbs and herbal mixtures have been utilized in traditional Chinese medicine for centuries for the treatment of various ailments. Western countries have also developed interest in the use of alternative or complementary therapies including herbs for different diseases, such as asthma, but no prior research into the use of herbal remedies in food allergy had been conducted until relatively recently [46, 73].

The first study on the use of herbs to treat food hypersensitivity in a murine model of peanut allergy utilized Food Allergy Herbal Formula-1 (FAHF-1), which is a formulation containing 11 different herbs. Mice were started on 7 weeks of therapy with FAHF-1 after being sensitized to peanut. Following therapy, the mice were challenged to peanut and had anaphylactic symptoms, body temperatures, plasma histamine, and peanut-specific IgE levels measured. Results showed that FAHF-1 completely blocked peanut-induced anaphylactic symptoms and reduced mast cell activation and histamine release. Serum IgE levels were also significantly reduced compared to controls. There were no observed toxic effects on the liver or kidneys, even at high doses [46, 74].

Following this study, FAHF-1 was reformulated to a nine-herb regimen after two herbs were removed to improve safety as they had potentially toxic properties if processed incorrectly. This simplified formula was named FAHF-2, and its safety was demonstrated in a study where mice were administered 24 times the effective daily dose. Several blood tests were obtained 2 weeks after the dose was given with no abnormalities noted in blood counts and renal or hepatic function. Histology of all major organs was normal as well [75]. The efficacy of FAHF-2 was then assessed using a murine model of multiple food allergy. Mice were orally sensitized to peanut, codfish, and egg and given daily orally administered FAHF-2 for 7 weeks afterwards. Following the completion of therapy, the mice underwent separate oral food challenges with peanut, codfish, and egg. Mice treated with FAHF-2 were completely protected from anaphylaxis based on symptom scores, body temperature, and serum histamine levels after challenge with each allergen, suggesting that FAHF-2 offers protection from anaphylaxis in an allergen non-specific manner [76].

Based on the encouraging data from mouse models displaying effective and safe protection from anaphylaxis with FAHF-2, a phase II, double-blind, placebo-controlled trial to examine its safety and efficacy in humans was recently conducted. Sixty-eight subjects with a history of peanut, tree nut, sesame, fish, or shellfish allergy were assigned randomly to either treatment with FAHF-2 or placebo. Although many subjects had allergies to multiple foods, only one food allergen was studied during the trial for each participant. After 6 months of therapy, an oral challenge with 5 grams of allergen protein was performed. Although treatment with FAHF-2 was well tolerated, significantly more placebo-treated subjects had improvements from baseline in the amount of allergen able to be consumed following treatment compared to FAHF-2 treated subjects. In contrast, in vitro studies looking at FAHF-2 effects on cytokine levels in peripheral blood mononuclear cells (PBMCs) showed that incubation with FAHF-2 and food allergen produced significantly less IL-5, greater IL-10, and increased regulatory T-cells compared to untreated cells, suggesting favorable immunomodulatory effects. The study authors suggested that further research into optimization of the treatment dose and duration of FAHF-2 and consideration of combination therapy with concurrent allergen exposure (such as with OIT) may result in improved clinical efficacy [77]. A phase II, double-blind, placebo-controlled clinical trial investigating the use of FAHF-2 as an adjunct to multi-food OIT and omalizumab is currently underway (NCT 02879006).

Probiotics

The "hygiene hypothesis" suggests that a lack of early childhood exposures to infections or microorganisms may contribute to the abnormal development of immune tolerance, leading to an increasing incidence of allergic disease [78,

79]. Support for this hypothesis comes from studies performed on germ-free mice that reveal that immune tolerance does not develop appropriately in the absence of a gut microbiota. The microbiome of the GI tract is a major source of microbial exposure and differences in bacterial colonization, which can be affected by geographical or other environmental factors, may play a role in observed differences in disease prevalence throughout the world. This has prompted researchers to study the use of probiotics as a potential solution to the allergic epidemic.

Several clinical studies have been conducted to evaluate the efficacy of probiotics for the prevention or treatment of different allergic diseases with conflicting results [78, 80–86]. There have been few trials looking at the use of probiotics in the treatment of food allergy that utilize oral food challenges in their study design. A trial looking at the use of *Lactobacillus casei* and *Bifidobacterium lactis* on the acquisition of oral tolerance in milk allergic children did not show a difference between children treated with probiotics for 12 months versus children on placebo [87]. However, treatment with *Lactobacillus rhamnosus* combined with extensively hydrolyzed casein formula increased the rate of milk allergy resolution in children compared to control subjects that received only hydrolyzed formula alone [88, 89].

The use of probiotics as an adjuvant to OIT has also been evaluated. In a double-blind, placebo-controlled trial, *Lactobacillus rhamnosus* was administered with peanut OIT in children with confirmed peanut allergy. Subjects were treated for approximately 18 months and had sustained unresponsiveness (SU) assessed with 4 g oral peanut challenge performed 2–5 weeks after the completion of therapy. About 82% of subjects treated with OIT and probiotics achieved SU compared to 3.6% in the placebo group, which was statistically significant. However, due to the lack of an OIT-only or probiotic-only control group, it is unclear through this trial alone how much additional effect the use of probiotics adds to the use of OIT alone [90].

If a benefit to the use of probiotics exists, it is likely that the benefits of supplementation are strain specific, but there is insufficient evidence to support the use of one particular bacterial strain over another at this time. Other factors that could influence responsiveness to treatment include individual differences in bacterial colonization or immune development which can be affected by things like genetics, susceptibility to bacterial colonization, maternal flora, or diet [78, 91]. More research into these individual differences in food allergic patients could aid in the development of future randomized clinical trials that can focus on the appropriate probiotics to use in people with food allergy.

Considerations for Future Use of Immunotherapy in Clinical Practice

Food allergen immunotherapy is not currently a recommended part of routine clinical care, given persistent safety concerns, questions regarding appropriate dosing and treatment schedules, accurate identification of responders, and ultimately the lack of an FDA-approved product. However, as more information is being gathered and questions clarified through ongoing research, the landscape of food allergy treatment is changing and immunotherapy in the form of OIT, SLIT, and EPIT to treat IgE-mediated hypersensitivity reactions to major food allergens seems likely to be a standard part of food allergy management in the near future.

An important inclusion in treatment guidelines should be recommendations on how to select appropriate patients to undergo therapy. Currently, no strict criteria exist to help providers determine which patients might be too high risk to receive treatment, but factors like extreme sensitization to a food or a history of anaphylaxis would need to be taken into consideration prior to starting treatment. Immunotherapy trials almost always exclude individuals with a history of severe anaphylaxis, uncontrolled asthma, or other conditions that would place them at increased risk for a serious adverse reaction, and so data on immunotherapy response is not available in this subset of patients and individuals that fall in this category may not be appropriate to undergo food

immunotherapy. Other factors that may increase the risk for more frequent and severe adverse reactions include a lower tolerated threshold dose at initial study screening, higher food-specific serum IgE levels, higher food-specific serum IgE to total IgE ratios, larger skin prick testing wheal diameter, and a personal history of asthma or allergic rhinitis. Studies have shown that these factors can affect treatment adherence and attainment of desensitization and SU [92, 93]. But not enough is known at this point to provide specific recommendations on how immunotherapy dose or schedule adjustments should be made in patients with these associated risk factors.

Individual patient preferences will also need to be taken into consideration when deciding whether or not immunotherapy is appropriate. Some patients and their families may find the risks associated with immunotherapy to be unacceptable. Other individuals may be hesitant or unwilling to treat potential reactions with an epinephrine autoinjector or be unwilling to avoid cofactors around the time of dosing that can lower the reactivity threshold, like exercise. For safety reasons, these patients should be excluded from treatment. Other potential roadblocks to treatment could include issues with adherence due to patient or family anxiety about dose administration, taste or food aversions, or a lack of resources for appropriate monitoring and follow-up.

With the possibility that multiple forms of immunotherapy will eventually be available for public use, clinician knowledge about the risks and benefits of different delivery routes for immunotherapy and how they compare with each other will be key to selecting the appropriate type of treatment for each patient. Combination therapy, such as having a patient start with SLIT and transitioning to OIT at a later time, or the use of adjunctive therapies like omalizumab may also be viable strategies to improve tolerability and adherence. It will be important that an open discussion about personal and family goals, ability to adhere to therapy, appropriate expectations, potential outcomes, and possible adverse effects be conducted with each patient while taking into consideration each individual's specific history and preexisting risk factors.

Future Directions

While the availability of an FDA-approved, readily accessible, safe, and effective treatment for food allergy appears to be on the near horizon, standardized protocols are needed to guide clinicians on implementation of such therapies into daily practice. Nearly 40% of children with persistent food allergies are also allergic to multiple foods, so the development of treatments for other common food allergens including milk, egg, wheat, fish, and shellfish are needed in addition to a safe approach to combine therapies to concomitantly address these issues [4]. Ways to improve safety and enhance efficacy of immunotherapy or achieve permanent oral tolerance through the use of DNA-based vaccines, recombinant allergen vaccines, adjunctive therapies, or combination therapy need to be further studied. Current clinical trials on food allergy therapies also exclude patients with a history of severe anaphylaxis, but it could be argued that this subset of patients is in most need for a safe and effective treatment. Although much progress has been made, further research into desensitization and tolerance needs to be performed to find a permanent cure for food allergy.

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