

Current and Emerging Therapies for IgE-Mediated Food Allergy

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Abstract Food allergies are a growing clinical problem leading to increased health care utilization and decreases in patient quality of life. Current treatment recommendations include strict dietary avoidance of the offending food as well as use of self-injectable epinephrine in case of accidental exposure with allergic reaction. Although many individuals will eventually outgrow their food allergies, a substantial number will not. Significant effort has been made to find novel treatments that protect patients from food-triggered reactions as well as to develop immune-modulating therapies that could lead to tolerance. In this review, three therapies that have shown the most promise for the treatment of food allergies are highlighted: oral immunotherapy, sublingual immunotherapy, and epicutaneous immunotherapy.

Keywords Oral immunotherapy · OIT · Sublingual immunotherapy · SLIT · Omalizumab · Epicutaneous immunotherapy · EPIT · Food allergy

Introduction

The incidence of food allergy has increased significantly over the past 20 years leading to increased health care utilization as well as decreases in quality of life [1–3]. While a significant number will outgrow their food allergies, only 20 % of children with peanut allergy will do so confirming that food allergies, in some cases, can be a life-long problem [4]. Food-allergic individuals and families frequently struggle with food avoidance diets and often live in fear of accidental exposures that could lead to allergic reactions. Current treatment recommendations include strict avoidance of the culprit food allergen, dietary counseling to train patients and families in food label reading, and ready availability of self-injectable epinephrine. Despite this, nearly 40 % of food allergic subjects will have an accidental exposure each year [5, 6]. There continues to be a high incidence of emergency department visits for food-related anaphylaxis and even food-related deaths [4, 7]. Although there are currently no clinically available treatments for food allergies, there are a variety of novel approaches that have undergone extensive study. These investigations may lead to FDA-approved, clinically available treatment options in the near future (Table 1).

Concepts of Food Allergy Treatment

Research of potential food allergy treatments has focused on two primary outcomes: desensitization and tolerance. Desensitization occurs when there is a change in the threshold dose of a food allergen required to trigger an allergic reaction. Patients who are desensitized require regular exposure to the food allergen in order to continue this state of protection. If stopped, desensitization ceases and the risk of reaction upon exposure to the food allergen is higher. Tolerance allows for ingestion of a food allergen without continuous exposure and

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Table 1 Summary of food allergy treatments

	OIT	SLIT	EPIT	Extensively heated proteins	Omalizumab
Form/route	Powder ingested orally	Liquid placed under the tongue or swallowed	Imbedded patch applied directly to skin	Cooked form of food	Subcutaneous injection
Schedule	1. Initial escalation 2. Buildup 3. Maintenance	1. Buildup 2. Maintenance	Daily	1–3 times/day	Once or twice monthly
Dose	300–4000 mg	2–7 mg	50–500 µg	1000–2000 mg milk/egg	150–375 mg every 2–4 weeks
Side effects	Oropharyngeal, GI, EoE, anaphylaxis	Oropharyngeal; lower risk of systemic reactions	Local skin reactions; lower risk of systemic reactions	Anaphylaxis; OFC should be performed before introduction	Anaphylaxis
Mechanism	Activation of gut dendritic cells	Activation of oral Langerhans cells	Activation of skin dendritic cells	Altered IgE binding to epitopes	Binds to free IgE molecules
Immunologic changes	↓ allergen specific IgE, basophil activation, IL-5, IL-13 ↑IgG4, IL-10, TGF-β, IFN-γ, TNF-α, Treg Altered IgE/IgG4 binding to epitopes	↓ allergen specific IgE, basophil activation ↑IgG4, IL-10, TGF-β	Pre-Clinical Induction of Tregs; Epigenetic changes of FoxP3/Gata-3 Clinical ↓ allergen specific IgE	↓ allergen specific IgE Induction of Tregs	↓ expression of FcγRI receptors on mast cells/basophils ↓ IL-4 production ↑IgG4 ↓ basophil histamine release
Current state	Phase II, III trials	Phase II trials Clinical practice (aeroallergens)	Phase II, III trials	Phase II clinical practice	Phase IIb trials

is the result of underlying immune system changes, but these may take significant time to develop. The concept of “sustained unresponsiveness” has been introduced to reflect the state in which some of the immune changes found with tolerance are seen, but the duration of these changes is uncertain. The mechanisms for inducing sustained unresponsiveness and/or long-term tolerance are not completely delineated, although significant progress in their understanding has been made in recent years.

Oral Immunotherapy

Oral immunotherapy (OIT) involves three phases of treatment. The first phase, initial escalation, involves taking 6–8 doses of the food allergen in increasing increments over a single day. Dosing typically starts with a microgram amount and increases to several milligrams. This is followed by the buildup phase during which a daily dose of the food allergen is ingested with increases every 1–2 weeks, typically reaching several hundred milligrams or even grams of food protein. The maintenance phase is reached when a stable, daily dose of the food allergen is ingested. This phase can be variable in length lasting for months to years and is frequently followed by oral food challenges (OFCs) to determine if the patient has been successfully desensitized to the food allergen. Maintenance dosing may be discontinued for a period of time followed by an additional OFC to determine if sustained unresponsiveness or tolerance has developed. OIT has been successfully completed to a variety of foods including cow’s milk, egg, and peanut [8–12, 13•, 14–16].

OIT is effective in desensitizing food allergic patients, and a portion of these have also developed sustained unresponsiveness. In a study of 23 peanut-allergic children, ages 3 to 14, subjects were placed on peanut OIT with a goal of reaching 500 mg/day of peanut protein; 14 of the 23 subjects achieved this dose. After a median dosing period of 7 months, subjects were able to tolerate a median dose of 1 versus 0.19 g prior to treatment with OIT [15]. Similar findings have been demonstrated in trials of egg and cow’s milk OIT. In a randomized controlled trial of 55 children ages 5–11 who were randomized to egg OIT versus placebo, 55 % of subjects were able to pass a 5 g egg challenge after 10 months of therapy with 75 % of subjects passing the same challenge after 22 months [13•]. Skripak et al. demonstrated an increase in tolerated median dose of 5140 mg following milk OIT versus 40 mg prior to treatment in 19 milk-allergic children [8].

OIT has been considered for multiple food allergens as well. It is estimated that 30 % of children have more than one food allergy, thus treatment for multiple foods at one time would be an attractive option for many families [17]. In a study of 40 subjects, ages 4 to 46 years with a history of peanut allergy alone or to multiple foods, subjects were randomized to receive OIT to peanut or OIT up to five food allergens, including peanut

[18]. Of those, 25 subjects received multiple food allergen OIT with a goal of achieving a tenfold increase in tolerated dose at the 12-month treatment OFC, up to 4000 mg of each food protein. The rate of reaction between treatment for single versus multiple food allergens was similar (median rate 3.7 versus 3.3 %, respectively). Epinephrine use was rare and not increased in those receiving treatment for multiple food allergens. Subjects treated for multiple food allergens did require a longer time to reach a tenfold increase in dose tolerated than those receiving single food OIT (median time difference: +4 months, $p < 0.0001$). These results show promise that OIT can be used safely for multiple food allergens, although more work is needed to determine effectiveness and development of tolerance with this approach.

Vickery et al. demonstrated sustained unresponsiveness in 24 peanut-allergic subjects who underwent peanut OIT for a total of 5 years (maximum dose 4 g/day peanut) [19]. After completion of therapy, subjects removed peanut from their diet and underwent a 5-g OFC 1 month later. Fifty percent of subjects were able to pass the challenge indicating sustained unresponsiveness and peanut was able to be incorporated into their diet. Follow-up over the next 40 months showed consumption of a median daily dose of 555 mg of peanut protein (0–4000 mg/day) on average 3 days per week. Similar findings were demonstrated in the previously described egg OIT study [13•]. Subjects who successfully passed the OFC following 22 months of treatment removed egg from their diet and were re-challenged at 24 months. Twenty-eight percent of subjects passed this challenge and were able to incorporate egg into their diet. At 4 years post treatment, 68 % of all OIT-treated subjects were able to incorporate egg in their diet compared to only 18 % of the placebo group. All subjects that demonstrated sustained unresponsiveness at 2 years continued this state at 4 years and were able to ingest all forms of egg [20]. Caminiti et al., in a randomized, placebo-controlled study, also found that 31 % of egg-allergic children achieved sustained unresponsiveness through treatment with OIT for 4 months followed by the addition of egg into the diet for 6 months [21]. These studies highlight that OIT is effective not only for desensitizing patients to food allergens, but may also provide an avenue for development of tolerance.

Long-term follow-up studies of subjects who have completed OIT show a significant decrease in the number of subjects who continue to ingest the allergenic food. In a 7-year follow-up of 24 children who were treated with milk OIT for up to 36 months, 14 (58.3 %) continued to ingest >200 ml/day of milk while the remaining 10 subjects chose either to reduced their milk intake or eliminated it from their diet due to adverse symptoms. [12, 22•] Keet et al. performed a long-term analysis of two studies during which subjects received milk OIT or sublingual immunotherapy (SLIT) versus SLIT plus OIT [8, 11, 23]. A total of 16 subjects from each study were followed for a median of 4.5 years and 3.2 years, respectively. Twenty-two percent of subjects limited their milk intake due to adverse

symptoms, 9 % due to anxiety, and 13 % due to taste. Thirteen percent reported symptoms associated with exercise, 6 % with illnesses, and 6 % when dosing was missed for several days.

There are a variety of immunologic changes associated with OIT including reductions in skin prick test (SPT) wheal size as well as decreases in allergen-specific IgE levels. Those treated demonstrate increases in allergen-specific IgG4 levels, decreased IL-4 and IL-13 production, suppressed basophil activation through CD63, and increased production of IFN- γ , TNF- α , and IL-5 [13•, 14, 24]. There is also modulation of IgE and IgG4 binding to allergen-specific epitopes [25]. These changes point to a shift from a predominant Th2 response to Th1 with less clinical reactivity to the food allergen. There is evidence that allergen-specific T cells are deleted and replaced by different T cell clones that may facilitate these immune changes [26]. In subjects who display sustained unresponsiveness there is increased production of allergen-specific FoxP3+ regulatory T cells and hypomethylation of FoxP3 CpG. [27, 28] Some immunologic changes reverse when OIT is discontinued, raising the question of short-term rather than long-term immune modulation [29•].

With efficacy demonstrated through the use of OIT, determination of factors that could predict successful treatment and development of sustained unresponsiveness is important. In a study of 24 peanut-allergic subjects who completed OIT for up to 5 years, smaller SPT size, lower peanut-specific IgE, IgE to Ara h 1 and 2, and ratio of peanut-specific IgE to total IgE were associated with an increased likelihood of achieving sustained unresponsiveness [19]. Six egg-allergic children with a median age of 5 years and egg white-specific IgE of 12.5 kU_A/L were given OIT, dosing was based upon the IgE level. Subjects underwent interval increases every 4 months as long as their egg white IgE level remained above 2 kU_A/L, to a maximum dose of 3600 mg. With this regimen, all subjects who completed the protocol achieved sustained unresponsiveness [30]. In a study of 61 children who were randomized to egg OIT for 3 months versus food avoidance, 11 of 30 children (37 %) who received OIT were able to pass a tolerance OFC after 1 month off of therapy versus only one patient in the control group. IgE to egg white >7.1 kU_A/L at the end of treatment was associated with a greater than 90 % probability of failing the tolerance challenge [31]. In a study of 51 egg-allergic subjects, lower baseline specific IgE levels to egg white and ovomucoid (OVM) were associated with a higher rate of achieving sustained unresponsiveness following OIT. (Wright et al. Component-resolved analysis of IgA, IgE, and IgG4 during egg OIT identifies markers associated with sustained unresponsiveness; *Submitted for publication*) In a study of 76 milk-allergic children, ages 5–17 years, who underwent milk OIT for 6 months, those with higher IgE to α -lactalbumin, β -lactoglobulin, and casein were less likely to achieve the goal maintenance dose [32]. These studies indicate that allergen-specific immunoglobulins levels including

those to IgE, IgA, IgG4, and components can be useful for predicting outcomes in those treated with OIT.

Adverse reactions are the primary concern during OIT treatment and occur commonly during dosing. The highest risk occurs during initial escalation and buildup phases, but adverse reactions are also common during maintenance dosing. The majority of reactions are considered mild and commonly consist of oral pruritus and/or abdominal pain [13, 14, 33]. Despite this, 10–15 % of treated subjects may experience significant gastrointestinal reactions that lead to discontinuation of therapy [34]. Systemic reactions and anaphylaxis are rare, but have been reported. There are several factors that are associated with increased risk of adverse reaction including concurrent illnesses, suboptimal control of asthma, physical exertion following dosing, timing of dosing after food, and dosing during menses [35, 36]. In a study of 50 egg-allergic subjects that completed OIT for a median of 18 months, 7.6 % of doses were associated with adverse reactions with epinephrine needed in 26 % of subjects. Subjects could be stratified into three groups based upon reactivity: those who had infrequent, mild reactions; those with frequent, moderate reactions; and those with frequent, severe reactions. Subjects were more likely to have adverse reactions, tolerate a lower dose at OFC, and quit OIT if they had higher specific IgE to egg white, OVM, ovalbumin (OVA), and concomitant asthma. Subjects with OVM IgE >8.8 kU_A/L were also more likely to have ongoing reactions and discontinue OIT [37]. Levy et al. found that a starting dose >30 mg of milk protein (odds ratio (OR) 4.6), not requiring epinephrine during induction (OR 5.2), and no anaphylactic symptoms (OR 15.6) predicted success in tolerating the full dose during an OIT treatment protocol used in 280 milk-allergic subjects [38]. In a study by Vazquez-Ortiz et al. of 81 milk-allergic subjects who underwent OIT, 95 % had adverse reactions, although 91 % of the reactions were considered mild. Seventy-eight percent of these reactions occurred in 25 % of subjects and were associated with cow's milk IgE >50 kU_A/L, SPT wheal size greater than 9 mm, and/or Sampson's grade 2, 3, or 4 reactions during the baseline OFC. Subjects with two (hazard ratio (HR) 2.26) or three (HR 6.06) of these variables were more likely to have persistence of reactions during continued dosing. The overall rate of reaction did decrease by 25 % at 3 months and 50 % at 8 months of treatment [39]. Elizur et al. also demonstrated that reaction rate decreases over time in a study of 197 milk-allergic children that were followed for 6 months after completion of OIT [40]. One hundred and eighty subjects (92.3 %) continued to ingest milk products in their diet although half continued to have adverse reactions, mostly mild. Reaction rates decreased over time from 0.28/month (6–16 months post therapy) to 0.21/month (15–30 months) to 0.15/month (>30 months). Subjects that had a history of anaphylaxis to milk prior to treatment with OIT and those that required epinephrine during the induction phase were more

likely to have persistence of adverse reactions post treatment. In a long-term follow-up of egg-allergic subjects treated with OIT for 3–4 years, 54.5 % experienced reactions with dosing although most were mild. Ninety-five percent of all doses during the study were symptom free and less than 2 % lasted longer than 30 min or required treatment with antihistamines. Eight percent of doses were associated with symptoms during the first 2 years of treatment versus only 0.2 % in years 3–4. No subjects required epinephrine during this dosing period compared to 3 subjects who required epinephrine during previous study OFCs. One subject self reported anaphylaxis approximately 20 months after achieving sustained unresponsiveness but was able to resume consumption of all egg products without further problem [20]. These studies highlight that although adverse reactions are relatively common with OIT they likely become less frequent and less severe over time. However, the potential risk for reactions with long-term treatment remains thus close monitoring should be continued.

OIT has been associated with the development of eosinophilic esophagitis (EoE). In a systematic review of 711 subjects (567 children), the incidence of EoE following OIT was 2.7 %, which frequently resolved after OIT was discontinued [41]. Given these findings, subjects who note persistent gastrointestinal symptoms while being treated with OIT should be evaluated for the development of eosinophilic gastrointestinal disorders.

Several meta-analyses have been performed to review the evidence regarding OIT effectiveness and safety [42–45]. OIT demonstrates effectiveness in desensitizing subjects as well as sustained unresponsiveness but there remain no studies documenting long-term tolerance. Significant concerns remain regarding safety given the high rate of adverse reactions, although most are considered mild. There are ongoing, multi-center phase II and III clinical trials that aim to develop an FDA-approved OIT product that will provide clinical efficacy while minimizing potential side effects.

Extensively Heated Food Proteins

Use of extensively heated foods, primarily milk and egg, has been considered as a treatment option in food allergy due to the ability of heat to disrupt conformational epitopes leading to decreased IgE binding to food allergens. In trials of milk- and egg-allergic children, up to 80 % were able to tolerate extensively heated versions of these foods [46, 47]. When introduced into the diet on a daily basis, subjects have demonstrated a faster rate of tolerance to non-baked versions of these foods. In a study of 65 baked milk-tolerant subjects followed over a median of 37 months, 60 % were able to tolerate unheated milk, 28 % were able to tolerate baked milk/cheese, while 12 % chose to avoid all milk-containing products. Subjects that were baked milk tolerant were 28 times more likely to develop tolerance to non-baked products

compared to those who were baked milk intolerant [48]. Identification of those that are tolerant to extensively heated foods cannot be readily identified through SPT or allergen-specific IgE levels, thus an OFC is often required before introduction of these foods.

Omalizumab

Omalizumab, a humanized antibody which binds free IgE and prevents binding to the high affinity IgE receptor (FcεR1), is approved for the treatment of allergic asthma and chronic urticaria. Omalizumab has been used in trials of OIT to reduce the risk of adverse side effect during induction, to hasten the time to maintenance, and to assist with achieving a higher tolerated dose [49, 50]. In the first randomized, double-blind trial, placebo-controlled trial of omalizumab and OIT, 57 milk-allergic subjects were randomized to receive omalizumab or placebo for 4 months followed by milk OIT for a total of 24 months at which time both groups underwent an OFC to milk. Those that received omalizumab had significantly fewer adverse side effects (2.1 %) compared to the placebo group (16.1 %). The omalizumab group required less treatment when reactions occurred and needed fewer doses to reach maintenance [51]. Omalizumab has also been studied in peanut allergy. Twenty-six peanut-allergic subjects who were unable to tolerate more than 250 mg of peanut protein at a qualifying OFC were randomized to receive omalizumab versus placebo for 20–22 weeks. A post-treatment OFC, completed by 14 subjects, was performed at 24 weeks and threshold tolerability was assessed. Those who received omalizumab were more likely to tolerate a dose ≥ 1000 mg (4 treated subjects versus 1 placebo), although the study did not reach statistical significance [52]. Larger studies are currently underway to evaluate the effectiveness of omalizumab in peanut-allergic subjects receiving OIT.

Sublingual Immunotherapy

Sublingual immunotherapy (SLIT) has been used successfully in the treatment of allergic rhinitis with several advantages over traditional therapy including home dosing and fewer adverse side effects [53, 54•]. Patients place a gradually increasing dose of an allergen extract under the tongue which triggers Langerhans cells in the oral mucosa, suppressing the allergic response [55, 56]. Although not approved for the treatment of food allergy, it has been utilized in clinical trials for kiwi, hazelnut, peach, milk, peanut, and egg allergies [11, 57–61]. In a randomized trial of 18 peanut-allergic subjects who received peanut SLIT, there was a 20-fold increase in peanut threshold compared to baseline (median, 1710 versus 85 mg, respectively). Subjects also displayed decreases in peanut SPT wheal size and basophil activation with increases in peanut-specific IgG4. There were no changes in induced regulatory T cells or levels of IFN- γ , IL-10, or IL-13 [62]. Similar results were found by

Fleischer et al. in a study of 40 peanut-allergic subjects treated for a total of 44 weeks [61]. Subjects were then continued on therapy for 3 years after which it was discontinued for 8 weeks before performing a tolerance challenge. In long-term follow up of this cohort, 98 % of doses were tolerated without side effects other than those limited to the oropharynx and no doses of epinephrine were required. Four of 37 subjects (10.8 %) were desensitized to 10 g and all achieved sustained unresponsiveness. More than 50 % of subjects discontinued therapy during the trial, but only one subject withdrew due to dosing-associated symptoms. [63•] This study highlights an ongoing concern with long-term SLIT compliance. In contrast to the findings by Burks et al., a systematic review of 81 SLIT treatment studies estimates a dropout rate of 14 % with no difference compared to placebo [64]. Compliance in the clinical setting appears to be much lower with only 43.7 % refilling SLIT at 1 year and 13.2 % in the third year [65].

There have also been several trials comparing the efficacy of SLIT versus OIT. In a randomized trial of 21 peanut-allergic subjects comparing treatment with peanut SLIT versus OIT, all subjects that completed either treatment had at least a tenfold increase in threshold dose at 12 months. The increase in threshold dose was much greater with OIT (141-fold) than with SLIT (22-fold) and more subjects achieved sustained unresponsiveness (3 with OIT and 1 with SLIT). Reactions were more common with OIT (43 % of doses) than with SLIT (9 %), although the majority of reactions with both forms of treatment were mild. Subjects receiving OIT did require more epinephrine and beta-2 agonists and were more likely to drop from the study [66•]. A similar comparison between SLIT and OIT has been made in milk-allergic subjects. Thirty milk-allergic subjects were assigned to milk SLIT alone or SLIT followed by OIT. Subjects then underwent a milk challenge after 60 weeks of therapy and if passed, therapy was stopped with additional challenges 1 and 6 weeks later. Only 1 of 10 subjects treated with SLIT alone was able to pass the 60-week challenge compared to 14 of 20 subjects treated with SLIT followed by OIT. Six of 15 subjects that passed the 60-week OFC regained reactivity with subsequent challenges. The overall reaction rate was similar between SLIT and OIT but those that received OIT had a higher rate of systemic reactions [11]. As seen in these studies, SLIT can be utilized to desensitize food allergic subjects with fewer side effects than OIT; however, compliance to SLIT in the clinical setting is poor and the ability to induce sustained unresponsiveness and long-term tolerance remain in question.

Epicutaneous Immunotherapy

Epicutaneous immunotherapy (EPIT) is one of the newest forms of immunotherapy and involves the presentation of food to Langerhans cells in the skin through direct contact with an allergen-embedded patch [67]. This allows for the

allergen to be presented to T cells in regional lymph nodes with downregulation of the effector cell response [68]. In pre-clinical studies, EPIT appears to create a population of regulatory T cells that are long-lasting. EPIT-treated mice also display epigenetic changes including hypermethylation of Gata-3 and hypomethylation of FoxP3 CpG repeats [69–71]. In a randomized study of 19 milk-allergic children who received milk EPIT versus placebo for 3 months, those who received milk EPIT had an increase in tolerated dose of milk of 23.61 ml (± 28.61 ml) versus baseline (1.77 ± 2.98) which was much higher than the placebo group (4.36 ± 5.87 ml (baseline) versus 5.4 ± 5.88 ml). Adverse events primarily included localized erythema or eczema at the site of the patch placement, but this typically resolved within 2–14 days [72]. A similar safety profile was found in a randomized, phase 1 safety trial of 100 peanut-allergic subjects ages 6–50 years who received 250 μ g (children) or 500 μ g (adolescents/adults) over a 2-week period [73]. Eighty-four percent of treated subjects and 60 % of the placebo group experienced local reactions at the site of the peanut patch. Approximately half of subjects had an adverse event outside of localized reactions, but most were mild and transient with no epinephrine required. There were no differences between the treatment arm and the placebo in regards to these types of reactions. There were several systemic reactions, but none required treatment with epinephrine. Adherence to the study product was excellent with 96 % of subjects completing recommended dosing.

Overall, EPIT appears to be relatively safe. Ongoing studies will determine the effectiveness of this form of immunotherapy in desensitizing food allergic subjects. A phase IIa study of 54 peanut-allergic children treated with a 100- μ g peanut patch showed a tenfold increase in the threshold dose at 18 months in up to 67 % of those treated [74]. A randomized phase IIb trial (VIPES) of EPIT for peanut allergy using the Viaskin® patch was completed in 2014. Preliminary results demonstrated that 50 % of subjects had at least a tenfold increase in tolerated peanut dose at the post-treatment OFC compared to baseline. Subjects 6–11 years of age had the best response with 53.6 % achieving a tenfold increase in tolerated dose compared to only 19.6 % in the placebo group [75]. A multicenter phase III study is scheduled to begin enrollment in 2016.

Other Treatments

Multiple other therapies have been or are currently under investigation as food allergy treatments. Subcutaneous immunotherapy (SCIT) is highly effective in treatment of allergic rhinitis and Hymenoptera allergy. In the treatment of food allergy, SCIT can increase the dose threshold needed to trigger a food reaction, but is complicated by a high rate of systemic reactions [76, 77]. Modified food allergens have also been investigated with the hope of inducing immune interaction while minimizing the potential for anaphylaxis. Techniques

studied include use of heat-killed *Listeria monocytogenes* (HKL) and *Escherichia coli* (HKE) attached to recombinant food allergens, peptide and plasmid DNA immunotherapy, and synthetic oligodeoxynucleotides with unmethylated CpG motifs (ISSs) [78–81]. In animal and early human studies, these therapies have shown a reduction in clinical symptoms upon exposure to a food allergen as well as immune changes associated with desensitization. A phase 1 study of peanut-allergic subjects and health volunteers utilizing HKE with recombinant peanut proteins has been performed. Although it appeared safe in healthy volunteers, half of the peanut-allergic subjects were unable to complete dosing due to adverse reactions [82].

Omalizumab use has been described here, but other biologic agents such as IL-4, IL-5, and IL-13 antagonists, toll-like receptor (TLR) agonists, and utilization of Th1 adjuvants such as chitosan have been studied for potential application in food allergy [83•]. Novel delivery routes including intralymphatic immunotherapy, which may require significantly fewer doses to achieve efficacy, have also been studied [84]. Most of these therapies are in early stages of development, but with further work may provide additional roles in the treatment of food allergy.

Conclusions

There is clearly a need for novel food allergy treatments. A variety of therapies have undergone extensive evaluation, but none are FDA approved or recommended for use in clinical practice. Thus far, OIT has shown the most promise in effectively desensitizing food allergic patients with some showing the development of sustained unresponsiveness. Concerns remain regarding the safety of this therapy as well as the ability to induce long-term tolerance. Sublingual immunotherapy appears to have fewer side effects than OIT, but seems less effective at providing significant desensitization or tolerance as well as poor long-term adherence. EPIT represents a novel therapy that also appears safe with high adherence, and studies of efficacy are forthcoming. Until one of these therapies can find the balance between safety and efficacy, it is important that strict avoidance of suspected food allergens continue. Large-scale multicenter trials are underway that will address the questions regarding these therapies and pave the way for clinically available treatments.

Compliance with Ethical Standards

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