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The future of food allergy therapeutics

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Abstract

Food allergy is increasing in prevalence in westernized countries, leading to significant morbidity including nutritional deficiencies and growth delay as well as psychosocial burdens and the potential for fatal anaphylaxis. There is currently no effective form of therapy, and the mainstay of treatment remains strict avoidance. However, there are a number of promising therapeutic strategies currently being investigated for the treatment of food allergies. Allergen-specific approaches, such as various forms of immunotherapy, have been a major focus of investigation and appear to be promising methods of desensitization. More recently, the addition of anti-IgE monoclonal antibodies (mAbs) to immunotherapy regimens has been studied. Early work with antigen-fixed leukocytes in a murine model has shown promise in inducing tolerance, as have vaccines containing modified recombinant food proteins coadministered with heat-killed *Escherichia coli*. Nonspecific approaches include a Chinese herbal formulation, anti-IgE mAbs, and *Trichuris suis* ova therapy. The array of treatment modalities currently being investigated increases the likelihood of finding one or more effective therapies for the treatment of food allergy.

Keywords

Food allergy; Oral immunotherapy (OIT); Double-blind, placebo-controlled food challenge (DBPCFC); Anti-IgE antibody/omalizumab; Desensitization

Introduction

Food allergy, along with other allergic diseases, has increased in prevalence in westernized countries over the past decade. A cross-sectional survey of data on food allergy among children less than 18 years of age revealed an 18 % increase in the prevalence of food allergy from 1997 to 2007 [1]. In a meta-analysis of 51 studies looking at the rates of allergy to cow's milk, hen's egg, peanut, fish, and shellfish, self-reported allergy ranged from 3 to 35 %; whereas estimates from six studies using oral food challenges (OFCs) revealed rates of 1–10.8 % [2]. Based on a 2008 Centers for Disease Control and Prevention report, an estimated 3.9 % of children living in the USA are currently affected by food allergy [3]. Studies in the UK and North America focusing on peanut indicate that prevalence rates have tripled, going from 0.4 % in 1997 to 1.4 % in 2008 [1, 4, 5]. Children with food allergy were found to be two to four times more likely to have other atopic diseases such as asthma, allergic rhinitis, and atopic dermatitis [3].

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Food allergy can be associated with significant morbidity as well as mortality if accidental ingestion is not adequately treated. In the USA, food allergy is the most common cause of anaphylaxis evaluated and treated in the emergency department, accounting for 33 % of all episodes of anaphylaxis in one study [6]. From 2004 to 2006, there was an average of 9,537 hospital discharges per year with a diagnosis related to food allergy among children aged 0–17 in the USA, representing a greater than 3-fold increase over the past decade. Similar trends have been reported in the UK [1, 3, 7]. Unfortunately, food-induced anaphylaxis can be fatal, with more than 90 % of these fatalities caused by reactions to peanuts or tree nuts in the USA [8]. Nutritional deficiencies and growth delay have been shown in children with food allergies who are required to be on a restricted diet. In one study, children with two or more food allergies were found to be shorter, based on height-for-age percentiles, compared to children with one or no food allergies. A greater number of children with cow's milk allergy or multiple food allergies were found to consume less than the recommended age- and gender-specific dietary intake of calcium [9]. A recent study revealed that healthy infants fed a protein hydrolysate formula had significantly lower weight-for-length *z* scores when compared to infants fed with cow's milk formula [10]. These findings could be extrapolated to children with cow's milk or soy allergies who are required to remain on an extensively hydrolyzed protein formula. There is also significant psychosocial impact on patients and families with food allergies. Poorer overall health, more limitations in social activities, and less vitality were reported among patients with food allergies compared to the general population. Food-allergic patients reported poorer generic health-related quality of life than patients with insulin-dependent diabetes mellitus [11, 12]. The rates of reported bullying among pediatric patients with food allergy is also of concern. In one study, 24 % of food-allergic respondents reported being bullied, teased, or harassed because of food allergy, with 86 % of these individuals reporting multiple episodes [13].

Given the fact that there are currently no curative treatments for food allergy or effective means of preventing disease, the current guidelines for the management of food allergy in the USA include strict dietary avoidance, nutritional counseling, and emergency treatment in the setting of accidental ingestions [14, 15]. Fortunately, there are a number of therapeutic strategies currently being investigated for the treatment and prevention of food allergy [16]. In this review, we will discuss current efforts to treat IgE-mediated food allergy, including both allergen-specific and nonspecific approaches (Table 1). Allergen-specific approaches have largely focused on administering gradually increasing doses of antigen via various routes, either subcutaneous, oral immunotherapy (OIT), sublingual immunotherapy (SLIT), or epicutaneous immunotherapy (EPIT). Recently, the addition of anti-IgE mAbs to immunotherapy regimens has also been explored as a potential means for improved safety and a shortened time to achievement of maintenance dosing. Antigen-coupled splenocytes, which have been shown to both prevent allergic responses and induce tolerance in a murine model, offer an alternative allergen-specific approach. Vaccination with modified recombinant food proteins co-administered with heat-killed *Escherichia coli* reduced the severity of anaphylaxis compared to sham-treated mice in an animal model. Nonspecific approaches include the use of a Chinese herbal formulation, which prevented peanut-induced anaphylaxis in a murine model. The use of anti-IgE mAbs to reduce the threshold dose to reactivity to various food allergens is also being investigated. Parasitic helminth infections have been shown to ameliorate the allergic response in a murine model of peanut allergy with decreased production of peanut-specific IgE, therefore the use of *Trichuris suis* ova in humans with food allergy is also being investigated. These various therapeutic strategies represent just a portion of the wide array of investigation currently underway into the treatment of food allergy.

Pathogenesis: oral tolerance induction

The failure to develop oral tolerance or a loss of oral tolerance has been hypothesized to be the primary problem in food allergy [17]. The gastrointestinal tract plays a critical role in the development of oral tolerance, as it is the largest immunologic organ in the body [18]. The gastrointestinal tract must perform a balancing act, processing ingested food into a form that can be absorbed and used for energy and growth, while at the same time preventing the entry of harmful pathogens into the circulation [19]. It accomplishes this through both physiologic and immunologic mechanisms, and disruption of any of these pathways may lead to breakdown in oral tolerance induction.

The physiologic barrier is comprised of a single-cell layer of columnar epithelial cells joined by tight junctions and covered with a mucous layer that collectively works to keep the internal sterile environment separate from the outside world. Normally, when food is ingested, luminal and brush border enzymes, bile salts, and gastric acids break down food proteins, rendering them less immunogenic. These same factors also serve to destroy pathogens [18]. Alterations in gastric pH with the use of antacids have been shown to impede gastric protein digestion, thereby inducing a higher risk for food sensitization [20]. In mice, antacid treatment with sucralfate induced changes in the structure of the gut epithelium and villi, as well as an increase in eosinophils and mucus-producing cells in the intestine [21]. Additionally, altered intestinal permeability, whether genetically predetermined or as seen in various disease states as well as during the newborn period, may promote sensitization via increased exposure to intact proteins [22].

The immunologic component of the gastrointestinal tract consists of innate and adaptive immune cells, which work together to both promote oral tolerance and provide another layer of defense against foreign pathogens. The immunologic components of the innate immune system include polymorphonuclear neutrophils, macrophages, natural killer cells, epithelial cells, dendritic cells, and Toll-like receptors. Dendritic cells and macrophages in the intestine appear to play a critical role in both mucosal tolerance as well as initiating robust immune responses against pathogens. Exactly how this balance is maintained has not been clearly elucidated, but at least one study found that Wnt-beta-catenin signaling in intestinal dendritic cells regulates the balance between inflammatory versus regulatory responses in the gut [23]. The components of the adaptive immune system include intraepithelial and lamina propria lymphocytes, Peyer patches, and secretory IgA, along with circulating antibodies such as IgG and IgE that specifically recognize foreign molecules [19].

The development of tolerance ultimately depends on multiple important factors, including the form and dose of the antigen, underlying host genetics, age, intestinal flora of the host, as well as other environmental factors. In susceptible hosts, oral tolerance might not develop after antigen ingestion, or it may be bypassed by presentation of antigen via an alternate route, such as the respiratory tract or skin [19]. Sensitization can occur via the respiratory route, as seen in oral allergy syndrome. In this syndrome, sensitization to pollen proteins by the respiratory route results in IgE that binds certain homologous, typically labile, food proteins in various fruits and vegetables. Sensitization also appears to be possible after direct exposure of skin to antigen. This was first shown in a mouse model in which food proteins were applied to the skin of mice, followed by oral exposure that resulted in systemic allergic symptoms [24]. Epidemiologic studies from Israel and the UK have suggested that environmental, rather than, or in the absence of, oral exposure to peanut might promote sensitization and allergy [25, 26]. More recently, numerous studies have reported that loss-of-function mutations within the *filaggrin* (*FLG*) gene are associated with the development of atopic dermatitis and other atopic diseases [26]. A recent study evaluated *FLG* as a candidate gene in the cause of peanut allergy and found a significant association with peanut

allergy and loss-of-function mutations in the *FLG* gene with an odds ratio of 5.3 [27]. The association of the *FLG* mutation with peanut allergy was highly significant ($P = 0.0008$) even after controlling for coexistent atopic dermatitis. Collectively, these findings may suggest that early exposure to food protein via the skin, particularly through a disrupted skin barrier, leads to allergic sensitization and that early oral exposure to food allergen may induce tolerance.

Allergen-specific therapy

Immunotherapy for food allergy

Allergen immunotherapy refers to the treatment of disease by modulating the immune response. The ultimate goal of immunotherapy, or any therapy aimed at the treatment of food allergy, is to achieve tolerance to the inciting food allergen. Tolerance, as it relates to food allergy, is the state in which a person can consume a food without any allergic symptoms in weeks, months, or years after cessation of regular exposure to the food antigen to maintain clinical nonreactivity [14]. This is in contrast to desensitization, which depends on the regular ingestion or exposure to the food allergen. In this case, when dosing is interrupted or discontinued, the protective effect may be lost or decreased [16]. The immunologic mechanisms underlying the development of tolerance are not yet well understood. It is thought to involve the initial development of regulatory T cells and deviation away from a T_H2 response, followed at some later stage by anergy [28, 29]. Immunologic changes reported after desensitization to food allergens include decreased reactivity of mast cells and basophils, increased food-specific IgG_4 antibodies, and eventually decreased food-specific IgE antibodies [30–33]. To date, studies using food-specific immunotherapy have been successful at achieving desensitization; however, evidence of sustained tolerance has not been shown.

Subcutaneous immunotherapy

The concept of subcutaneous immunotherapy for the treatment of food allergy dates back to the 1930s when Freeman [34] reported that with the use of immunotherapy consisting of “rush inoculations,” he induced a state of tolerance in a fish-allergic patient. He found that this state of desensitization could be maintained if the patient consumed daily cod liver oil. The use of subcutaneous immunotherapy for the treatment of numerous aeroallergens as well as stinging-insect allergy has been performed for over a century and is a well-established practice among allergists [29, 35]. These ideas led one group to study the use of subcutaneous immunotherapy for the treatment of peanut allergy using aqueous peanut extract [36]. This double-blind, placebo-controlled trial demonstrated a 67–100 % decrease in symptoms during a double-blind placebo-controlled food challenge (DBPCFC) in three subjects who completed the study on peanut immunotherapy. These subjects also had a 2–5-log reduction in end point skin prick test reactivity to peanut extract. The one placebo-treated subject who completed the study did not have changes in these parameters [36]. Unfortunately, the study was terminated prematurely after a pharmacy error resulted in a placebo-treated subject receiving a dose of peanut extract, which tragically ended in death. This event served to highlight the need for better treatment modalities for peanut allergy but also demonstrated the serious risks associated with peanut immunotherapy.

A follow-up study was performed in which 12 subjects with peanut allergy were recruited [37]. Six were treated with injections of peanut extract while six served as untreated control subjects. In the six treated subjects, a maintenance level of tolerance was first achieved by a rush protocol and then maintained with weekly injections for at least 1 year. All treated subjects achieved the maintenance dose of 0.5 ml of 1:100 wt/vol peanut extract; however, only three subjects remained tolerant of the full dose. At the end of the study, all subjects

underwent a DBPCFC. The treated group all tolerated an increased peanut threshold dose and had decreased skin prick test reactivity to peanut extract. Once again, the control group did not exhibit any of these findings. However, anaphylaxis with respiratory involvement was induced during 23 % of the doses during the rush phase, with an average of 9.8 epinephrine injections per subject treated with peanut immunotherapy. The safety parameters did not improve during the maintenance phase, with a rate of systemic reactions of 39 % and an average of 12.6 epinephrine injections per subject [37]. These studies, although providing proof of concept that injected food allergen could induce desensitization, were wrought with significant adverse reactions and therefore discouraged further investigation of this form of therapy.

Oral immunotherapy

To date, OIT is one of the most actively studied therapeutic approaches for the treatment of food allergy. OIT involves the regular administration of small amounts of allergen (usually in a protein powder formulation) orally, mixed in a vehicle such as apple sauce [38]. The amount of protein powder ingested is gradually increased with dose escalations typically occurring in a controlled setting, and daily regular ingestion of tolerated doses during the buildup and maintenance phases occurring at home [16]. The immediate goal of OIT is to induce desensitization, with the ultimate goal being tolerance. Before and at the end of OIT, a DBPCFC is often performed to measure the improvement in the amount of allergen tolerated [39].

The first report of successful OIT was in 1908 and involved a boy with egg-induced anaphylaxis [40]. There were several additional case reports over the past 100 years; however, work on OIT did not begin in earnest until 1984, when Patriarca et al. [41] showed that standardized OIT protocols could successfully treat allergies to cow's milk, egg, fish, and fruit. The next major advancement in the area of OIT came from a 1999 case report in which a 12-year-old girl with milk allergy was successfully desensitized using a rush protocol [42]. In this case, doses were elevated rapidly over a period of days instead of weeks or months.

One of the earliest and largest studies evaluating the role of OIT in the treatment of food allergy was published by Patriarca et al. in 2003 [30] and included both children and adults. This was also the first OIT study to begin evaluating associated immunologic changes. Fifty-nine patients were enrolled in the study with an additional 16 patients enrolled as controls. The OIT protocol consisted of administering progressively increasing doses of food allergen, with dose escalations occurring over a period of 4–6 months. A successful treatment in 83.3 % of the patients was completed. Several immunologic changes accompanied successful completion of OIT therapy, namely a decrease in food-specific IgE levels, an increase in food-specific IgG_4 levels, and skin prick test responses, initially positive and became negative after 18 months. These immunologic changes were similar to those seen in subcutaneous aeroallergen immunotherapy, suggesting that the defect in oral tolerance causing food allergy could potentially be overcome with OIT [38].

In 2007, two additional studies were published evaluating the use of OIT to treat cow's milk and egg allergies in children. Buchanan et al. [43] performed a 24-month pilot study, enrolling seven children with egg allergy. The OIT protocol consisted of three phases: modified rush desensitization, buildup, and maintenance. Fifty-seven percent of the subjects in this study showed evidence of desensitization during the DBPCFC that followed the study. All subjects tolerated a higher dose of egg during the poststudy DBPCFC compared to the prestudy food challenge. This study was able to demonstrate desensitization with OIT, however, did not demonstrate evidence of long-term tolerance, as two subjects reacted to a second DBPCFC that was administered 3 months after the study. Staden et al. [44]

performed a study in which 45 children with cow's milk and egg allergies were randomly assigned to either OIT or an elimination diet. In this study, nine patients (36 %) did not complete the induction phase secondary to intolerable side effects. After completing OIT, oral tolerance was assessed with a follow-up oral food challenge after subjects had strictly avoided either egg or milk for 2 months. Of the 16 patients who completed OIT, nine (36 % of the original 25 patients) showed tolerance in the follow-up food challenge. However, seven of the 20 (35 %) control subjects (those who had remained on an elimination diet) developed spontaneous tolerance, making these results difficult to interpret.

In order to address whether or not OIT could be safely performed in a subgroup of patients with severe allergic disease, Longo et al. [45] performed a randomized clinical trial with children older than 5 years of age with severe cow's milk-induced allergic reactions. Children were randomized to OIT or a strict elimination diet. After 1 year, 11 (36 %) of the patients treated with OIT tolerated a daily intake of at least 150 mL of cow's milk. Another 16 (54 %) of patients were able to consume between 5 and 150 mL of milk daily. None of the children in the elimination diet group showed evidence of desensitization on a follow-up DBPCFC and were unable to tolerate even 5 mL of milk. Not surprisingly, side effects in this subgroup of patients were common; however, only three of the 30 subjects on OIT were unable to complete the protocol, demonstrating that OIT could be administered in patients with severe food allergies.

Skripak et al. [46] performed the first double-blind, placebo-controlled OIT trial. Twenty children with cow's milk allergy were randomly assigned to OIT or placebo. Children in the OIT group showed a significant increase in the amount of milk they were able to tolerate without a reaction (median of 5,140 mg after OIT). This was in contrast to the placebo group, in which all children reacted at 40 mg. Reported side effects were notably higher in the treatment group than in the placebo group, with 45 % of daily doses resulting in symptoms, compared with 11 % in the placebo group.

Despite the fact that about 85 % of children allergic to foods such as cow's milk, egg, wheat, and soy develop tolerance and “outgrow” their allergy whereas only 15–20 % of children allergic to peanut, tree nut, and shellfish develop spontaneous tolerance, little research had focused on the use of OIT in peanut allergic individuals [47, 48]. This changed in 2009, and there have since been four seminal papers published evaluating the use of OIT in peanut-allergic patients. Clark et al. [49] described four patients with challenge-documented peanut allergy who underwent OIT. All four children had significant increases in the amount of peanut tolerated, each ingesting between 10 and 12 peanuts during the postintervention food challenge. That same year, Jones et al. [32] reported on a larger, open-label peanut OIT study. Thirty-nine patients were enrolled with a median age of 57.5 months. Of the 39 patients, 29 (74 %) completed the trial. During the final food challenge, 27 of these patients were able to safely consume 16 peanuts, and the other two patients were able to consume nine peanuts. These results were exciting, as they appeared to provide evidence that OIT could be used to protect peanut-allergic individuals from anaphylaxis after accidental peanut ingestion.

An important aspect of the Jones' study was the evaluation of several immunologic parameters [32]. They found that there was a distinct pattern of immunologic changes leading to a dampened allergic response underlying the clinical benefits of OIT. Some of the observed changes, namely a decrease in allergen-specific IgE and an increase in allergen-specific IgG_4, were confirmation of previously reported findings. Novel findings included suppression of mast cells and basophils, an increase in peanut-specific Fox $P3^+$ T regulatory cells (Tregs) for 12 months, followed by a decrease in these cells, as well as a change in the secretion of IL-10, IL-5, IFN-γ, and TNF-α [32, 38, 50].

A subsequent study, published in 2010 by Blumchen et al. [51], attempted to evaluate whether or not peanut OIT could induce tolerance, as measured after a 2-week period of complete peanut elimination. Subjects underwent a rush desensitization, buildup dosing, and then remained on maintenance dosing for 2 months. This was followed by 2 weeks of avoidance of any peanut-containing products and then a DBPCFC to assess early tolerance. They found that even after 2 weeks of therapy, all patients ($n = 14$) showed a median 4-fold increase in the threshold dose of peanut tolerated when compared to their entry DBPCFC. The tolerated dose of peanut increased to a median of 1 g of peanut (equivalent to three to four peanuts) at the final DBPCFC. Three patients did not react at all during the final challenge, tolerating 4 g of peanut. Regarding the utility of a rush desensitization protocol for peanut-allergic subjects, the authors concluded that, although safe, it was unlikely to be useful since only children with low levels of peanut-specific IgE reached a maintenance protective dose after undergoing OIT by using the rush protocol. Furthermore, many of these subjects subsequently had their dose decreased because of refusal to take the dose or of adverse events [51].

Varshney et al. [31] published the first randomized, double-blind, placebo-controlled study of OIT for peanut allergy in 2011. Twenty-eight subjects were enrolled with 19 of them randomized to the OIT group and nine randomized to the placebo group. The median age in this study was 69 months. Of the 19 patients treated with OIT, 16 (84 %) completed the OIT protocol, reaching the maintenance dose of 4,000 mg by 40 weeks. All subjects in the OIT group were able to tolerate a cumulative final dose of 5,000 mg of peanut compared to a median cumulative dose of 280 mg in the placebo group. One of the OIT subjects reacted with clinically significant symptoms during the final DBPCFC compared to eight of the nine subjects treated with placebo [31, 50]. Unlike previous studies, peanut-specific IgE increased initially, but was unchanged at 12 months compared with initial levels. Increased peanut-specific IgG_4 was again observed. The ratio of Tregs increased significantly between baseline and 12 months.

A meta-analysis published in 2011 sought to determine whether OIT was more effective than allergen avoidance in the induction of tolerance. It included the previously discussed studies by Staden et al. [52]. Although all of the included individual studies found tolerance more likely to occur after OIT compared to avoidance/placebo, analysis of the studies collectively using χ^2 found no significant difference between the treatment and avoidance groups. The meta-analysis of the included studies found a lower relative risk of allergy after OIT; however, this did not meet statistical significance. The authors concluded that OIT could not yet be recommended as a part of routine practice as a means to induce tolerance in children with IgE-mediated food allergy.

Taken collectively, these studies examining the role of OIT in food-allergic patients demonstrate the ability of OIT to induce a desensitized state; however, demonstration of long-term tolerance (i.e., cure) remains elusive. Although many patients can be successfully desensitized, allergic reactions occurred in most of the subjects in these studies, some of which were severe [50]. This presents a significant safety concern, especially when maintenance doses are administered at home without medical supervision. Interestingly, 10–20 % of patients among the studies fail the initial rush/escalation phase and withdraw from the protocols secondary to intolerable adverse reactions. The primary reason that most patients cannot tolerate the daily OIT dosing is significant gastrointestinal symptoms, including abdominal pain and sometimes vomiting. Another 10–20 % are unable to reach the full planned maintenance dose [16]. These findings suggest that some patients may be more difficult than others to desensitize. It is not yet clear what unique qualities this patient population possesses, but further investigation is ongoing. Before oral immunotherapy can be used in clinical practice, additional high-quality RCTs are needed to determine optimal

maintenance doses, ideal duration of therapy, the degree of protection provided, efficacy in different age groups, cost of therapy, and the need for emergency medications or other safety precautions during home administration [53].

Sublingual immunotherapy

Sublingual immunotherapy involves the administration of small amounts of allergen, on the order of micrograms to milligrams, of extract under the tongue with the expectation that it will be held there for a set amount of time and then swallowed, spit, or dissolved. The mouth is an optimal site for allergen delivery given the presence of oral Langerhans cells that take up antigen and have tolerogenic properties. The sublingual mechanism of allergen delivery has shown clinical efficacy for the treatment of allergic rhinoconjunctivitis caused by aeroallergens [54].

SLIT with food allergens was first described in a 29-year-old woman with kiwi allergy. Homogenized and filtered fresh kiwi pulp extract was placed under the tongue three times daily. After the patient reached maintenance dosing, she was advised to continue to eat daily kiwi and was able to do so without any adverse symptoms [55]. The first randomized, double-blind, placebo-controlled trial of SLIT was conducted in adults with hazelnut allergy confirmed by means of DBPCFC [56]. Of note, 54.5 % of these patients had a history of oral allergy symptoms, a more limited form of oral pruritus caused by epitopes cross-reactive with pollens. Treatment extract solution was held under the tongue for at least 3 min and then spit out. All subjects receiving hazelnut SLIT reached the planned maximum dose with a 4-day rush protocol, followed by a daily maintenance dose. Systemic reactions were very rare, occurring in just 0.2 % of the total doses during the rush buildup phase, none of which required epinephrine. The rate of reactions during the maintenance phase was also very low. The mean hazelnut quantity provoking objective symptoms increased from 2.29 to 11.56 g ($P = .02$, active group) versus 3.49–4.14 g (placebo, not significant). Nearly 50 % of patients who underwent active treatment reached the highest dose (20 g) compared to only 9 % in the placebo group. Laboratory data revealed an increase in hazelnut-specific IgG_4 and total serum IL-10 levels after immunotherapy in only the active group [56].

Similar findings were reported in a randomized, double-blind, placebo-controlled trial of SLIT with Pru p 3, the major peach allergen, in adults with peach allergy [57]. After 6 months of SLIT, the active group tolerated a higher amount of peach (3–9-fold) had a 5.3-fold decrease in their peach-specific skin prick test, and a significant increase in IgE and IgG_4 to Pru p 3. No significant changes were observed within the placebo group. Adverse reactions were rare, and most commonly consisted of local reactions restricted to the oral cavity.

In the first double-blind, placebo-controlled study of peanut SLIT, 18 children (age 1–11 years) were randomized 1:1 to peanut SLIT or placebo and underwent 6 months of buildup dosing, followed by 6 months of maintenance dosing [33]. The crude peanut extract, containing the maximum peanut protein concentration of 500 μg/mL, was administered sublingually, held under the tongue for 2 min, and then swallowed. Subjects receiving peanut SLIT had a significant increase in the reaction threshold, safely ingesting a median cumulative dose of 1,710 mg of peanut protein, which is equivalent to six or seven peanuts. This is in contrast to those receiving placebo, who only safely ingested a median cumulative dose of 85 mg equivalent to less than one peanut. Subjects receiving SLIT had distinct immunologic changes as compared to the placebo group. There was a significant decrease in skin prick test wheal diameter in those in the active treatment group, indicating decreased mast cell reactivity. Basophil activity was also significantly diminished after 12 months of peanut SLIT, as evidenced by a lower percentage of $CD63^+$-activated basophils after stimulation with peanut extract. Peanut-specific IgE levels initially increased over the first 4

months in the treatment group and then significantly decreased over the remaining 8 months, a finding not seen in the placebo group. Peanut-specific IgG_4 levels significantly increased in the treatment group compared to the placebo group, in which levels remained unchanged. After treatment, IL-5 levels were significantly lower in the active treatment group compared with those in the placebo group. There was an increased percentage of Tregs seen in the active treatment group when compared to the placebo group; however, the finding was not statistically significant. This study again had a very favorable safety profile, with only 0.3 % of active treatment doses requiring treatment with an antihistamine, 0.02 % requiring treatment with a β-agonist, and no use of epinephrine [33].

In an exploratory study, 30 children with persistent IgE-mediated cow's milk allergy were randomized to either SLIT or SLIT followed by OIT to assess the safety and efficacy of these methods in a head-to-head comparison [58]. This group sought to minimize the rate of adverse reactions by initiating therapy with SLIT and then to determine whether subsequent treatment with SLIT or OIT might be most promising for use in the treatment of food allergy. They found that SLIT followed by OIT was much more effective at desensitization than SLIT alone but was accompanied by a higher risk of systemic side effects. One of ten subjects treated with SLIT alone was able to consume a full serving of milk without symptoms after therapy compared to 14 of 20 subjects treated with SLIT followed by OIT. Multisystem reactions were more than 11 times more likely when OIT was added to the regimen. These findings can likely be explained in large part by the difference in the dose of allergen given; the cumulative dose received by subjects in the SLIT group was at least 140-fold lower than the minimum cumulative OIT dose. The optimal use of SLIT and OIT, either separately or in combination, remains to be determined.

Epicutaneous immunotherapy

A final approach to delivery of allergen for immunotherapy is through the skin. In this method, an epicutaneous patch containing soluble allergen is placed on the skin, which leads to dissemination of the allergen into the stratum corneum. The epicutaneous approach targets the outermost layer of skin, the epidermis, which has potent immune surveillance via keratinocytes and Langerhans cells, making it another ideal site for delivery of allergen [59]. In a double-blind placebo-controlled pilot study performed in 18 children (3 months–15 years of age) with physician-confirmed cow's milk allergy and positive OFCs, participants were assigned to receive therapy with active epicutaneous delivery of either milk powder or placebo consisting of glucose for 3 months [60]. Treatment consisted of three 48-h applications of the epicutaneous delivery system per week. At 3 months, the active group was able to tolerate a cumulative dose of 23.61 mL of milk compared to a cumulative tolerated dose of 1.77 mL at baseline. The cumulative tolerated dose of cow's milk did not change in the placebo-treated group. The most common side effects were local pruritus and eczema at the site of the patch [60].

Peanut EPIT has been studied in several murine models and was shown to be as efficacious as subcutaneous immunotherapy, based on biologic and physiologic responses in the mice [61, 62]. A phase I trial is currently underway in the USA to evaluate the safety of peanut EPIT in peanut-sensitized individuals and a phase II trial is underway in France (http://ClinicalTrials.gov).

Anti-IgE mAbs (omalizumab) as adjunctive therapy

Humanized monoclonal murine anti-IgE antibodies have been produced that bind to the constant region of IgE antibody molecules and prevent IgE from binding to high-affinity FcεRI receptors expressed on the surface of mast cells and basophils as well as low-affinity FcεRII receptors expressed on B cells, dendritic cells, and intestinal epithelial cells [16].

Anti-IgE therapy leads to a decrease in free IgE molecules, thereby downregulating the expression of FcεRI receptors on mast cells and basophils. This results in decreased activation and release of histamine and other inflammatory mediators [63]. Currently, the most widely used anti-IgE mAb is omalizumab (Xolair; Genentech, South San Francisco, CA, USA). It is a recombinant humanized antibody composed of human IgG_1 skeleton (95 %) and murine complementarity-determining regions (5 %) [64]. Talizumab (TNX-901; Tanox, Houston, TX, USA) is a humanized IgG_1 mAb administered subcutaneously. Talizumab's mechanism of action is similar to that of omalizumab with the addition of inhibiting allergen-specific T-cell activation through interfering with antigen processing and presentation activities mediated by the FcεRI receptors [65]. Talizumab is currently not commercially available because of multiple legal battles related to patent infringement.

The use of anti-IgE mAb alone to treat food allergy has been investigated and will be discussed separately as an example of allergen-nonspecific therapy. However, the concept of anti-IgE mAb as adjuvant therapy to specific immunotherapy warrants further discussion here. It was first investigated for the treatment of allergic rhinitis. Several studies showed that combination therapy significantly reduced symptom burden during the pollen season [66]. Also of significance, pretreatment with omalizumab showed added safety to the rush phase of allergen immunotherapy. In one study of ragweed-allergic patients, those treated with omalizumab and immunotherapy had a 5-fold decrease in the risk of anaphylaxis caused by rush immunotherapy [67].

Given the preliminary success of food allergen oral immunotherapy and the observations that anti-IgE mAb can reduce allergic reactions to food allergen challenges, recent studies have been initiated to examine the role of anti-IgE mAb in combination with oral immunotherapy [50]. The first study of omalizumab in combination with OIT was a pilot study, which enrolled 11 subjects (mean age 10.2 years) with IgE-mediated cow's milk allergy [68]. This study demonstrated that pretreatment with omalizumab was safe and allowed for a rapid oral desensitization in most of the 11 subjects. Subjects were treated with omalizumab for 9 weeks and then underwent rush desensitization to milk, increasing the dose of oral milk from 0.1 to 1,000 mg over a 6-h period. During the ensuing 7–11 weeks, the dose was escalated to 2,000 mg. Subjects remained on omalizumab throughout the dose escalation period. Nine of the ten subjects who remained in the study passed a DBPCFC, with a cumulative dose of 7,250 mg of milk (equivalent to 220 mL of milk) and an additional open challenge of greater than 4,000 mg of milk without symptoms. The safety profile was similar to that seen in other milk OIT studies. In an ongoing study using omalizumab and peanut OIT combination therapy being conducted by Dr. Wesley Burks, early analysis has revealed a decreased number of side effects during rush desensitization and dose escalations. Similar to the milk OIT/omalizumab study, achievement of maintenance dosing of peanut OIT was more rapid compared to OIT alone. Additional OIT and omalizumab adjunctive therapy studies are underway in New York and in Boston as well (http://ClinicalTrials.gov). These early studies suggest that omalizumab adjunctive therapy could improve the rapidity and likelihood of success of oral desensitization in patients with food allergy, while at the same time improving safety.

Other allergen-specific approaches

Despite the promising preliminary findings in numerous studies examining the role of immunotherapy in the treatment of food allergy, there remain several significant weaknesses. One cited weakness is the safety profile of various forms of immunotherapy. As previously discussed, subcutaneous immunotherapy for food allergy was halted because of severe side effects [37]. In one of the cited peanut OIT studies, 93 % of subjects experienced symptoms during the initial escalation day. The estimated risk of symptoms in this study during dose escalation was 46 and 3.5 % with home dosing [69]. Another limitation to oral

immunotherapy is the relatively long time period required to reach maintenance dosing and desensitization, which often takes between 4 months and 1 year [30, 31, 44, 70]. Given these limitations, several groups have undertaken other allergen-specific approaches for the treatment of food allergy.

Antigen-coupled splenocytes

One such method under investigation is the injection of antigens attached to the surface of syngeneic splenic leukocytes (antigen-coupled splenocytes [Ag-SPs]) with the chemical cross-linking agent 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide [71]. The intravenous administration of such Ag-SPs has previously been shown to safely and efficiently induce Ag-specific immune tolerance [72]. Ag-SP tolerance has been shown to prevent and treat preestablished symptoms of Th1/Th17-mediated autoimmune disease, such as type 1 diabetes mellitus, and promote potent alloantigen-specific tolerance for specific long-term protection of transplanted allogeneic pancreatic islets in the absence of immunosuppressant drugs [73]. In this most recent series of experiments, authors demonstrate efficacy of antigen-coupled splenocyte treatment both in the prevention of allergic responses and in induction of tolerance in a presensitized murine model of peanut allergy. Specifically, in their whole peanut extract/SEB-induced food allergy model, whole peanut-extract splenocytes effectively inhibited the anaphylactic symptoms and drops in body temperature seen after oral whole peanut extract challenge [71]. This data demonstrate that Ag-SP treatment can induce protective antigen-specific tolerance in models of Th2-mediated immune responses and may serve as a future therapy in the prevention and treatment of food allergy.

Modified recombinant food protein vaccines

Another allergen-specific approach being investigated is the administration of a vaccine containing recombinant modified peanut proteins. This approach has been pursued because modifying the antigenic epitopes can diminish the risk of immediate allergic reactions during immunotherapy. This is accomplished with point mutations introduced by site-directed mutagenesis or with protein polymerization [74, 75]. Modified food allergens can be combined with bacterial adjuvants such as heat-killed *Listeria monocytogenes* or nonpathogenic *E. coli*. This serves to enhance the T_H1 skewing effect, thereby decreasing the T_H2 skewing effect. In a mouse model, rectal administration of a vaccine containing heat-killed *E. coli* expressing the modified peanut proteins Ara h 1–3, led to reduced severity of anaphylaxis when compared to a sham-treated group [74]. This finding led to the development of EMP-123, a vaccine containing three recombinant modified peanut proteins (Ara h 1–3) encapsulated within heat or phenol-killed *E. coli* developed for rectal administration in humans. A phase I clinical safety trial is currently ongoing (http://ClinicalTrials.gov).

Allergen-nonspecific therapy

Chinese herbal formulation

Traditional Chinese medicine (TCM) has a long and rich history of use in treating human disease in China and other Asian countries and is gaining more widespread acceptance in Western countries as well. Numerous publications have shown that TCM shows promise in the treatment of allergic asthma [76–80]. More recently, a specific Chinese herbal formulation, Food Allergy Herbal Formula-2 (FAHF-2), has been investigated for the treatment of food allergy. FAHF-2 is derived from Wu Mei Wan, which has been used to treat parasitic infections and food allergy-like symptoms and is an extract of nine herbs [81]. Studies have shown that FAHF-2 protects against peanut-induced anaphylaxis in a murine model and that this protection persists for at least 6 months after a single 7-week course of

therapy, suggesting the development of tolerance [82–84]. FAHF-2 appears to have immunologic effects on T and B lymphocytes, as well as effector cells such as mast cells and basophils [85]. A reduction in T_H2 cytokine and serum IgE levels as well as increased levels of IFN-γ and IgG_{2a} were observed in these murine studies. Basophil and mast cell numbers as well as mast cell activation was also reduced [84, 86].

The early animal studies using FAHF-2 demonstrated efficacy as well as safety, as mice fed 24 times the effective dose of FAHF-2 showed no morbidity or mortality [83]. Given these promising findings, a randomized, double-blind, placebo-controlled, dose-escalation phase I trial in subjects with peanut, tree nut, or both; fish; and shellfish allergies followed. In this 1-week study, FAHF-2 was found to be safe and well tolerated [87]. To further ensure the safety and tolerability of this formulation before phase II study, an open-label, single-dose, 6-month extension of the phase I study was conducted. The results of this study were consistent with the acute phase I study, namely FAHF-2 was found to be safe and well tolerated by patients with food allergy. They also found that FAHF-2 reduced allergen-stimulated basophil activation, hyperreleaseability, and percentages of circulating basophils. The suppression of basophil activation and FAHF-2's in vitro effects on PBMCs (increased IL-10 and IFN-γ and reduced IL-5 levels in mice with peanut allergy) suggests that FAHF-2 leads to beneficial immunologic effects [83–85, 87]. A phase II extended safety and efficacy trial is currently enrolling subjects with peanut, tree nut, sesame, fish, or shellfish allergy (http://ClinicalTrials.gov).

Anti-IgE monoclonal antibodies

There have been a limited number of studies evaluating the efficacy of anti-IgE mAb in the treatment of food allergy. In the largest randomized, double-blind, placebo-controlled study conducted in 2003, 84 patients (aged 12–60 years) with a history of peanut allergy were enrolled [65]. Prior to enrollment, a DBPCFC was performed to confirm peanut reactivity. Patients were randomly assigned to receive talizumab, the anti-IgE mAb used in this study, at varying doses or placebo every 4 weeks. The mean amount of peanut flour that elicited symptoms during a food challenge, i.e., the sensitivity threshold, increased in all groups but was statistically significant only in the group receiving the highest dose of talizumab. The study drug was well tolerated. This study demonstrated the ability of an anti-IgE mAb to offer some level of protection against unintended ingestion of peanuts.

A phase II, randomized, double-blind, parallel-group, placebo-controlled trial of omalizumab followed this initial study to further assess the ability of an anti-IgE mAb to prevent severe allergic reactions in the setting of an accidental ingestion of peanut [88]. Subjects aged 6 years and older were randomized 2:1 to omalizumab or placebo. An entry DBPCFC was performed to confirm peanut reactivity. Unfortunately, the study was terminated early secondary to two severe allergic reactions that occurred during the initial screening peanut challenge. At the time of termination, 26 subjects had completed 24 weeks of therapy followed by a second DBPCFC. Omalizumab seemed to increase tolerance to peanut ingestion in the treated subjects: 44.4 % of omalizumab-treated subjects versus 20 % of placebo subjects could tolerate a peanut challenge of greater than 1,000 mg [88]. Further study of the use of anti-IgE monoclonal antibody for the treatment of food allergy is warranted and is being planned.

T. suis ova therapy

T. suis, a parasitic helminth, is currently being studied for its role in modifying the allergic response. This is based on observational studies that revealed that parasitic helminth infections could protect against allergic airway inflammation, leading to a milder course of asthma [89]. In a murine model of peanut allergy, helminth infection led to greatly

diminished anaphylactic symptoms as well as a decrease in the production of peanut-specific IgE. This downregulation of peanut-specific IgE was associated with a decrease in the secretion of IL-13 by peanut-specific T cells [90]. A phase I study is currently recruiting patients with peanut and tree nut allergy to be given between 100 and 2,500 *T. suis* ova every other week for 3 months. This initial study will assess the safety of this therapy (https://ClinicalTrials.gov).

Conclusions

Food allergy, along with other allergic diseases, has increased in prevalence in westernized countries and has led to significant morbidity. There is currently no cure for those individuals suffering with one or more food allergies. Considerable effort has gone into the development of strategies aimed at curing food allergy over the past 15–20 years. These studies have not only advanced our understanding of the clinical phenotype and natural history of food allergy but have also provided valuable insight into the underlying immunologic mechanisms involved in the development of food allergy as well as the development of tolerance. While the therapies discussed in this paper remain investigational at this time, there is hope that one or more therapies will become clinically available in the near future.

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Table 1

Allergen-specific and nonspecific therapies for the treatment of food allergy

Allergen-specific therapies	Allergen-nonspecific therapies
Clinical trials	Clinical trials
Immunotherapy[a]	Chinese herbal formulation FAHF-2[a]
Subcutaneous[a]	
Oral[a]	Anti-IgE mAb[a]
Sublingual[a]	
Epicutaneous[a]	
Anti-Ige mAb adjuvant therapy[a]	Probiotics
Extensively heated milk or egg diet	Anti-IL-5 mAb
Modified recombinant food protein vaccines[a]	*Trichuris suis* ova[a]
Preclinical studies	Preclinical studies
Antigen-coupled splenocytes[a]	TLR-9 agonist
Peptide immunotherapy	*Lactococcus lactis* expressing IL-10 or IL-12
Plasmid DNA immunotherapy	

[a]Therapies discussed in this review paper