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Novel Approaches to Food Allergy

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Abstract Food allergies have increased in recent decades. However, they cannot be effectively treated by the current management, which is limited to the identification and avoidance of foods that induce allergies and to the use of medicines for symptoms relief. To meet the medical need of prevention and cure of food allergies, several therapeutic strategies are under investigation. Some newly developed biologics such as anti-IgE antibody and anti-interleukin (IL)-5 antibody directed against significant molecules in the allergic process have shown their potential for the treatment of food allergies. Allergen-specific immunotherapy is the therapy that induces immune tolerance and may reduce the need for conventional medication, severity of allergic symptoms and eliminate hypersensitivity. In this article, clinical studies of immunotherapy via subcutaneous, oral, sublingual, and epicutaneous routes are extensively reviewed for their safety and effectiveness on various food allergies. In addition, to reduce the risk of anaphylaxis and increase toleragenic immunity, many studies are focusing on the modification of traditional allergens used for immunotherapy. Moreover, a Chinese herbal formulation with potential anti-allergic effects is being evaluated for its efficacy in patients with peanut allergy. Although more studies are needed, accumulated data of current studies represent compelling evidence of curative effects of some strategies and give a hope that food allergies are likely to be successfully treated in the future.

Keywords Food allergy · Biologics · Immunotherapy · Pharmaceuticals

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Introduction

Food allergies are immune-mediated adverse responses to food proteins. Like other atopic disorders, they appear to have increased in prevalence [1]. A recent epidemiology study of American children younger than 18 years revealed that the prevalence of food allergy has increased by 18 % and the prevalence of peanut allergy has tripled (from 0.4 % to 1.4 %) from 1997 to 2008 [2]. In the westernized countries, food allergies currently affect 3–5 % of whole population [3, 4]. Some food allergies like egg allergy and cow's milk allergy (CMA) that commonly occur in young children may be outgrown within 2–3 years. However, most children with peanut, nut, or sea food allergies retain their allergy for life [5]. According to different immune mechanisms, food allergies can be induced by IgE- and/or none IgE-mediated pathways. In individuals with IgE-mediated food allergy, food-specific IgE antibodies are formed after exposure to certain food allergens that subsequently bind to Fcε receptors on mast cells, basophils, and macrophages. When allergens penetrate mucosal barrier and are captured by the above cell-bound IgE antibodies, mediators from the activated cells are released and result in local or systemic symptoms immediately. Those mediators may attract other cells like eosinophils and lymphocytes to prolong the inflammation [3, 4, 6]. IgE-mediated food allergies usually affect skin (urticaria, angioedema, and flushing) and gastrointestinal tract (oral pruritus, mucosa swelling, nausea, vomiting, and abdominal

pain), and sometimes, respiratory tract and cardiovascular system. Importantly, food allergy is one of the most common causes of anaphylaxis that may lead to fatalities. Studies in the United States and United Kingdom showed that the number of hospitalizations for food-induced anaphylaxis has increased more than 3-fold in the past decade [7, 8].

Identification and elimination of foods responsible for allergic reactions are the primary and the only validated treatments for food allergies [3]. However, it is not easy to totally avoid the contact of food allergens. Various medications can provide relief for allergic symptoms induced by foods. Antihistamines block the action of histamine, which causes blood vessels to dilate and become leaky to plasma proteins. They can therefore relieve urticaria, pruritus, flushing and mild angioedema. Steroids are more effective than antihistamines due to their comprehensive anti-inflammatory effects. However, steroids take several hours to start working that limits their use in emergency conditions. Epinephrine is commonly used to reverse the acute and severe allergic reaction by improving blood circulation. For those people have experienced food-induced anaphylaxis, epinephrine autoinjector (EpiPen) should be provided for self-prescription [3–5]. In addition to the traditional management for food allergies, in this review we will further focus on some newly developed or developing therapeutic regiments and strategies for IgE-mediated food allergies (Fig. 1).

Biologics

Humanized Monoclonal Anti-IgE Antibody

Humanized monoclonal anti-IgE antibodies have been developed that bind to an epitope in the CH_3 domain of IgE Fc portion, masking a region responsible for binding to both high-affinity FcεRI receptors expressed on the surface of mast cells and basophils and low-affinity FcεRII receptors expressed on B cells, dendritic cells, and intestinal epithelial cells. In addition to decrease in free IgE, anti-IgE antibodies also markedly down-regulates the expression of FcεRI on mast cells and basophils, resulting in decreased activation and release of histamine and other inflammatory mediators [9]. A double-blind, randomized, dose-ranging trial in 84 patients with a history of immediate hypersensitivity to peanut was conducted to evaluate the therapeutic effect of humanized anti-IgE antibody (TNX-901) on peanut allergy. The results showed that TNX-901 was well tolerated and significantly and substantially increased the threshold of sensitivity to peanut [10]. Omalizumab is another humanized monoclonal anti-IgE antibody approved for patients with moderate-to-severe or severe allergic asthma. Using omalizumab to treat peanut allergy, the results were consistent with findings of TNX-901 [11]. A pilot study was recently performed to assess the efficacy of omalizumab in 22 patients with persistent asthma and concomitant IgE-mediated food allergy. Treating with omalizumab, all patients subjectively observed a reduction in their concomitant IgE-mediated food allergy symptoms like urticaria, angioedema, and anaphylaxis [12].

The combination of omalizumab and specific allergen immunotherapy has been investigated with environmental aeroallergens in patients with allergic rhinitis [13, 14]. The encouraging results provide the opportunity to develop strategies using omalizumab pretreatment to enhance the safety and efficacy of allergen-immunotherapy to treat food allergies.

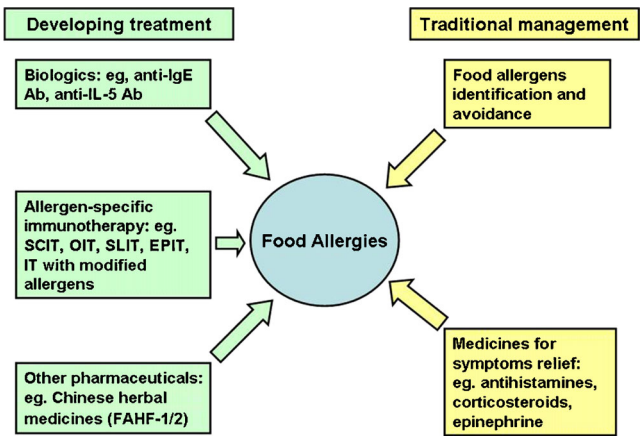

Fig. 1 The optimal management of food allergies

Anti-Interleukin (IL)-5 Monoclonal Antibody (Mepolizumab)

Eosinophil-associated gastrointestinal disorders (EGIDs), including eosinophilic esophagitis (EE) and eosinophilic gastroenteritis (EG), are a spectrum of increasingly recognized inflammatory diseases of mixed pathophysiology, with IgE-mediated and none IgE-mediated mechanisms [15]. Since IL-5 is a major activator and regulator of eosinophils, mepolizumab has been applied to the therapy of EGIDs. Some pilot studies treating patients with EG or EE with mepolizumab resulted in a decrease in peripheral eosinophilia and tissue eosinophilia, but minimal improvement in symptoms [15–17]. Obviously, larger randomized, controlled trials are needed to further clarify the efficacy and safety of this therapy in patients with EGIDs.

Allergen-Specific Immunotherapy

Allergen-specific immunotherapy (SIT) is a form of therapy in which patients are vaccinated with increasing larger doses of allergens that induce allergic symptoms. Allergen-SIT has been shown its effectiveness on various allergic diseases like asthma, allergic rhinitis, and insect allergies and

represents the only curative treatment that is known to modify the allergic process, whereas current medications merely suppress the symptoms [18, 19]. The mechanisms by which allergen-SIT has its effects may include the modulation of the immune effector cells such as T cells, B cells, eosinophils, basophils, and mast cells, the generation of allergen-specific regulatory T cells, a significant increase in allergen-specific IgG4, and also IgG1 and IgA, and a decrease in IgE [20]. Conventional subcutaneous allergen administration is highly efficacious to treat allergic diseases. However, due to a rare serious side effect of anaphylaxis and the need of repeated subcutaneous injections for several years, there have been several attempts to overcome these limitations including offering more convenient treatment routes like oral or sublingual immunotherapy (SLIT), and modification of the allergen to eliminate the IgE binding epitopes [19]. Since allergen-SIT is a well established therapy for some allergic diseases, there have been several clinical trials (Table 1) and animal model studies to investigate the efficacy and safety of conventional and modified allergen-SIT on IgE-mediated food allergies.

Subcutaneous Immunotherapy (SCIT)

In a double-blind, placebo-controlled (DBPC) study, patients with confirmed peanut allergy were treated with peanut SCIT or placebo. Three patients completed the study and displayed a 67 % to 100 % decrease in symptoms induced by peanut challenge. They also had a 2- to 5-log reduction of reactivity to peanut extract in end point prick skin tests [21]. Another clinical trial was subsequently conducted in which 12 patients with peanut allergy were recruited. Half were treated with subcutaneous injections of peanut extract for at least 1 year. The other six were not treated as controls. All patients underwent DBPC oral peanut challenges initially, after approximately 6 weeks, and after 1 year. Compared with controls, all patients receiving SCIT experienced increased tolerance to DBPC peanut challenge and decreased sensitivity on titrated skin prick testing with peanut extract. However, systemic reactions were common in the treated group both during rush immunotherapy and with maintenance injections [22]. Concerning the safety, this therapeutic strategy using peanut extract is currently not suggested for the treatment of peanut allergy.

Oral allergy syndrome (OAS) or pollen-food allergy is a type of IgE-mediated food allergy that occurs in patients with pollen or ragweed induced allergic rhinitis and characterized by the allergic reactions like mucosa swelling in oral cavity. It is developed in response to certain fruits that share some similarity to pollen [23]. With the concept of cross-immunotherapy, pollen SCIT has been applied to treat this allergic disease. One study showed that SCIT with birch pollen extracts effectively reduced clinical apple sensitivity and skin reactivity in most cases with birch pollen allergy and OAS [24]. Another 27 patients allergic to birch pollen with OAS induced by apple or hazelnut underwent an open trial. Fifteen patients were treated with birch pollen SCIT, while 12 were not. The results showed that 13 of 15 (87 %) SCIT-treated patients could eat significantly more of apple or hazelnut without any symptoms/signs. The average tolerated quantity increased from 12.6 to 32.6 g apple after 1 year [25]. Due to the small tolerated quantity, the clinical effects remain limited. However, these findings still revealed the therapeutic potential of pollen SCIT in people with OAS.

Oral Immunotherapy (OIT)

Instead of an injection, the allergen extract is immediately swallowed in OIT that provides a more convenient and theoretically safe therapeutic approach than SCIT. Thus, OIT to food is now one of the most commonly investigated immunotherapies for IgE-mediated food allergies [5, 26, 27].

Skripak et al. [28] conducted the first randomized, double-blind, placebo-controlled study of milk OIT for CMA. Twenty children were randomized to milk or placebo OIT (2:1 ratio). Dosing included three phases: the build-up day (initial dose, 0.4 mg of milk protein; final dose, 50 mg), daily doses with 8 weekly in-office dose increases to a maximum of 500 mg, and continued daily maintenance doses for 3 to 4 months. Nineteen patients completed treatment: 12 in the active group and seven in the placebo group. One dropped out because of persistent eczema during dose escalation. The median milk threshold dose in both groups was 40 mg at the baseline challenge. After OIT, the median cumulative dose inducing a reaction in the active treatment group was increased from 40 to 5,140 mg, whereas all patients in the placebo group remained unchanged (P= 0.0003). Among 2,437 active OIT doses versus 1,193 placebo doses, there were 1,107 (45.4 %) versus 134 (11.2 %) total reactions. The most common types of reactions in the active group were local (mostly oral pruritus) and gastrointestinal (mostly abdominal pain). Milk-specific IgG4 levels increased significantly in the active treatment group [28].

A larger study of 60 children with severe CMA was performed to evaluate the safety and efficacy of milk OIT. Thirty children immediately began therapy, whereas the remaining 30 were kept on a milk-free diet and followed for 1 year. A total of 36 % of 30 children were able to tolerate the goal dose (150 ml) at 1 year, 16 (54 %) could take limited amounts of milk (5–150 ml), and three (10 %) were not able to complete the protocol because of persistent respiratory and abdominal symptoms. Some patients in both groups needed additional medications to resolve the adverse effects [29].

Table 1 Summary of human clinical trials of immunotherapy for food allergies

Types of immunotherapy	Types of food allergies	Study designs	Effects	References
SCIT	Peanut allergy	DBPC	A 67–100 % decrease in symptoms induced by peanut challenge. The rate of systemic reactions with rush immunotherapy was 13.3 %.	[21]
SCIT	Peanut allergy	Open label	Although injections of peanut extract increase the tolerance of patients with peanut allergy, that also result in repeated systemic reactions in most patients.	[22]
SCIT	Pollen-food allergy	Open label	Injection of birch pollen extracts effectively reduces clinical apple sensitivity and skin reactivity in most cases after only 1 year of treatment (84 % vs. 0 %).	[24]
SCIT	Pollen-food allergy	Open label	Eighty-seven percent of pollen SCIT-treated patients could eat more apple or hazelnut without allergic symptoms/signs. The average tolerated quantity increased from 12.6 to 32.6 g apple after 1 year	[25]
OIT	Cow's milk allergy	DBPC	The median cumulative dose inducing a reaction in the treatment group was 5140 mg, while that was 40 mg in the placebo group.	[28]
OIT	Cow's milk allergy	RCT	After one year, 36 % of children in the treatment group had become completely tolerant, while none of the controls could tolerate milk intake.	[29]
OIT	Cow's milk allergy	RCT	Full tolerance to cow's milk (200 ml) was achieved in ten of 30 patients in the treatment group and partial tolerance in one.	[30]
OIT	Egg allergy	Open label	Seven subjects completed the protocol; all tolerated significantly more egg protein than at study onset.	[31]
OIT	Egg allergy	Open label	All six patients who completed the entire protocol developed clinical tolerance to egg during the study.	[32]
OIT	Peanut allergy	Open label	All subjects (n=4) tolerated at least ten whole peanuts (approximately 2.38 g protein) in postintervention challenges.	[33]
OIT	Peanut allergy	Open label	Of the 29 subjects who completed the study, 27 ingested 3.9 g peanut protein during food challenge. Most adverse reactions resolved spontaneously or with antihistamines.	[34]
OIT	Peanut allergy	DBPC	All peanut OIT subjects (n=16) ingested the maximum cumulative dose of 5000 mg (approximately 20 peanuts), whereas placebo subjects (n=9) ingested a median cumulative dose of 280 mg.	[35]
SLIT	Peach allergy	DBPC	After 6 months of SLIT, the treatment group tolerated a significantly higher amount of peach (3- to 9-fold). No significant changes were observed within the placebo group.	[37]
SLIT	Hazelnut allergy	DBPC	Mean hazelnut quantity provoking objective symptoms increased from 2.29 to 11.56 g (treatment group) vs. 3.49 to 4.14 g (placebo group).	[38]
SLIT	Peanut allergy	DBPC	After 12 months of SLIT, the treatment group safely ingested 20 times more peanut protein than the placebo group (median, 1,710 vs. 85 mg).	[39]
SLIT	Pollen-food allergy	Open label	Pollen SLIT reduced respiratory symptoms to birch pollen, but not apple-induced oral allergy syndrome.	[40]
EPIT	Cow's milk allergy	DBPC	In the active group, although not statistically significant, EPIT tended to increase cumulative tolerated dose at the end of study.	[43]

SCIT subcutaneous immunotherapy, *OIT* oral immunotherapy, *SLIT* sublingual immunotherapy, *EPIT* epicutaneous immunotherapy, *DBPC* double-blind placebo control, *RCT* randomized control trial

A milk OIT protocol with weekly up-dosing was recently evaluated in a randomized, single blind, controlled trial. Thirty children with CMA were equally randomized to desensitization with cow's milk or soy milk as control. The weekly up-dosing lasted 18 weeks. Two active patients and one control patient dropped out. Full tolerance to milk (200 ml) was achieved in ten active patients and partial tolerance in one, whereas the sensitivity to milk remained unchanged in all controls. Two active patients discontinued the treatment due to severe reactions. None of controls experienced adverse reactions [30].

Seven patients with a history of egg allergy underwent a 24-month egg OIT protocol involving modified rush, build-up, and maintenance phases. Egg-specific IgG concentrations increased significantly, whereas egg-specific IgE concentrations did not significantly change. Three of seven patients tolerated accidental egg ingestions during the treatment. At the end of study, all tolerated significantly more egg protein than at the study onset [31]. In an open-label clinical trial of egg OIT, the daily egg doses were gradually increased according to individual egg white-specific IgE levels. Six patients who completed the entire protocol developed clinical tolerance to egg. The median wheal diameter on egg white skin prick testing decreased from 10 to 2.5 mm during OIT (P=0.03). Compared with the baseline data, egg white-specific IgE levels significantly decreased, and corresponding IgG4 levels increased during the study [32].

OIT has also been applied to the treatment of peanut allergy. Four children with peanut allergy underwent OIT. Oral challenges were performed to confirm the diagnosis and determine the dose thresholds before the study. One

patient had anaphylaxis during challenge and required epinephrine injection. OIT was then administered as daily doses of peanut flour increasing from 5 to 800 mg of protein with 2-weekly dose increases. After 6 weeks of treatment, all subjects tolerated immunotherapy updosing to 800 mg protein and no epinephrine was used during the therapy. Each subject tolerated at least ten whole peanuts (approximately 2.38 g protein) in postintervention challenges, an increase in dose threshold of at least 48-, 49-, 55- and 478-fold for the four subjects [33].

Another open-label study recruited more patients. Of the 29 subjects who completed the study, 27 ingested 3.9 g peanut protein during food challenge. Most adverse reactions occurred during OIT resolved spontaneously or with antihistamines. In addition to the clinical efficiency, the investigators found that titrated skin prick tests and activation of basophils significantly declined by 6 months. Peanut-specific IgE decreased by 12 to 18 months, whereas IgG4 increased significantly. Peanut-specific regulatory T cells increased until 12 months and decreased thereafter [34].

Recently, a randomized DBPC trial was conducted. In this study, 28 patients were enrolled in the study to evaluate the effectiveness and safety of OIT for peanut allergy. Three patients withdrew early in the study because of allergic side effects. During the DBPC food challenge, all remaining peanut OIT subjects (n=16) ingested the maximum cumulative dose of 5,000 mg (approximately 20 peanuts), whereas placebo subjects (n=9) ingested a median cumulative dose of 280 mg (range, 0–1,900 mg; P<0.001). The laboratory findings of active treatment group are similar to the above open label study [35].

Taken together, although adverse reactions were noted during the treatment, most of them were mild and curable. OIT seems to be a relative safe and effective therapy for food allergies. More studies are necessary to establish the protocols for each food allergen OIT before it becomes a routine practice.

Sublingual Immunotherapy

SLIT involves placing small quantities of allergens in a liquid or tablet form under the tongue. It is currently a treatment option for allergic rhinitis in many European countries and has a good safety profile and overall therapeutic efficacy comparable with SCIT. Therefore, many controlled studies are being extended to evaluate SLIT for other indications including food allergies [26, 36].

Thirty-one patients with peach allergy completed a randomized DBPC study of SLIT with Pru p 3 quantified peach extract. After 6 months of treatment, the active group tolerated a significantly higher amount of peach (3- to 9-fold), presented a significant decrease (5.3 times) in skin prick tests, and a significant increase in Pru p 3-specific IgE and IgG4. In contrast, no significant changes were observed in the placebo group. There were no serious adverse effects during the treatment. Local reactions were significantly more frequent in the active group (three times) and 95 % of them restricted to the oral cavity [37].

SLIT for hazelnut and peanut allergies were also evaluated. Twenty-three patients were enrolled into the hazelnut SLIT study and randomized into two groups. Systemic adverse reactions were observed in only 0.2 % of the total doses administered. Mean hazelnut quantity provoking objective symptoms increased from 2.29 to 11.56 g (active group; P=0.02) versus 3.49 to 4.14 g (placebo; NS). Moreover, almost 50 % of patients in active group reached the highest dose (20 g), but only 9 % in the placebo. An increase in hazelnut-specific IgG4 and IL-10 levels after immunotherapy was observed only in the active group [38]. Eighteen children with peanut allergy participated in and completed a 12-month peanut SLIT trial. Side effects were primarily oropharyngeal and uncommonly required treatment. Finally, the treatment group safely ingested 20 times more peanut protein than the placebo group. Peanut-specific IgE levels increased over the initial 4 months (P=0.002) and then steadily decreased over the remaining 8 months (P=0.003), whereas peanut-specific IgG4 levels increased during the 12 months (P=0.014). In addition, IL-5 levels decreased at the end of the study (P=0.015) [39].

As mentioned above, SCIT with pollen is potentially effective to treat OAS. Twenty patients with birch pollen rhinoconjunctivitis and apple-induced OAS were recruited into a trial to investigate the effects of SLIT with birch pollen extract on apple allergy. The results were not consistent with that of SCIT and showed although patients experienced improved seasonal allergic symptoms after treatment, apple-induced OAS was not significantly reduced [40].

Epicutaneous Immunotherapy (EPIT)

EPIT provides another allergen delivery route for immunotherapy that has been successfully tested in humans [41, 42]. Using epicutaneous patch, 19 children with CMA underwent a DBPC study in which they were randomized to receive EPIT with cow's milk allergen or placebo. In the active group, although not statistically significant, EPIT tended to increase cumulative tolerated dose at the end of study. Local erythema with or without pruritus was commonly seen at the site of application. No serious adverse events occurred. Generally, EPIT was well accepted by the patients [43].

Immunotherapy with Modified Allergens

The most pressing issue in immunotherapy is immediate reactions resulting from the interaction between IgE and allergens. Although altering the administration routes for allergens as discussed above can significantly increase the compliance and safety of immunotherapy, severe adverse reactions like anaphylaxis still happen sometimes. Modifying IgE-binding epitopes on allergens may interfere with the IgE binding to allergens and reduce the risk of allergic reactions during immunotherapy [44].

Extensively heating or food process generally decreases protein allergenicity by destroying conformational epitopes. Two nonrandomized clinical trials showed most children (70–80 %) with CMA or egg allergy tolerate well to extensively heated milk and egg products [45, 46]. Recently, a study reported the long-term effects of inclusion dietary baked milk on CMA. In this study, children with CMA underwent sequential food challenges to baked cheese (pizza) followed by unheated milk. Some children with CMA who did not receive dietary baked milk were enrolled as controls. The results showed that children who were initially tolerant to baked milk were 28 times more likely to tolerate unheated milk compared with baked milk-reactive children ($P<0.001$). More importantly, subjects who incorporated dietary baked milk were 16 times more likely than the comparison group to become unheated milk tolerant ($P<0.001$), whereas IgE values did not change [47].

Using recombinant technology, food allergens can be produced in commercial quantities with standard quality. The IgE-binding epitopes of such recombinant protein can be further modified, for example, by site-directed mutagenesis to reduce the allergenicity. In addition to humeral immunity, allergen-specific T cells also play an important role in allergy and are another therapeutic target. Several studies have shown that immunotherapy with synthetic peptides containing immunodominant T cell epitopes from an allergen can induce T cell nonresponsiveness [48]. DNA vaccine encoding specific modified allergens can provide in vitro synthesized allergens persistently and induce prolonged humeral and cellular immune responses [49, 50]. Some adjuvants such as heat-killed *Listeria moncytogenes* (HKLM), CpG motifs, and mannoside were used with modified allergens during immunotherapy to enhance the type I helper T cells and/or regulatory T cells responses [5, 50]. The above approaches to food allergies have been evaluated in many animal studies, and preliminary results of most studies were encouraging [51–53]. In the future, more human trials should be conducted to investigate the possibility of clinical application of these treatment strategies for food allergies.

Other Pharmaceuticals

Chinese Herbal Medicine

Some traditional Chinese medicines have antiallergic properties, which might be useful for treating food allergies. A Chinese herbal formula, FAHF-1, containing 11 herbs has been used to treat the anaphylaxis in a mouse model of peanut allergy. Mice were sensitized with peanut in the presence of cholera toxin and boosted 1 and 3 weeks later. FAHF-1 treatment was initiated 1 week later and continued for 7 weeks. After treatment, FAHF-1 completely blocked peanut-induced anaphylactic symptoms, markedly reduced mast cell degranulation and histamine release, and also significantly reduced peanut-induced lymphocyte proliferation as well as IL-4, IL-5, and IL-13 synthesis [54]. Subsequently, an improved formula (FAHF-2), from which two herbs in FAHF-1 were eliminated due to the possible toxicity, was tested in the same model. Similar to FAHF-1, FAHF-2 could completely protect the mice from peanut-induced anaphylaxis as long as 5 weeks after therapy [55]. In a randomized, DBPC, dose escalation, phase 1 trial, FAHF-2 was evaluated for its safety and tolerability in patients with food allergies. Of the 18 patients who completed the study, one patient in active group and one patient in control group reported mild gastrointestinal symptoms. Vital signs, physical examination results, basic laboratory data, and lung function were not different between patients in active and control groups before and after treatment. In addition, peripheral blood mononuclear cells treated with FAHF-2 in vitro demonstrated a significant reduction in IL-5 and increases in interferon (IFN)-γ and IL-10 production. The results showed that FAHF-2 with potential immunomodulation effects was safe and well tolerated for patients with food allergies [56]. Phase 2 and phase 3 trial are needed to confirm the efficacy of FAHF-2 on food allergies.

Conclusion

The prevalence of food allergies is increasing; however, the standard management is limited to food avoidance and symptom relief. Since there is an unmet medical need for an effective therapy for food allergies, development of therapeutic interventions for food allergies is a research priority and of clinical significance. Currently, more and more animal studies and clinical trial are undergoing to investigate the safety and clinical and immunological effectiveness of biologics, immunotherapy, and other pharmaceuticals on the treatment of food allergies. Some encouraging results from above studies indicate a future therapeutic direction. In addition to conventional management, the combination with biologics, various immunotherapies, and/or other newly

developed medicines is likely the most optimal treatment strategy for food allergies.

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