YALE JOURNAL OF BIOLOGY AND MEDICINE 93 (2020), pp.749-758.

REVIEW

YALE JOURNAL OF BIOLOGY AND MEDICINE
YJBM
CELEBRATING 90 YEARS 1928–2018

Advances in Food Allergy Treatment

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Food allergies represent life-threatening diseases which are increasing in prevalence with no definitive treatments currently in place. Current treatments are no more than preventative avoidance and symptom management. Research within the field has focused on therapeutic developments to modify the immune response in allergen-specific and non-specific methods. This review of the advances made in treatments intends to cover methods such as oral immunotherapy, modified food protein vaccines as well as the use of alternative medicine. Thus, this review aims to inform and further extend discussion surrounding the potential clinical applications as well as novel routes for further research into an, as of yet, unsolved question.

INTRODUCTION

Food allergies are an adverse health effect (AE) due to a specific immune response, which occurs reproducibly, on exposure to a given food [1] in predisposed individuals. Food allergens are specific components of food which are recognized by specific immune cells to elicit an immunological reaction, giving rise to characteristic symptoms [1]. Food allergens are commonly found in foods such as fruits, peanuts, fish, soy, seeds, cow's milk (CM) and hen's eggs (HE). The common disorder is suggested to affect up to 10% of certain populations [2]. The prevalence of the condition is rising [2,3]. Current treatments are centered around the avoidance of triggers and symptomatic management. Therapeutic advances made within the field can be categorized into allergen-specific and non-allergen specific approaches. This review aims to inform and further extend discussion surrounding the potential clinical applications as well as novel routes for further research into an, as of yet, unsolved question.

PATHOGENESIS OF FOOD ALLERGY

In order to appreciate the therapeutic approaches adopted, a brief discussion of the pathogenesis of food allergy is required. The mechanism leading to food allergy is yet to be fully elucidated. It is thought that the perturbation of physiological oral tolerance is central to the development of food allergy. Oral tolerance, defined as the state of apparent local and systemic immune unresponsiveness induced by oral administration of an innocuous antigen, such as food proteins, is critical to the maintenance of

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Abbreviations: AD, Atopic dermatitis; AE, Adverse effects; APC, Antigen-presenting cell; CM, Cow's milk; CMHAA, chemically modified aluminum-hydroxide adsorbed allergen; DBPCFC, Double-blind, placebo-controlled, food challenge; EoE, Eosinophilic esophagitis; EPIT, Epicutaneous immunotherapy; GI, Gastrointestinal; HE, Hen's eggs; IPEX, Immunodysregulation Polyendocrinopathy Enteropathy X-linked Syndrome; LAMP, Lysosomal associated membrane protein; SCIT, Subcutaneous immunotherapy; SLIT, Sublingual immunotherapy; OIT, Oral immunotherapy; VLP, Virus-like particle.

Keywords: Food, allergen, treatment, specific, allergic reactions, IgE, immunotherapy, tolerance, sensitization, oral challenge, adverse effects

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the physiological state [4]. Where oral tolerance is yet to be fully established, non-oral exposure, for example via epicutaneous application, to stable proteins can provoke allergy, by causing sensitization such that it induces a systemic allergic reaction following an oral challenge [5]. Sensitization, in the context of food allergy, is implied as to the formation of food antigen-specific IgE produced as part of the immune response [6]. The loss of the skin barrier is another potential site of food sensitization [7] and has been implicated in atopic dermatitis (AD) where skin basophils have been found to participate in the sensitization to food allergens [7]. The significance arises in the association of AD with food allergy development given that the loss of integrity of the skin barrier is common in AD patients. Where environmental exposure is low, this presents a potentially significant mechanism which illustrates Lack's Dual Allergen Hypothesis [7,8].

The allergic reaction is initiated following the contact of pre-existing IgE antibodies to the food allergen antigen, leading to mast cell activation via cross-linking of high-affinity FcεRI receptors by the antigen-IgE complex. The resulting mast cell degranulation releases preformed inflammatory mediators such as histamine and serotonin as part of the early-phase allergic reaction. Enteric eosinophils are a key initiator component in the complex interaction network of immune cells in controlling DC-mediated initiation of Th2 responses [9-11]. The release of vasoactive mediators can give rise to vascular collapse and anaphylactic shock, which can become life-threatening [9]. This also induces *de novo* synthesis and release of other inflammatory mediators, proteases, cytokines, and chemotactic molecules as part of the secondary, late-phase response. Little is known about the function of the late-phase response, although there have been suggestions that it may be involved in food allergen-induced forms of eosinophilic gastroenteritis [12]. In theory, the late phase reaction can be divided into two types, with the latter "delayed" type reaction occurring 24-48 hours after contact, in contrast to the earlier late-phase reaction which may occur within a few hours [13]. The delayed-type reaction proceeds via either an IgE-dependent or IgE-independent pathway to resemble a Type IV hypersensitivity reaction [13]. While said responses are localized (*e.g.* to the mouth, esophagus, and/or intestines), should the allergen-IgE complex cross the mucosa of the gastrointestinal (GI) tract, this can give rise to deleterious systemic reactions. Drawing this distinction between phase reactions is important to guide the clinical approach [13]. The time of onset of the allergic reaction after an allergen intake and its presentation determines the therapy chosen. Anti-histamines and adrenaline are common therapies of choice for the early-phase response while corticosteroids are used to prevent late-phase symptoms [13].

Hypersensitivity can be defined as immune responses that are exaggerated or inappropriate against an antigen or allergen. The most common form of immune-mediated adverse reactions to food is characterized by IgE-mediated Type I hypersensitivity reactions as per the Coombs and Gell classification. Patients with IgE-associated food allergy can be identified by either skin "wheal and flare" tests or by assaying serum and body fluids to detect food allergen-specific IgE as part of *in vivo* and cellular responses [14]. Food allergen-specific T-cell responses, which can damage the gut mucosa, are part of Type IV hypersensitivity reactions [12]. There is no experimental evidence to support food allergen-specific IgG reactions via Type II or Type III reactions [13]. The Th2 profile is integral to the allergic reaction. It mediates the synthesis and release of IL-4, IL-5, and IL-13, which mediate downstream responses. The professional antigen-presenting cell (pAPC) role of GI DCs is central to shift the T-cell response to a Th2 profile [15,16]. Furthermore, the variation of clinical outcomes observed is thought to be, in part, due to the spectrum of Th2 responses which a Th1 profile would fail to account for [17]. Our discussion of the cells implicated would be incomplete without a reference to the role of Treg cells. Their depletion in murine models during oral exposure to peanut allergen saw a stronger allergic reaction compared to controls in sensitized mice [18]. In a study looking at children who did or did not resolve their CM allergy, it was found that children who became tolerant had a higher frequency of circulating Treg cells [19]. This has led to the conclusion that while the function of Treg cells is to maintain tolerance and regulate the intensity of the IgE response, they are not critical for preventing sensitization [19].

FOOD ALLERGY TREATMENTS

The current state of food allergy treatments centers around the avoidance of trigger foods, preparedness in symptom management and symptomatic drug therapy (*e.g.* antihistamines and steroids). This represents the contemporary nature of the clinical approach which presents itself to be nutritionally and socially limiting for patients and families alike while fatalities still occur. In exploring the advances in treatments, such can be categorized into allergen-specific and non-allergen-specific approaches.

ALLERGEN-SPECIFIC THERAPIES

The guiding principle of allergen-specific therapies is to modulate the allergic response to the causative antigen without inducing an adverse immune response to the therapy itself [20].

One of the fundamental mechanisms exploited by such therapies is to alter the Th2 profile. The gen-

eral principle aims to increase the Treg response while downregulating the AEs of the allergic response. By initial presentation of the allergen to GI DCs, this leads to the production of Treg cells, as characterized by the production of IL-10 and TGFβ-9, which suppresses mast cell reactivity [21]. Concomitant Th1 production of IFNγ induces a shift of the major antibody class from IgE to specific IgG and IgA production [21]. Allergen-specific IgG binds to, and neutralizes, the food allergen, via inducing FcγRIIB-mediated inhibitory signaling on mast cells and basophils [21]. Prolonged exposure, as part of treatment regimens, is thought to lead to anergy and depletion of the allergen-specific Th2 cells [22].

By adopting allergen-specific therapies, this enables a normal quantity of consumption while preventing symptomatic reactions. However, given the specific nature of the treatment, this targeted therapy fails to be a wide-encompassing treatment for food allergies, which is pertinent in individuals who may suffer from multi-food allergy.

Immunotherapy

There are four different forms of immunotherapy that have been utilized for food allergy treatment, with variable success.

Subcutaneous Immunotherapy: Subcutaneous immunotherapy (SCIT) involves applying repeated weekly build-up doses of specific unmodified allergen extracts to build tolerance followed by maintenance doses at longer intervals [23]. It aims to induce an allergen-specific immune deviation shift from IgE to IgG, reflecting the Th2 to Th1 profile shift. The results for birch pollen immunotherapy and native peanut allergen have shown clinical improvements, albeit at the expense of significant AEs [24,25]. Efficacy has been shown for the method, especially in other allergens such as venom [26]. However, in addition to mild localized symptoms at the site of administration (*e.g.* erythema, pruritus, and edema), the method is avoided due to a high frequency of anaphylaxis and a high drop-out rate [25].

Epicutaneous Immunotherapy: The epicutaneous immunotherapy (EPIT) method involves delivering the food allergen via an adhesive patch. Water loss from the skin displaces the allergen from the patch [21]. Langerhans cells can then selectively deliver allergen antigens to regional lymph nodes [21]. A recent randomized, double-blind, placebo-controlled Phase 3 trial (n = 356) conducted at 31 sites across five countries for peanut-allergic children aged between 4-11 years saw daily treatment with a peanut patch, containing 250 μg of peanut protein (n = 238) or placebo (n = 188) for 12 months [27]. Following observations for the development of objective symptoms after a double-blind, placebo-controlled food challenge (DBPCFC), a statistically significant difference in the responder rate to the treatment was found with a rate of 35.3% for the treatment group and 13.6% for the placebo group (95% CI, 12.4%-29.8%; P< .001) [27]. The study had multiple encouraging findings within the context of a high adherence rate including a well-tolerated treatment protocol, a low rate of serious adverse events and a low rate of systemic allergic reactions (of which none were severe) [27]. However, participants with a history of severe life-threatening anaphylactic reactions to peanuts were excluded, reducing the generalizability of the findings [27]. Moreover, visible skin reactions were thought to potentially create a false perception to the caregiver of an unblinded protocol, albeit such was common across both groups [26]. Finally, long-term benefits of the therapy could not be derived given that the duration of the study was limited to 12 months which would have failed to show what continued and steady response to a long-term exposure may have been possible as demonstrated in an earlier Phase 2 study [28]. One must also consider that despite the significant difference found, the rate of efficacy was nonetheless relatively low.

Oral Immunotherapy: In oral immunotherapy (OIT), the food allergen is ingested in gradually increasing amounts until a maintenance dose is attained [29]. It is hypothesized to restore or induce a tolerant state. As per our discussion, it is important to ensure that we do not conflate desensitization and tolerance. Desensitization ensures that the biological response to the food allergen diminishes when it is ingested regularly. However, in a tolerant state, the loss of the biological response is more gradual despite not undertaking regular intake [20]. Current findings suggest that OIT may induce desensitization, however, it does not induce tolerance [20]. A systematic review and meta-analysis into OIT for CM allergy reported similar findings with children reportedly more likely to achieve tolerance compared to elimination diet alone [30]. However, there was a high degree of uncertainty due to a lack of clarity regarding the representativeness of the study populations, a judged high likelihood of publication bias and imprecision in the estimation of effects, given a reported high fragility of results in several studies with small sample sizes [30]. One such example is a randomized clinical trial (n = 45) which explored a specific oral tolerance induction (CM: n = 14; HE: n = 11) compared to an elimination diet (control) (CM: n = 10; HE: n = 10) protocol for children with CM or HE allergy [31]. Following a median of 21 months of therapy, DBPCFCs were administered where it was found that for the treatment group, who had two months of discontinued therapy and were rechallenged, while 64% had shown a partial response, post-treatment, only 36% showed continued (true) tolerance which was found to be statistically insignificant [20,31]. The small sample size, especially

for different groups within each protocol (*i.e.* CM and HE) alongside varying times of evaluation (minimum 12 months and a maximum of 47 months) and the vast age range, with implications for confounding developmental factors, all represent shortcomings of the study [31]. Since then, a peanut OIT product (Palforzia™), has debuted as the first-ever FDA-approved peanut allergy treatment. A statistically significant difference was found with 67% of the treatment group (n = 372) able to tolerate the 600 mg dose of peanut of the DBPCFC at the completion of the Phase 3 clinical trial compared to 4% of the control group (n = 124) (95% CI, 53.0% - 73.3%; P < 0.001) [32]. Limitations of the study included the statistically insignificant improvement in the exit food challenge between the treatment and control group for older participants [32]. In addition, participants were selected on the basis of their sensitivity to less than 100 mg of peanut protein and that the majority of participants were white males, thereby limiting the representativeness of the sample group [32]. Long-term safety and efficacy evaluations were not possible with the initial study given that only desensitization was evaluated following 6 months of the maintenance regimen, albeit further extended maintenance therapy and placebo-controlled trials were sufficiently favorable to lead to the FDA approval. The treatment group did see a higher frequency of AEs compared to the placebo group, which corroborated findings from a systematic review and meta-analysis of 12 peanut OIT trials which found an increased anaphylaxis relative risk ratio of 3.12 [32,33].

The benefits of this method relate to the decreased infection risk otherwise associated as a complication of vaccination/injection-mediated therapies, while the use of natural foods gives rise to convenience. However, the risk of allergic reactions which can arise, at the expense of a failure to induce true tolerance can be worrying. In addition, the side effect profile of local AEs, as well as systemic, potentially serious reactions, are limiting for patients and physicians who value the avoidance of serious AEs in light of the absence of robust supporting data [30]. It has been found that the use of auto-injectable adrenaline in treatment subjects is significantly higher than in placebo-treated subjects [33]. In addition, there is a greater risk of adverse systemic reactions, whereas, for EPIT and sublingual immunotherapy (SLIT), side-effects are normally limited to localized reactions. Cohort simulations have suggested that broad usage of peanut OIT may cause more anaphylaxis than it would likely prevent [34]. There further remains uncertainty of the potential long-term benefits, where a Phase 2 escalating-dose study found that desensitization levels were maintained until treatment was stopped or the daily dose was lowered [35]. Combined with the suggested increased risk rate of eosinophilic esophagitis (EoE), and the failure of multiple studies to discuss the improvements, or lack thereof, on quality of life with considerations to the effects of long-term compliance, the commitment of individuals (and families) to treatment regimes, and the access to resources and support to immediately treat severe AEs, the cost-benefit analysis of future OIT treatments and products must be considered [30,36].

Sublingual Immunotherapy: SLIT involves the gradual oral exposure of a patient to native food allergens by placing a small amount of the solubilized food allergen under the tongue [37]. Theoretically, this aims to avoid the acute reactions seen with large doses, while enabling the coveted immune deviation associated with oral tolerance. The application of SLIT regimens for environmental allergens in the case of respiratory allergies has shown an early induction of Tregs as well as a latter deviation from a Th2 to a Th1 profile [38]. The findings were corroborated for a food allergy randomized, double-blind, placebo-controlled multicenter trial for peanut-allergic adolescents and adults (n = 40) where 70% of the treatment group saw a significant 10-fold or more increase in the reaction-triggering threshold compared to 15% of the placebo group (P < .001) [37]. Moreover, the median reactive dose increased from 3.5 mg to 496 mg after the 44-week regimen (P = 0.02) [39]. Limitations of the study included a high drop-out rate, a significant side-effect profile, of primarily oropharyngeal pruritus, which is thought to have possibly affected the blinding of the study, albeit the DBPCFC protocol would most likely have mitigated any issues [39]. In addition, the limited dosing range is not comparable to those found in OIT and the results reflect desensitization, with no indication of long-term tolerance or incorporation of the food into a normal diet [39]. Similar findings of a significant rise in the symptom-triggering threshold for hazelnut-allergic patients as part of a randomized, double-blind, placebo-controlled study have been reported, demonstrating representative results of SLIT [40]. The benefits of SLIT are similar to those discussed in OIT with the decreased infection risk compared to injection-mediated therapies and convenience of using natural food. Nonetheless, findings that there are low rates of sustained unresponsiveness are concerning given that the bearing of potential adverse reactions for patients does not necessarily guarantee an induction of true tolerance [41].

Vaccinations

While immunotherapy may be used in later life as a curative attempt to enable the integration of the food as part of a normal diet, vaccination represents a viable strategy which may be utilized earlier in life to enable long-term tolerance development.

Modified Proteins: The use of modified recombinant proteins in vaccinations relies upon the principle of epitope modification of IgE binding sites to food allergen

antigens, which retains TCR binding but prevents IgE binding and thus downstream mast cell activation [42]. Therefore, while there is a loss of allergenicity, immunogenicity is preserved. These principles have been utilized to generate hypoallergenic mutants of peanut, fish, and apple allergen proteins [43-45]. A Phase 1 trial (n = 15) studying the effects of delivering a combination of recombinant major peanut allergens (Ara h 1, Ara h 2, and Ara h 3) delivered using an *Escherichia coli* vector (favoring a Th1 profile) found a high rate of AEs [44]. No significant change in peanut-specific IgE or IgG4 were reported [46]. The small sample size of peanut-allergic subjects (n = 10) however does limit the representativeness of the findings. The approach of using recombinant protein vaccines does, in theory, enable the avoidance of potential immune reactions due to the ablation of IgE binding and thus downregulation of downstream IgE effects [20]. However, one must consider this in balance to the potential expense given the allergen-specific nature of the production process [20].

Peptide Immunotherapy: Peptide immunotherapy is considered in the vaccination section and not the preceding immunotherapy section due to the greater similarity and alignment with the approaches adopted for this therapeutic measure. While SLIT and SCIT may require nearly 3 to 5 years of treatment, intra-lymphatic peptide immunotherapy treatment can be achieved after three injections [20,47]. The guiding principle involves the use of overlapping peptides which represent the entire sequence of the specific food allergen protein [48]. In murine models, it has been shown that pre-treatment with two doses of the peptide mixture of the Ara h 2 peptide mixture before an oral peanut challenge blocked anaphylactic reactions in peanut-sensitized mice [49]. Similar results were found for peptide immunotherapy for the major HE allergen, Gal d (also known as ovalbumin). Using a mixture of three mitogenic sequences, AR-12, SR-12, and AE-12, for the treatment cohort in a Gal d2-sensitized mice saw significantly lower anaphylaxis scores following an oral challenge of 20 mg of Gal d2 compared to the placebo and sham-treated control groups [50]. Limitations include the extent of reproducibility of murine models for humans and the expensive limiting factor of validation standardization for multiple peptides per food allergy [20]. However, costs can be offset given that multiple modified allergen proteins with ablated IgE binding sites do not need to be generated since said sites do not need to be identified [20].

Plasmid DNA: Plasmid DNA vaccinations are based on the hypothesis that endogenously produced antigens are not thought to stimulate allergic immune responses, instead, these self-antigens undergo tolerization. This has led to the exploitation of bacterial plasmid DNA to encode food allergens. For AKR/J mice, treatment with Ara h 2 DNA embedded within bacterial plasmid DNA saw a substantial reduction of allergen-induced anaphylaxis as well as reduced plasma allergen-specific IgE, plasma histamine and vascular leakage in the treatment group compared to the controls [51]. However, this was not replicated in C3H/HeJ mice [51]. This strain variability is suggestive that a homogenous effect in humans is unlikely to occur [51,52], thereby relating to our earlier discussion of factors related to the clinical heterogeneity of food allergy presentation. Nonetheless, this approach can limit the number of required treatments to single doses which subverts the need for continued therapies which may otherwise interfere with a normal social life.

Recent advances include the LAMP (lysosomal associated membrane protein)-DNA vaccine which has its origins from pollen allergies vaccine approaches. DNA encoding the allergen is targeted to the endosome via the addition of the LAMP sequence such that when APCs take up the plasmid, the allergen-LAMP fusion protein can be presented on MHC Class II molecules which is hypothesized to lead to downstream Th1 responses as shown in treating Japanese red cedar allergy [53]. Currently, a Phase 1 trial (NCT02851277) for peanut allergens Ara h 1, Ara h 2, and Ara h 3, is in progress [54].

Other plasmid vaccines currently in development include virus-like particles (VLPs) conjugated to allergens. VLPs conjugated to roasted peanut extracts as well as major allergens Ara h 1 and Ara h 2 saw a protective effect against anaphylaxis following an IV peanut challenge [52] in sensitized mice [55]. An IV challenge may not be a physiological representation of normal peanut-allergic human contact, however, it has been suggested that the parenteral mode of administration can be a model of systemic exposure, thereby enabling an investigation of the protective effects against systemic allergic reactions [56].

NON-ALLERGEN-SPECIFIC THERAPIES

Comorbidities such as uncontrolled asthma, severe AD or EoE are contraindications for many allergen-specific therapies. This acts to prevent the inclusion and treatment of many patients who may stand to benefit the most from therapy. Therefore, this necessitates a non-allergen-specific approach as either alternative monotherapies or adjunctive therapies. It is important to determine if these therapies only alter the threshold of allergic reactivity or induce an actual cure [21].

Biologics

Biologics are any type of medical therapy derived from a living organism or containing their components. Current biologics are used for the treatment of other atopic disorders such as asthma and AD. Their repurposing represents a viable route for food allergy therapeutics.

The two most viable routes are via anti-IgE and anti-IL4 receptor antibody therapies.

Anti-IgE Antibody: The use of anti-IgE antibodies to induce neutralization is hypothesized to reduce or eliminate food allergen-induced AEs. The prototypical example is illustrated by a study into the humanized anti-IgE monoclonal antibody TNX-901 which underwent a randomized, double-blind, placebo-controlled, dose-ranging clinical trial with patients who had a history of peanut hypersensitivity (n = 84) [57]. For the 450 mg dose, the study found a significant increase in the threshold of reactivity to an oral challenge from 178 mg to 2.8 mg ($P < 0.001$) [57].

The development of TNX-901 was shelved due to legal issues in development, however, another anti-IgE biologic, omalizumab, is undergoing trials as an adjunct as well as a monotherapy (NCT03881696). Preliminary data from real-life studies for the application of omalizumab treatment found an increased threshold dose following treatment for CM, HE, wheat, and hazelnut from 1012.6 mg to 8727 mg ($P < 0.001$) while other foods were partially tolerated [58,59]. A reduction in dietary restrictions was observed with the reintroduction of the tolerated foods into the patients' diets without the need for any oral immunotherapy procedures [59]. Limitations of the study include its observational design rather than a prospective trial and its arbitrary measures of selective criterion [59]. Findings from the ongoing clinical trial will be indicative of whether omalizumab represents a viable route of further research.

Anti-IL4 Receptor Antibody: Dupilumab, an anti-IL4 receptor antagonist, is another potential candidate currently undergoing a Phase 2 clinical trial to assess its viability as a monotherapy or adjunct for peanut allergy (NCT03682770). Its actions can prevent the downstream effects of IL-4 and IL-13 produced during the acute inflammatory reaction to promote Th2 responses [60].

Chinese Herbal Medicine

FAHF-2 is a nine-herb preparation which has been found to block anaphylactic symptoms in a murine model of peanut allergy [61]. In contrast to the sham-treated group, the treated group saw full protection for as long as 5 weeks post-therapy with no signs of anaphylactic reactions, no elevation of plasma histamine levels and a significant reduction of plasma IgE levels up to 5 weeks post-therapy ($P < 0.001$) [61]. Splenocyte cytokine profiles from the treated group saw a significant reduction in IL-4, IL-5, and IL-13 production ($P < 0.01$, $P < 0.001$, and $P < 0.01$, respectively) and a higher IFNγ synthesis ($P < 0.01$), indicating a potent inhibitory effect on the peanut-induced Th2 response profile, reflecting a shift to a Th1 profile, throughout the five-week post-therapy period [61].

While the initial Phase 1 human double-blind, randomized, placebo-controlled study (n = 68) found promising *in vitro* immunomodulatory effects of FAHF-2 in subjects with allergies to peanut, tree nut, sesame, fish, and/or shellfish, clinical efficacy was not shown for the dose and duration of the protocol, which was suggested to be due to poor adherence given that a higher eliciting dose was found at the end-of-treatment DBPCFC for the placebo group ($P = 0.05$) [62]. However, a more recent study of B-FAHF-2 as an adjuvant therapy used alongside tree nut and peanut OIT in sensitized mice found a reduced frequency of, and less severe, adverse reactions alongside increased desensitization as well as a pro-tolerogenic profile [63]. There is an ongoing double-blind, placebo-controlled, randomized trial into the efficacy of multi-allergen OIT with omalizumab, followed by an OIT with B-FAHF-2 (NCT02879006) which represents a synoptic protocol that may have promising results.

Cytokines

The use of cytokines to alter the cytokine profile of the allergic reaction has been postulated as a potential therapeutic avenue. The use of a *Lactobacillus lactis* delivery system of IL-10, which is an inhibitory regulatory cytokine, has been found to diminish sensitization and reactivity in a murine model of milk allergy [64].

Similarly, the use of TGF-β alongside ovalbumin as a treatment protocol of BALB/c mice has been associated with a significant reduction in ovalbumin-specific IgE and IgG ($P < 0.05$) as well as a reduction in T-cell reactivity as per immunologic assays ($P < 0.05$) [65].

IFNγ has been proposed as another alternative cytokine therapy given that it promotes Th1 responses while suppressing Th2 responses [66]. When used as an adjuvant for OIT for a pilot study with children (n = 25) who were allergic to CM, HE, and/or wheat, all 10 subjects of the treated group (IFNγ + OIT) showed successful induction of tolerance, as defined in the study controversially as the absence of anaphylactic reactions upon the oral challenge alongside the absence of the signs of acute allergic reaction signs and symptoms [67]. The tolerance was found to last up to a year for the small sample of subjects [67]. The control group of patients who received OIT alone (n = 5) failed to complete the protocol and withdrew due to frequent and adverse reactions. Thus, these results are suggestive of a potential role of IFNγ as an adjuvant for OIT to improve tolerability and desensitization.

Chemically Modified Aluminum-hydroxide Adsorbed Allergens

The concept for the use of chemically modified aluminum-hydroxide adsorbed allergens (CMAHAAs)

arose in response to the severe systemic reactions that were referred to earlier when native peanut allergens were used for SCIT. CMAHAAs have been found to reduce allergenicity while still retaining the immunogenicity of peanut extract, which has been shown in murine models [67,68]. Findings from a first-in-human human trial supported the safety and tolerability findings from the initial murine models [69].

Nanoparticle Delivery Systems

Nanoparticle delivery systems are in the process of being developed with properties to enable reduced degradation in the GI tract as well as increased uptake efficiency [70]. The use of a CpG coating has been suggested to promote a Th1/Treg profile via its property as a TLR9 ligand [21]. Findings from murine models suggest that the systems are well tolerated with favorable cytokine signatures [21]. Nonetheless, it is important to research the kinetics of the delivery and release to avoid the sudden release of large amounts of allergen which may potentially have deleterious systemic side effects.

Probiotics

Dysbiosis of the commensal gut flora has been linked as a possible role in the pathogenesis of food allergy [71]. The use of probiotics has been hypothesized as a potential therapeutic option through the utilization of a bacterial milieu to induce tolerance [71].

CM formula which contained the probiotic *Lactobacillus rhamnosus* GG was found to accelerate immune tolerance acquisition in children allergic to CM [72,73]. Similarly, the use of adjuvant probiotics as part of an 18-month OIT regimen in a randomized, double-blind, placebo-controlled trial (n = 62) saw 89.7% of the treatment group (n = 31) exhibit desensitization following a DBPCFC compared to 7.1% of the placebo group (n = 31) ($P < 0.001$) [74]. A 4-year follow-up showed that 58% of the initial treated group who participated in the follow-up study (n = 12) showed sustained unresponsiveness compared to 7% of the placebo group (n = 15), which is suggestive of a long-lasting clinical benefit of this combined therapy [75]. Limitations included the fact that subjects did not undergo entry DBPCFCs to verify their allergic status, albeit the randomized design would be expected to evenly distribute the subjects [74]. Furthermore, the period post-therapy upon which sustained unresponsiveness was calculated had a wide range of 2 to 5.3 weeks [74]. However, the follow-up study mitigated this issue by its assessment of prolonged sustained unresponsiveness, which is of greater clinical significance [75]. Despite the promising follow-up findings, the small sample size restricts the generalizability of the findings, which is further compounded by the single-center design [74]. While these features may be similar to other OIT studies, the lack of a probiotic-only group and an OIT-only group as seen in the IFNγ-adjuvant OIT therapy discussed earlier, limits the conclusions that can be drawn with regards to the individual contributions of the constituents of the combined therapy [67,75]. Taking into account these limitations, some of which were mitigated, for example by inverse probability weighting, and others were in line with common conditions for other OIT follow-up studies [76,77], the long-term efficacy of the dual therapy alongside its favorable safety profile is promising [75].

CONCLUSIONS AND FUTURE OUTLOOK

It is critical to have an appreciation of immune mechanisms underlying food allergic responses. Manipulation of tolerance to ensure its establishment is important for long-term prospects in contrast to transient desensitization which is not maintained in the absence of treatment. Many studies explored fail to enroll food-allergic patients with a history of life-threatening reactions due to ethical concerns. However, this is a key detractor of the validity of the studies. These subjects are more likely to seek treatment and thus the potential different therapeutic responses are critical to consider. Future clinical trials need to recruit patients with all severities of allergic reactions to eliminate the current bias present within the field. The advances that have been made in food allergy treatments have occurred with the potential costs of an increased risk of AEs (*e.g.* anaphylaxis) and treatment protocols which can impact the patients' daily social lives, leading to extensive treatment burdens. Clinical management must still focus on issues such as ingredient labelling, symptom recognition, and altering reactivity thresholds via lifestyle factors until a cure can be found, if at all [70]. With the advent of innovative therapies in the coming years, the navigation of this landscape still will necessitate a shared decision-making effort within a patient-centered framework, alongside caregivers, with regards to goals related to expected outcomes, potential AEs and the burdens of therapy [54]. Very few studies have addressed the needs of patients with multiple food allergies. Non-allergen-specific therapies represent a significant opportunity for treatments with wide potential applications. To reiterate, investigative therapeutics must ensure both an efficacious profile of future treatments as well as a safe profile. The increasing prevalence of food allergy is not thought to only be due to genetic predispositions, which is suggestive of environmental factors at play [78]. Combined with multi-variable factors such as dose, the timing of exposure, and food processing methods, all of which can alter allergenic potential and disease phenotype as well as clinical outcomes, all such represent

novel routes of questioning and research as potential targets for treatment and disease prevention.

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