Food Allergen Immunotherapy for IgE-Mediated Food Allergy Treatment

Subjects: Allergy

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Implementation of an elimination diet is not a sufficient therapeutic strategy in patients with food allergy, whose quality of life is significantly impaired. In recent years, new effective therapeutic strategies have been developed, such as the application of oral, sublingual, and epicutaneous immunotherapy. Oral immunotherapy is the most often applied strategy because of its effectiveness and ease of application, with an acceptable safety profile. The effectiveness of oral immunotherapy in patients with egg, cow's milk, and peanut allergy has been proven both in terms of raising of the threshold and the development of tolerance, and in some patients, the development of sustainable unresponsiveness. Although oral immunotherapy is an effective treatment for food allergy, several limitations, including a long duration and a significant rate of reported adverse events, reduces its success.

Keywords: food allergy ; IgE-mediated food allergy ; oral immunotherapy ; OIT ; sublingual immunotherapy

1. Introduction

Food allergen immunotherapy (FAIT) has been used in recent years as a novel and sustainable treatment strategy for patients with clinically relevant IgE-mediated food allergy [1][2][3]. As in the treatment of other allergic diseases, food allergen immunotherapy is the only etiological therapy. Unlike traditional approaches in which a patient with a proven food allergy is recommended keeping a strict elimination diet and using symptomatic drugs such as adrenalin in case of anaphylaxis, allergen immunotherapy is a new approach in the treatment of food allergy [3][4]. Complete elimination of the food allergen in question from the patient's diet and avoidance of any contact with the food by ingestion, skin contact, inhalation is difficult to implement in practice due to the risk of cross-contamination or accidental exposure [2][3]. It is undoubtful that patients with food allergies have a significantly impaired quality of life, both because of the constant fear of a life-threatening reaction as well as of demanding diets that can affect their nutritional status and a balanced diet if important nutrients are avoided. Because of that, the introduction of allergen immunotherapy in patients with clinically relevant food allergies has offered a significant improvement in the management of such patients [5].

Certain specificities in the immune response during FAIT related to the different application routes (oral, sublingual, and epicutaneous), type of food allergen, protocols (doses and frequency of administration) appear to be associated with the effectiveness but also with the risk of side effects [5][6][7].

The primary goal of FAIT is to increase the response threshold and achieve desensitization or tolerance, and in some patients, sustained unresponsiveness (SU) even after discontinuing the regular use of allergens. This increase in the threshold is achieved after a variable period of application of increasing food allergen doses. The challenge of FAIT is to achieve SU to a food allergen, after the discontinuation of immunotherapy. Gaps persist in our understanding of the immune mechanisms of food allergy and how FAIT can lead to SU, especially since the number of patients with relapse increases over time after discontinuation of treatment [6][7].

2. Mechanisms of Food Allergen Immunotherapy

FAIT is considered as an effective method for treating patients with IgE-mediated food allergies [8]. The mechanisms involved in the development of tolerance and immune modulation during FAIT are not fully understood. Development of immune tolerance and T and B cell responses changes were found in patients during FAIT [9][10]. A switch in immune responses from Th2 to Th1 cell polarization with an increase in INF-γ and a decrease in Th2 related cytokines (IL-4, IL-13) were reported. During immunotherapy exposure to continuous high doses of food allergens leads to Th2 and Th2A anergy and/or deletion and an increase in T regulatory cells which leads to the suppression of downstream allergic responses.

FAIT incompletely targets subsets of Type 2 immune cells which is a transient and non-permanent shifting [11]. Additionally, studies show that the function and number of Treg cells increase during FAIT [9][12]. In the development of peripheral tolerance Treg cells have a critical role, including the activation of specific cell subpopulations such as: inducible T regulatory (iTreg) cells, natural T regulatory (nTreg) cells and Tr1 cells and TGF-β producing Th3 cells [13]. However, the impact of FAIT on the differentiation Treg subpopulations is not well-understood. Certain studies showed an association between increased Tregs and improved outcomes in immunotherapy [14][15] while others did not prove the same effect [11][16]. A significant suppression in T follicular helper cells (Tfh) cells and transformation of follicular regulatory T (Tfr) cells following FAIT were found. Tfr cells may have important roles during FAIT and the development of immune tolerance which results in a significant decrease in Th2 responses. Modification of the Th2-mediated immune response appears to be essential for the achievement of tolerance to a particular food allergen, i.e., in the prediction of the efficacy of FAIT [17]. In FAIT with egg, high baseline levels of egg specific CD4+ Th2 cells strongly predicted failure of FAIT treatment [20

Generally, every form of FAIT, i.e., oral, sublingual, and epicutaneous immunotherapy is characterized by decrease in basophil and mast cell activation [18][19]. Peanut oral immunotherapy (OIT) and milk sublingual immunotherapy (SLIT) have shown early but transient decreases in basophil activation with the loss of tolerance after the discontinuation of the immunotherapy [20][21]. During the up-dosing phase of FAIT, there is an initial rise of allergen-specific IgE levels, which is a consequence of the proliferation of allergen-specific memory B cells, followed by a gradual decrease in allergen sIgE at the end of the therapy [22].

Changes in the humoral response during FAIT are manifested by an increase in food protein specific immunoglobulin G, subclass 4 (IgG4) and specific immunoglobulin A (IgA) as well [23][24]. The increase in food-specific IgA may play a role in the induction of tolerance [25].

Decreased activation of basophils and mast cell are observed during the desensitization phase of FAIT measured by the suppression of the allergen-specific skin prick test and basophil activation test [26].

Modulation in the response of CD8+ T lymphocytes can be a predictor of response to OIT as well. The POISED study with peanut OIT showed that baseline levels of naïve CD8+ T cells and peanut -and Ara h 2-specific IgE were in positive correlation with treatment efficacy [27]. The role of dendritic cells during FAIT is not well-established. An association between positive response to therapy and decreased TNF-α producing myeloid dendritic cells (mDCs) was also reported [28]. The mechanisms related to the modulation of the immune response and the development of tolerance during FAIT are described independently of the method of exposure to the allergen.

Allergens delivered by SLIT are downloaded by oral Langerhans cells or myeloid dendritic cells in the oral mucosa which migrate to oral-draining lymph nodes where they promote FOXP3-positive T regulatory cells and the production of tolerogenic cytokines including IL-10 and TGF-β, and downregulate Th2 related cytokines (IL-4, IL-13) [29].

During epicutaneous application, allergens pass through epidermis and are taken up by epidermal Langerhans cells or allergens can be captured directly by dermal dendritic cells. Epidermal Langerhans cells or dermal dendritic cells migrate to skin-draining lymph nodes where they can activate T cells and other cells of adaptive immunity to induce Th2/Th1 switch and development of immune tolerance [30].

3. Oral Immunotherapy (OIT)

3.1. Efficacy of OIT

3.1.1. Milk OIT

The first milk OIT double-blind RCT was carried out in 2008 by Skripak et al. involving 20 children with cow's milk allergy (CMA) [31]. All children were desensitized with median increasing reactivity threshold from baseline 40 mg to cumulative dose of 5140 mg milk protein on the end of OIT, with no change in threshold in the placebo group. AE were frequent in the OIT group, but nearly 90% were mild to moderate with no treatment requirement. OIT followed by measured dairy intake at home on daily basis led to a continuous threshold improvement, however accompanied by AE, sometimes to the previously tolerated dose [32].

There is emerging evidence that heat-processing and food matrix could change the allergenicity of milk protein. Baking milk within a wheat matrix reduces the potential of milk protein to cause allergic reactions. Heating processes induce conformational changes in certain cow's milk epitopes, especially whey proteins such as β-lactoglobulin, whose

allergenicity significantly decreases above 90 °C, while caseins are stable to heat-treatment [33]. Nagakura et al. compared the safety and efficacy of low-dose OIT with heated milk (HM) or unheated milk (UM) in children with anaphylaxis [34]. HM includes milk powder prepared by heating cow's milk at 125 °C for 30 s and spray-drying for 3 s, while UM refers to unheated cow's milk sterilized at 125 °C for 2 s (UHT milk). Although the treatment efficacy was a bit lower in the HM group, the frequencies of total AE, moderate as well as severe, were significantly lower in the HM than in the UM group.

Although OIT with baked milk is promising, the amount of proteins in such products is not standardized which has created the need for a safe product with a standard amount of protein. The iAGE-product is well-defined standardized heated and glycated milk protein product whose tolerance has been investigated in a small pilot study and showed that this product could be safe for ordinary OIT treatment in a infants and young children suffering from CMA, but future studies should confirm these results and assess the effectiveness of tolerance induction acceleration in larger samples [35].

Allergenicity of cow's milk protein could be decreased or lost by breaking down cow's milk proteins into short peptides by enzymatic hydrolysis, and the effect of allergenicity depend on the final peptide fragment size [33]. Partially hydrolysed formulas (pHF) consist of peptides with molecular weights of approximately < 5000 Da while extensively hydrolysed formula (eHF) contains only peptides with molecular weights < 3000 Da. In contrast to eHF, pHF is not intended for use with infants with CMA but possesses low allergenicity. OIT involving the ingestion of pHF improved tolerance to cow's milk in children suffering from severe CMA, compared with those consuming eHF, in a safe manner [36].

3.1.2. Egg OIT

The first egg OIT double-blind RCT dates from 2012. Burks et al. [37] reported that 78% children in the OIT group were desensitized after 22 months, while 28% children in same group achieved SU after 24 months. At the same time, no child in the placebo group has passed the (oral food challenge) OFC test. AE occurred most frequently in the OIT group, but less than 1% were considered moderate. However, some allergic reactions were of sufficient clinical significance that approximately 15% of the children from the OIT group did not finish the treatment, mostly due to allergic reactions [37]. In the long-term OIT follow-up study the same participants were followed up for 4 years. Half of OIT-treated subjects achieved SU by year 4 with mild symptoms reported throughout the study which demonstrated that the probability of achieving SU after OIT increases with longer duration of therapy [7].

Like with milk, allergenicity of egg proteins could be changed during processing due to protein unfolding which leads to conformational changes that can hide or destruct specific IgE binding epitopes. Generally, heating decreases the allergenicity of egg proteins, especially within a wheat matrix like cakes or biscuits [38]. The majority of egg allergic patients are tolerant to a certain amount of baked egg (BE) products, but it is questionable whether ingestion of low levels of BE boosts tolerance development, or this allergy phenotype is simply predictive of tolerance development [39][40]. It appears that in children allergic to unbaked egg but tolerant to BE, egg OIT was preferable to BE ingestion for inducing SU [6]. Egg OIT may also be safer and more effective in BE tolerant than in BE reactive children [6]. Sensitization to heat resistant egg white allergen Gal d 1 (ovomucoid) may be a useful predictor of clinically reactive BE allergy phenotype [41].

3.1.3. Peanut OIT

The prevalence rate of peanut allergy has increased several-fold during the past decades, especially in Westernized nations where it currently affects 1–4.5% children. It is one of the most frequent triggers for fatal anaphylaxis and generally persists to adulthood, which is why response management is crucial [42]. For this reason, most OIT studies have been carried out with the peanut allergen. The first peanut OIT double-blind RCT was conducted by Varshney in 2011 on a small sample of 25 children younger than 16 years of age with peanut allergy. All OIT-treated subjects, but no one in placebo group, were desensitized to the cumulative dose of 5 g peanut protein (equivalent of approximately 20 peanuts). This regimen was well-tolerated, accompanied with only mild clinically relevant symptoms during the build-up phase, but the trial did not include patients with a history of severe anaphylaxis [43]. The STOP II study reported that OIT to peanut was successful in the induction of desensitization in most children suffering from peanut allergy of any severity, raising the reactive threshold at least 25 times so that nearly 90% of participants can tolerate daily ingestion of 800 mg of protein (5 peanuts) which significantly improved their quality of life. Side-effects were mild in most participants [44].

Biomarkers associated with SU were higher baseline peanut specific IgG4/IgE ratio and lower Ara h 2 IgE and basophil activation responses [27].

Most OIT trials included school age children, but the hypothesis that early immunotherapy interventions potentially disrupt peanut allergy due to the plasticity of a relatively immature immune response, encouraged Vickery et al. to treat peanut allergic children under 3 years of age. They reported that 78% of subjects receiving OIT demonstrated SU to peanut.

Apart from the conventional food form usually used for OIT, commercial standardized products could also be used for this purpose. The ARC001 study has been the first phase 2 double-blind placebo RCT peanut OIT trial assessed the efficacy and safety of AR101, oral biologic drug product with defined peanut protein profile, intended to reduce clinical reactivity to peanut in children and young adults with peanut allergy. AR101 has met its primary endpoint, demonstrating desensitization to 300 mg peanut protein in 79% of the AR101 group compared with 19% in placebo group, which is more than the amount of peanut typically triggering a reaction with accidental ingestion (approximately one and a half peanuts). AE occurred in nearly all AR101 subjects, but more than 95% were mild [45].

3.1.4. OIT to Other Food Allergens

OIT studies with other food allergens are scarce, especially those of RCT design. In one of the rare double-blind RCT with wheat, high-dose wheat OIT induced desensitization in most participants after 1 year and SU in 13% of subjects after 2 years. Compared with egg OIT, efficacy of wheat OIT was lower, but the safety was similar [46].

3.2. Safety of OIT

OIT studies for food allergy are promising, but treatment is frequently complicated by AE including severe reaction requiring epinephrin. Although AEs are mainly related to the build-up phase, they also appear in the maintenance phase, sometimes to a previously tolerating dose, usually accompanied by certain risk cofactors like exercise, viral infection, or menses. This often causes anxiety and fear and is one of the main reasons for withdrawing from the study. Therefore, interventions to improve OIT for patients are needed. Changing patient mindsets about treatments and symptoms, encouraging the mindset that symptoms can signal desensitization, is a potential route to help patients cope with challenging medical treatments and may benefit both patient experience and physiological treatment outcomes [47].

4. Sublingual Immunotherapy (SLIT)

4.1. Efficacy of SLIT

SLIT, as a method of immunotherapy has been studied in the treatment of kiwi, apple, peach, hazelnut, peanut, and milk allergies. SLIT for food allergy treatment was first described in 2003 [48] where a subject underwent SLIT with kiwi extract and was successfully desensitized. Birch pollen–related apple allergy (BPRFA) represents one of the most prevalent food allergies in adult patients. Symptoms appear due to birch pollen allergen Bet v 1 which is highly cross-reactive with Mal d 1 (apple protein).

In RCT of Keet et al. [49] children with CMA underwent SLIT or SLIT escalation followed by OIT. After initial DBPCFC and SLIT escalation, participants either continued SLIT to 7 mg daily or began OIT (1000 mg allergen OITB group or 2000 mg the OITA group) using milk protein. After maintenance period at week 12 and week 60 participants underwent DBPCFC with 8 g of milk protein. A total of 1/10 participants in the SLIT group, 6/10 participants in the SLIT/OITB group, and 8/10 participants in the OITA group passed the 8 g milk protein DBPCFC after maintenance period (p = 0.002). This trial has found that 6 of the 15 participants who passed 60-week DBPCFC lost desensitization to milk in less than 6 weeks. They did not completely lose desensitization to milk, and they were able to consume at least 2.5 oz of milk (at the beginning of trial it was just a teaspoon of milk). OIT was much more effective than SLIT, but with more systemic AEs.

Kim et al. [50][51][52] conducted 3 significant clinical trials with SLIT in subjects with peanut allergy. All three studies included participants ages 1–11 years and they investigated efficacy and safety of SLIT for peanut allergy desensitization. The first study of SLIT treatment in children that have peanut allergy was the study of Kim et al. from 2011 [50]. It is a double-blind placebo RCT of 18 subjects with 6 months escalation plus 6 months of dose maintenance. During the DBPCFC median successfully consumed dose (SCD) for the treatment group was 1710 mg and for placebo group 85 mg, which represents significant difference between groups p = 0.011. These results represent potential protection from accidental peanut ingestion through everyday life situations and accidental exposure (often less than 100 mg peanut protein) [53].

4.2. Safety of SLIT

The majority of all AE in every trial were described as local oropharyngeal itching with no need for epinephrine use. SLIT is considerable as a very safe treatment with very good tolerance and very low rate of rate of side effects.

All studies with SLIT and peanut allergy to date excluded patients with anaphylaxis history although it is extremely important to help such patients find an effective and safe treatment that would certainly have a positive effect on their quality of life.

5. Epicutaneous Immunotherapy (EPIT)

5.1. Efficacy of EPIT

Prevalence of anaphylaxis and severe reactions to food in the paediatric population is the highest and most common in peanut food allergy [54]. It is very hard to avoid peanut consumption because of its widespread presence in various foods and dishes and unintentional exposure rates are high. There is a great need and longing for new and safe types of treatment for food allergies, especially peanuts so that patients and their families can have better overall quality of life [55]. It is estimated that most of peanut allergic children will have allergic reactions to < 1 peanut kernel (300 mg of peanut protein) [56].

Efficacy represents the success of the implemented therapy, a treatment that safely and feasibly results in desensitization. The primary efficacy end point of most reviewed trials was the difference in response rates between intervention and placebo groups after a period (patients underwent a DBPCFC to establish changes in eliciting dose (ED)). The “Viaskin® Peanut’s Efficacy and Safety” (VIPES) 2b double-blind placebo RCT looked at 3 doses of a peanut protein patch (50, 100, and 250 µg) doses across 221 subjects (6 to 55 years) at 22 centers for 12 months of treatment. After 12 months of treatment patients underwent a DBPCFC to establish changes in ED. Statistically significant difference in response rates (RR) was observed between the Viaskin peanut 250-µg (VP250) and placebo group $p = 0.01$. EPIT provided statistically better results in participants 6–11 years old with VP250 ($p = 0.008$) but not in participants older than 11 years [57].

CoFAR6 trial was conducted for 52 weeks and after that participant underwent to new open-label clinical trial for 130 weeks in total. In this study, all participants were in the VP250 group [58]. A total of 79.7% participants completed the 130 weeks of active treatment. This extended EPIT with VP250 was safe, well-tolerated with persistent desensitization during trial period. This study confirmed that treatment response was better in younger children (ages 4–11 years) receiving VP250. These three studies show better EPIT outcomes in younger participants which means that food allergy treatment should begin as early as possible to expect better treatment results.

Another randomized trial Peanut EPIT Efficacy and Safety (PEPITES) [59] used these findings and had 356 peanut-allergic children participants aged 4–11 years and used only VP250 patches on the intervention group.

The intervention group had significantly better treatment outcomes than the placebo group $p < 0.001$ but the lower bound of the 95% CI of the difference (12.4%) crossed the prespecified lower limit of 15%, and thus the trial could not be considered positive. Participants who completed PEPITES were offered enrolment in another study PEPITES Open-Label Extension (PEOPLE) [60].

A recently published RCT (EPITOPE) [61] made a step forward in efficiency research of EPIT in peanut allergic children age range 1–3 years. The primary efficacy end point in the active group was significant greater compared with the placebo group ($p < 0.001$). Participant in the active VP250 group had a median change in ED (from start of the trial to month 12) of 900 mg vs. 0 mg in the placebo group participants ($p < 0.001$). This showed that EPIT can be a useful tool in treatment of peanut allergy in children younger than 4 years. O

5.2. Safety of EPIT

EPIT is considered as a safe treatment, especially compared with other types of immunotherapies. Symptoms are mostly application site related, and mostly mild to moderate [57][58][59][60][61][62][63][64][65]. Adherence in most studies is very good, except SMILEE [64] where a high rate of protocol violations was reported (nonadherence to diet therapy, noncompliance with PPI dosing).

The only trial that included participants with a history of anaphylaxis and exclude DBPCFC as a part of trial procedure is REALISE (Real Life Use and Safety of EPIT) RCT [65] which provides more reliable results in regards of safety, closer to real life for people with food allergy. Participants were highly atopic and 72.3% participants had a history of anaphylaxis to peanut protein. Compliance to treatment was very high, most of reported AEs were mild (82.7%) or moderate (36.9%). Findings from REALISE suggest that EPIT is a safe and well-tolerated method of immunotherapy for food allergy regardless of the possibility of developing severe symptoms and anaphylaxis. Given all the above, it can be concluded that EPIT has a potential impact on substantial reduction in allergic reactions to peanut. These findings are essential for people with food allergies and their families, especially in regards of improving their quality of life. This could also lay a basis for the implementation of food allergy related immunotherapy in routine clinical use.

6. Food Allergen Immunotherapy and Biologics

There are many novel therapeutic approaches being investigated for the treatment of food allergy such as micobiome modulating drugs and biologicals. Biologicals are promising therapeutics which target the underlying immune response driving food allergy. Among these biological drugs, omalizumab, or anti-IgE antibody, is most commonly used, both in clinical studies and in clinical practice, as monotherapy in patients with severe IgE-mediated food allergy or in combination with FAIT [66][67]. It has shown favourable effects for improving the safety and efficacy of OIT as well as its potential use in the management of food allergies independently of OIT. Therapy with omalizumab increases the threshold of reactivity to foods and increases the tolerated dose of foods when given as monotherapy or in combination with OIT. Omalizumab administered during the up-dosing phase of OIT shortens the time required to reach the maintenance dose. Furthermore, omalizumab can also prevent systemic allergic reactions including anaphylaxis when given as an adjunct to immunotherapy [66][67][68].

Ibáñez-Sandín et al. [69] analysed the effect of omalizumab therapy as monotherapy or in combination with OIT in the treatment of patients with severe cow's milk allergy under real-life conditions. Omalizumab which is used as monotherapy induced tolerance to ≥6000 mg of cow's milk protein in 34.8% of patients, while in combination with milk OIT, up to 83.0% of patients has achieved tolerance to cow's milk proteins. They also analysed the safety effect of omalizumab and observed that stopping omalizumab therapy significantly increases the risk of AE including anaphylaxis (in 36.4% of patients, $p = 0.001$) compared with patients who received continuous omalizumab during OIT. In patients who abruptly discontinued omalizumab anaphylaxis was observed in 50.0%, and only in 12% of patients who gradually discontinued oamlizumab therapy during OIT.

Different biologics have different effects on the modulation of the immune response in the treatment of patients with food allergy directly targeting the specific underlying mechanism. This is precisely why an individualized approach is key for future research which should be focused on personalized criteria for patient selection, discovery of biomarker panels, therapy duration and proper dosing, monitoring of efficacy, etc.

7. Conclusions

FAIT is the only disease-modifying treatment option for individuals with IgE-mediated food allergy. It has been shown that FAIT is a clinically effective and safe treatment option for patients with clinically relevant food allergy. Although FAIT is generally an effective treatment option, some patients do not respond well. The understanding of underlying mechanisms in FAIT is lacking, but most are related to the modulation of the innate and adaptive immune responses, which are also related to the effectiveness of the treatment. There has been no clear relationship between the immunological changes observed and the level of response to FAIT. Further research is needed to confirm and interpret these associations with different route, doses, duration, frequency of application and clinical response to FAIT. On the other hand, the occurrence offside effects, including anaphylactic reactions during OIT are significant, and further narrow the indications for use, which calls for additional research as well.

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