Allergen-Specific Immunotherapy for Immunoglobulin E-Mediated Food Allergy

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Abstract

Food allergy is a potentially life-threatening condition and a significant public health concern worldwide. The current management includes food avoidance and use of emergency medications. The growing prevalence of food allergy drives research towards specific allergen immunotherapy (AIT), which represents a potential disease-modifying approach. AIT consists of the progressive administration of amounts of the offending allergen in order to induce food desensitisation, creating an increase in reaction threshold with regular exposure to the allergen. AIT can be performed through oral, sublingual, epicutaneous, and subcutaneous routes. The target is to achieve post desensitisation effectiveness: a long-lasting condition allowing patients to introduce food without reactions, even after a period of discontinuation of the offending food.

INTRODUCTION

Food allergy (FA) is a potentially life-threatening condition and has become increasingly common in children over the last two decades. FA affects up to 10.0% of the general population: approximately 5.0% of adults and 8.0% of children. The condition is considered a major public health issue in westernised countries, having a negative impact on quality of life, nutrition, and healthcare costs.[1] Currently, standard management includes food avoidance and the use of emergency medications. A food elimination diet is a troublesome and difficult task since the most common sources of allergens are widespread in daily diet: cow's milk (CM), hen's egg (HE), and peanut. These issues stimulate research on active and disease-modifying treatment for FA. Specific allergen immunotherapy (AIT) is a potentially active therapy indicated in those patients affected by persistent IgE-mediated FA in which food avoidance was ineffective, troublesome, or caused impairment of quality of life.[2] Other next-generation approaches, including probiotics, modified proteins, Chinese herbal supplements, biologics, and DNA vaccines, are under investigation.

ALLERGEN IMMUNOTHERAPY IN CLINICAL PRACTICE

The main goal of AIT is desensitisation, which is the ability to increase the amount of food the patient can tolerate without any reaction during

treatment. Desensitisation could achieve disease remission since the underlying allergic state persists but is temporarily modulated to a higher threshold and strictly dependent on regular consumption of the offending food.

AIT is potentially curative but does not guarantee permanent disease improvement or development of tolerance after stopping the desensitisation. The goal of FA-AIT is to achieve a post-discontinuation effectiveness, known as sustained unresponsiveness, so that a patient can eat a normal serving of the trigger food without being exposed daily to maintain desensitisation.[3] At present it remains unknown whether sustained unresponsiveness is equivalent to tolerance.[4]

Before starting any active treatment, the European Academy of Allergy and Clinical Immunology (EAACI) guidelines recommend confirmation of IgE-mediated FA and the threshold of reaction through allergy test (skin prick test, sIgE) and oral food challenge (OFC). AIT is recommended for persistent allergies to CM, HE, and peanut. In preschool age, especially when CM and HE are the culprit foods, it is preferable to wait for the natural resolution of FA and to start treatment at 4–5 years of age.

In AIT regimens, increasing amounts of allergen are delivered through oral immunotherapy (OIT), sublingual immunotherapy (SLIT), or epicutaneous immunotherapy (EPIT) routes at a scheduled time. The route of administration influences the amount of allergen delivered and, consequently, efficacy and safety. The best results in terms of efficacy have been reported with OIT, but they are counterbalanced by frequent adverse reactions, even if these are mild grade and not systemic.

Typically, an OIT protocol includes three phases: initial dose escalation, build-up, and maintenance. The first one consists of the consumption of predetermined and progressively increasing amount of an allergen source over several hours. During the build-up phase, the amount of allergen is periodically increased, usually weekly, until the target maintenance dose is achieved. Then, the maintenance dose is continued daily for months.[5] Dilutions of unprocessed products, raw extracts, and flours are used as allergen source.

SLIT efficacy is limited by the small volume of liquid antigen delivered sublingually, but conversely, adverse events (AE) do not occur as frequently as with OIT. In EPIT, smaller doses of antigen are delivered using a patch applied onto the skin. There are few pieces of evidence regarding the use of this route in FA-AIT; a recent randomised controlled trial showed positive results for peanut EPIT.[6] However, at the present time, SLIT and EPIT are not recommended for FA-AIT. The safety of OIT still represents one of the most important clinical aspects. The occurrence of AE remains quite frequent and common during the OIT maintenance phase. Home management presents additional safety issues. To improve the safety and efficacy, novel approaches investigated OIT combined with an immunomodulatory agent or an adjuvant, such as biologics, probiotics, and Chinese herbal supplements. Omalizumab is a recombinant, monoclonal antibody that selectively binds to freely circulating human IgE, but not mast cell or basophil-bound IgE. Its administration in addition to OIT or before starting the treatment decreases AE and can significantly reduce the time required to reach maintenance dosing. The rationale for the co-administration of probiotics is that they are potent stimulators of Th_1 immune response. Chinese herbal supplements have *in vitro* immunomodulatory effects and inhibit Th_2 cytokine response in murine models.

AIT is a safe approach, but it is not recommended in cases of comorbidities that could worsen during that treatment, such as uncontrolled or severe asthma, active malignant neoplasia, active systemic or autoimmune disorders, active eosinophilic oesophagitis, or other gastrointestinal eosinophilic disorders. Caution is needed when FA-AIT is proposed to patients with severe medical conditions such as cardiovascular diseases, systemic autoimmune disorders in remission (i.e., thyroiditis), uncontrolled active atopic dermatitis/eczema, chronic urticaria, mastocytosis, pharmacological treatments with beta-blockers, or ACE inhibitors. These are considered relative contraindications since the risk of AE has been demonstrated in other types of AIT.[3]

The setting of infection, exercise, or menses are described as frequent causes of acute AE, or temporary relapse of FA, during the maintenance or post desensitisation phases.[7] All patients should receive an emergency action plan and auto-injectable adrenaline. Therefore, according

to the available experimental data, a proper information and a structured written instruction plan (for example, avoiding physical activity within 2 hours of food intake, and reducing or interrupting the food intake during febrile illness) significantly reduce the risk of possible adverse reactions during the maintenance phase of food desensitisation, still maintaining the beneficial effect of treatment.

ORAL IMMUNOTHERAPY FOR COW'S MILK ALLERGY

After peanuts and tree nuts, CM is the third most common cause of anaphylactic reaction, and is the most common FA among children, affecting 0.6–2.5% of preschoolers and 0.3% of older children and teens.[7] CM contains >25 different proteins, but the allergenic source is represented by αS1-casein (Bos d 9), α-lactalbumin (Bos d 4), and β-lactoglobulin (Bos d 5), respectively, belonging to the casein and the whey fraction. Milk is one of the major components of children's diet, making it difficult to implement an elimination diet. The majority of children allergic to CM tend to naturally achieve tolerance by the age of 3 years, but lately, a higher incidence of persistence has been reported in adolescents, especially in cases of high sIgE concencetration.[8] Active immunotherapy is a good solution to this problem when the natural resolution does not occur.[9] AIT for the treatment of IgE-mediated FA has been discontinued for some decades. The current evidence shows that OIT is a good therapeutic approach to CM allergy and can successfully induce desensitisation. The Cochrane systematic review, including five randomised control trials, reported that 62.0% of children, following OIT, could tolerate a full serving of milk (approximately 200 mL), while 25.0% could tolerate a smaller amount (10–184 mL). In the control group, just 8.0% showed tolerance to a full serving, and none of them to a partial serving.[10]

Different protocols have been described, generally differing in the time needed to achieve the target dose (150–200 mL). Meglio et al.[11] demonstrated a desensitisation rate of 71.4% with a 6-month protocol. Starting with one drop of whole milk diluted 1:25 with water, increasing doses of CM were administered every 7 days for 10 weeks until the dose of 2 mL was scheduled every 16 days.[11] Pajno et al.[12] proposed a 4 month protocol with weekly increasing milk doses, starting with one drop of whole milk diluted 1:25. They reported that 77.0% of treated patients were successfully desensitised.[12] Berti et al.[13] proposed early OIT to be started in the first year. The target of the protocol was achieved in 97.0% of patients in a median time of 5.5 months.[13] The study included children who did not react to a low dose OFC performed at the baseline, so the authors could not exclude that some children would have developed tolerance spontaneously.

One of the major concerns about OIT protocols is safety. In the Cochrane review,[10] 91.5% of the treated patients experienced adverse reactions. In order to reduce the incidence of adverse reactions, new approaches are under investigation.

Up to 80.0% of CM allergic subjects can tolerate cooked milk. Heating destroys many conformational epitopes and reduces allergenicity of some foods. CM proteins may additionally be altered by their interactions with other substances, such as wheat, and their distribution in a food matrix. Casein is heat-resistant, while the whey fraction proteins are heat labile. Regular ingestion of baked milk has been demonstrated to induce immunologic changes and earlier development of tolerance to regular milk, suggesting its potential action as OIT.

Recent evidence showed that the combination of CM OIT with omalizumab shortens OIT protocol to achieve the maintenance dose and reduce the risk of associated adverse reactions, even in high-risk subjects. A pioneering study followed by other trials examined the combination of CM OIT with omalizumab. Omalizumab was started 9 weeks before oral rush desensitisation and discontinued at Week 16 during the maintenance phase. The authors concluded that OIT can be escalated more rapidly with omalizumab as an adjuvant therapy.[14] This approach, if confirmed by large double-blind placebo-controlled studies, could become an effective strategy for severe FA.

ORAL IMMUNOTHERAPY FOR HEN'S EGG ALLERGY

HE allergy is the second most common FA in infants and young children, following CM allergy.[15] The prevalence of HE allergy is up to 2.0% in young children.[16]

Over 50.0% of children with HE allergy develop natural tolerance at the age of 5 years; but for some, HE allergy can persist beyond adolescence[17] with a direct correlation to baseline levels of specific IgE. Subjects with sIgE above 50 kU/L (ImmunoCAP®) have a very low probability of resolving HE allergy before the age of 18.[16] Five major allergenic proteins from the egg of the domestic chicken (*Gallus domesticus*) are responsible for IgE-mediated reactions; these are designated Gal d 1-5.[18] Most of the allergenic HE proteins are found in egg white, including ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovotransferrin (Gal d 3), lysozyme (Gal d 4), and ovomucin. Ovomucoid is the dominant allergen in egg (i.e., the allergen to which the most patients are sensitised), although ovalbumin is the most abundant protein in HE white. Two additional proteins, lipocalin-type prostaglandin D synthase and egg white cystatin, with IgE reactivity in individuals with HE allergy, have been identified.[19] Chicken serum albumin, or alpha-livetin (Gal d 5), is the major allergen in egg yolk. A minority of patients with HE allergy are also reactive to chicken meat and to other bird eggs (turkey, duck, goose, seagull, and quail) because of serologic and clinical cross-reactivity. Chicken serum albumin (Gal d 5) is responsible for this cross-reactivity.[20] Some medical products use egg proteins during production or as an ingredient. These drugs have the potential to cause allergic reactions in egg-allergic individuals. The yellow fever vaccine is prepared in egg embryos and allergic reactions to this vaccine have been reported.[21] Influenza vaccines contain a very small amount of HE proteins, but both the injectable inactivated influenza vaccines and the live attenuated influenza vaccine intranasally administered, can be safely administered to recipients with HE allergy without special precautions.[22]

The best treatment for HE allergy is OIT that induces a state of desensitisation increasing the threshold reaction. Unfortunately, 30.0–75.0% of patients lose the achieved desensitisation after a period of food withdrawal.[23,24]

One of the most popular OIT protocol consists of weekly administration, in a hospital setting, of increasing amounts of dehydrated egg white, diluted in sterile saline, starting with 0.1 mg. The dose is doubled every week until Week 16, to achieve a cumulative dose of 4 g in approximately 4 months. The children who tolerate the maximum dose of 4 g dehydrated egg white receive one cooked or one boiled egg, according to the child's preference, and continue the protocol at home. This kind of protocol appears to be safe and effective, and the whole procedure lasts approximately 4 months.[23]

As previously mentioned, processing foods may decrease or increase protein allergenicity in different ways, inducing, for example, a destruction of conformational epitopes, causing a lower accessibility of the epitopes to the immune system due to links between the proteins, fats, and sugars in the matrix or giving rise to the formation of new epitopes (Maillard reaction). Ovomucoid has a higher heat stability compared to ovalbumin, ovotransferrin, and globulin. A significant proportion of egg-allergic children are tolerant to egg in its baked forms: about 88.0% of children tolerate donuts, 74.0% baked omelettes, and 56.0% boiled egg.[25] The incorporation of baked egg, after an OFC confirming no clinical reactivity to extensively heated proteins, appeared to accelerate the development of unheated egg tolerance, compared to its strict avoidance.[26]

PEANUT ALLERGY

Peanut allergy is one of the most common allergies in paediatric age in westernised countries, with a rising prevalence from 1.2% in 2002 to 2.1% in 2008.[27,28] These data range in various countries based on peanut consumption. Peanut allergy, differing from CM and HE allergy, does not generally resolve spontaneously with age.[29] Peanut belongs to Leguminosae family (which includes peas and lentils), and its allergens are derived from different protein families that can cross-react with other members of the Leguminosae family, but also with other foods such as tree nuts. Botanically related or unrelated families have very similar homologous allergens, so IgE directed towards different allergens can cross-react and patients with peanut allergy may have a positive skin prick test or serum test to tree nut extract as a result of cross-sensitisation.[30,31] A study involving 278 patients with tree nut allergy found that only 9.0% outgrew their allergy. However, as with peanut allergies, sIgE correlate with prognosis, as 63.0% of patients with sIgE to tree nuts less than 2 kUA/L and 75.0% of patients

with negative sIgE outgrew their allergy.[32,33] For both peanuts and many tree nuts, the amount required to trigger an allergic reaction (50.0% of the maximum response, or elicitation dose 50) is very low compared with other major food allergens.[33] Peanut allergens include storage proteins (seed storage proteins), oleosins, defensins, lipid transfer proteins, pathogenesis-related proteins (PR-10), and profilins. Allergenic proteins, except profilins and PR-10, are heat stable and their allergenicity is not modified by food processing. At least three broad categories of seeds storage proteins have been identified as potentially important in FA: 2S albumins, vicilins (7S globulins), and legumins (11S globulins). In peanuts, Ara h 1 is a vicilin, Ara h 2 is a 2S albumin, and Ara h 3 is a legumin; Ara h 2 is responsible for most anaphylactic reactions.[31,34,35]

The analysis of IgE towards the molecular components is particularly useful in the diagnostic algorithm of peanut allergy, considering the high prevalence of sensitisation to Ara h 2 and its early onset.[36] Peanut allergy treatment consists of strict avoidance of peanut-containing products and a recommendation for parents to carry out a careful reading of food labels. Patients should be provided with a personalised emergency plan, which may include self-injectable adrenaline, antihistamines, corticosteroids, and bronchodilators. The most promising active treatment of peanut allergy is represented by allergen-specific immunotherapy. Two new drugs, AR101 and Viaskin patch, employed for peanut OIT and EPIT respectively, were submitted for U.S. Food and Drug Administration (FDA) licensing. They will likely be integrated into therapeutic management soon. Studies on safety and efficacy of AR101, a new drug containing defatted roasted peanut flour for OIT, documented that AR101 significantly improved patients' symptoms by reducing its severity during a double-blind, placebo-controlled challenge and increasing the amount of peanut protein tolerated after treatment.[37] Experimental trials on Viaskin, compared two doses (VP 100 mcg and VP 250 mcg) to placebo in a group of children and young adults. After 1 year of therapy, 45.8% of VP100 patients, 48.0% of VP250 subjects, and 12.0% of placebo group passed the double-blind, placebo-controlled challenge with 5,044 mg of peanut proteins or with a dose 10 times higher than the basal one. Treatment was more effective in patients <11 years of age.[38] Tang et al.[39] conducted a double-blind placebo-controlled trial on the association of *Lactobacillus rhamnosus* CGMCC and probiotic and peanut OIT (PPOIT) in peanut-allergic children. The primary outcome was the achievement of the post desensitisation effectiveness from 2–5 weeks after treatment suspension: 82.0% in the active group compared to 3.6% in the placebo group, acquired a possible post-desensitisation effectiveness. Moreover, patients in the active group presented an improvement in the quality of life when evaluated 3 and 12 months after the end of the treatment.[39,40]

POST DESENSITISATION STRATEGY

In the last decade, immunotherapy for FA has been shown to successfully induce desensitisation, but after stopping treatment, a daily ingestion of the culprit food is required to maintain tolerance. In children desensitised to CM, a twice weekly regimen has proved effective in maintaining tolerance.[41] Post discontinuation effectiveness is easier to achieve for CM and HE allergy, but recently a study found that most patients treated with combined PPOIT 4 years after completing the protocol were symptom free after peanut ingestion.[42]

CONCLUSION

Immunotherapy, especially through the oral route, is a promising treatment for food allergies in children. It represents a next-generation active approach to FA that is still under investigation, but has already shown many significant clinical results. If the elimination diet is merely a passive, conservative approach, in whom no allergen means no allergy, AIT represents an active treatment that, through the continuous exposition to the allergen, increases tolerance.

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