



An overview of the current state of food desensitization

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Purpose of review

To highlight the current evidence on food desensitization in children with food allergy.

Recent findings

Food Allergen Specific Immunotherapy (FA-AIT) is currently recognised as a treatment option for treating children with allergy at least to the main common foods (i.e. milk, egg and peanut). The oral route of administration has been proven to be the most effective in achieving desensitisation. Efforts are devoted to overcome the current unmet needs mainly related to safety issues and long-term efficacy, as well as adherence to the treatment and improvement of health-related quality of life. In this perspective, alternative routes of administration and adjunctive treatments are under investigation.

Summary

The future of food allergy management is a personalised approach based on a shared decision-making that takes into account the needs of patients and families. Health professionals will be able to offer multiple treatment options, including FA-AIT with adjunctive or alternative therapies. Thus, patients should be correctly identified, using validated predictive factors, in order to select appropriate candidates for these therapies.

Keywords

allergen specific immunotherapy, biologicals, desensitization, food allergy, sustained unresponsiveness

INTRODUCTION

Food allergy (FA) is defined as an adverse reaction, potentially life-threatening, caused by the exposure to a specific food allergen through an immunologic mechanism, involving specific IgE (IgE-mediated), cell-mediated mechanisms (non-IgE-mediated), or both IgE- and cell-mediated mechanisms (mixed IgE- and non-IgE-mediated) [1]. Herein, we focus on IgE-mediated FA, to which is addressed food allergen specific immunotherapy (FA-AIT). The prevalence of FA is estimated between 1 and 10%, with higher rate in children than in adults [2]. Most studies have shown an increase in sensitization to foods and reported FA at the turn of the 21st century. Notwithstanding, it is still debated if an increase in prevalence is due to increased self-report, rather than a real change in sensitization, incidence, or persistence of FA [3,4]. Epidemiological data are predominantly related to the age, the local diet and study methodologies [5]. In industrialized countries, the most common foods responsible of FA in children are: cow's milk (CM), egg, peanut, tree nut, wheat, soy, fish, and shellfish [6]. The natural history of FA varies according to the allergen involved.

More than 50% of children with CM and egg allergy reach tolerance between 2 and 10 years of life. Only 10–20% of subjects with nut and tree nuts allergies achieve spontaneous clinical tolerance [3,7]. Fish and shellfish allergies are usually persistent [8]. FA has a negative impact on health-related quality of life (HR-QoL) of pediatric patients and their caregivers, because it may be associated with social isolation, fear of accidental exposure and depression [9], especially among teenagers [10]. The current main approach to FA is appropriate food allergen (s) avoidance and the use of adrenaline and other adjunctive medications in case of severe allergic

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KEY POINTS

- Oral Immunotherapy (OIT) is currently recommended as a treatment option which can provide desensitization in patients with food allergy (FA).
- Other routes of administration (e.g. epicutaneous and sublingual) as well as adjunctive therapies (e.g. anti-IgE treatment) are under investigation to improve mainly the safety profile of OIT.
- The future of FA therapy is a personalised approach, in which food allergy immunotherapy, with or without an adjunctive therapy, should be proposed on the basis of a correct selection of the patient, in a sharing a decision-making involving the needs of patients and families.

reactions [1]. However, allergen avoidance is not a curative treatment, and burdened by the risk of severe accidental reaction and impairment of HR-QoL. FA-AIT can provide desensitization, which is defined as the increase in the threshold of reaction to food allergen while on treatment [11,12²²]. As for other IgE-mediated allergic diseases, AIT for FA is potentially a curative therapy and may be effective also in improving HR-QoL of patients.

Therefore, efforts have been devoted to assess FA-AIT long-term efficacy, which is also called 'postdiscontinuation effectiveness' or 'sustained unresponsiveness' (SU), and consists of the ability to introduce the culprit food(s) without reaction even after a period of discontinuation of the offending food intake [12²²]. FA-AIT may be effective when the routine administration of the allergen is discontinued; however, the strength of evidence is currently low [13].

This review aims to highlight the current evidence on FA-AIT, by exploring different routes of administration and adjunctive approaches and discussing unmet needs

GENERAL PRINCIPLES

FA-AIT is potentially indicated for patients with evidence of an IgE-mediated FA and in whom avoidance measures are ineffective or cause severe limitations to HR-QoL [12²²]. Before commencing FA-AIT, it is mandatory to confirm the diagnosis, through a history of a recent IgE-mediated acute reaction, after ingestion of the offending food, and positive skin prick test and/or serum specific IgE assay (sIgE). However, if the diagnosis is unclear, an oral food challenge (OFC) should be performed, which is useful to define the reaction threshold dose and consequently the starting allergen dose to offer during FA-AIT [12²²]. Moreover, patients and their

families should be motivated, adherent and able to administer emergency treatment in case of adverse effects [12²²]. Main absolute contraindications include: poor adherence; uncontrolled or severe asthma; active systemic autoimmune disorders; active malignant neoplasia; eosinophilic esophagitis (EoE). Among relative contraindications, there are: severe atopic dermatitis; chronic urticaria; cardiovascular diseases; therapy with beta-blocker or ACE inhibitor [12²²]. FA-AIT is usually based on a build-up phase followed by a maintenance phase. During build-up phase increasing quantities of food are administered in hospital, then the maximum tolerated dose is assumed daily at home in the interval during dose increases, usually once a week or every 2 weeks [14,15]. Protocols are heterogeneous: the length may vary from one day/one week up to some months [16]. Instead, during the maintenance phase, the patient continues to take the most tolerated allergen dose periodically, mostly every day, for a variable period (months to years), to maintain a desensitized state [Fig. 1]. The dosing for each phase, is variable and depends on the route used, the type of offending food [17]. Low starting dose should be used in high-risk patients, while the more rapid introduction of an allergenic food could be performed in low-risk patients [18]. To test the SU, OFC should be performed after a period of food discontinuation (usually 4–12 weeks in trials) [13].

On the basis of the route of administration, FA-AIT can be divided into: oral immunotherapy (OIT), epicutaneous (EPIT), sublingual (SLIT), subcutaneous (SCIT).

IMMUNOLOGICAL MECHANISMS

There is evidence that FA-AIT may lead to a suppression of Th2 response through interaction of specific innate immune cells and modulation of adaptive immune system through different routes. OIT may activate dendritic cells in the gut mucosa, resulting in increased function of CD4⁺FOXP3⁺ Treg, production of Interferon gamma (INF γ), shift cytokine profile from Th2 to Th1 and decrease interleukin 4 (IL-4) and interleukin 13 (IL-13), thus promoting desensitization. SLIT and EPIT may allow Th2 downregulation and induce Tregs through interaction with Langerhans cells in the oral mucosa and in the epidermis, respectively [11,19]. SCIT can activate immature subcutaneous dendritic cells, which migrate to local lymph nodes, inducing suppression of Th2 response [20].

ORAL IMMUNOTHERAPY

According to the most recent European Academy of Allergy and Clinical Immunology (EAACI)

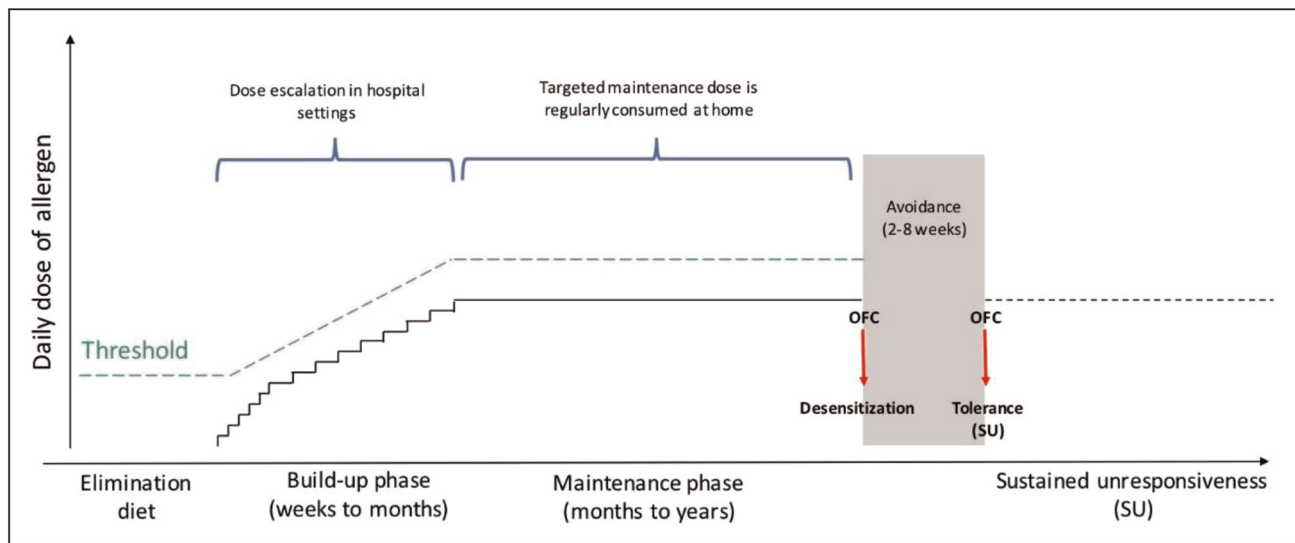


FIGURE 1. Example of classic protocol of immunotherapy. OFC, oral food challenge.

guidelines, OIT is actually recommended as a treatment option for persistent CM, hen's egg, or peanut allergies for children from around 4–5 years of age (grade A of recommendation) [13].

The very recent Diagnosis and Rationale for Action against Cow's Milk Allergy Guidelines on CM OIT are in agreement (grade A of Recommendation) [21]. However, it is known that up to 75% of children with cow's milk allergy can tolerate baked milk products and these have been used for desensitization with variable results [22]. For people who react to very small doses of baked milk, OIT with baked CM is not suggested [21].

Efficacy and safety of milk OIT have been demonstrated by different studies [23–25]. A recent randomized study analysed the efficacy of OIT in 28 children (aged 3–12 years) with CM-allergy. The treatment group received rush immunotherapy for 2 weeks, followed by a gradual increase until 100 mL for 1 year, and the control group completely eliminated CM for 1 year. Both groups underwent an OFC with 100 mL of CM after 1 year. The treatment group had significantly higher rates of a negative OFC compared with the control group [26]. No data have been reported about SU. Other authors have speculated that the duration of maintenance phase could influence the achievement of SU [27]. So far there are no reliable biomarkers of clinical outcomes. However, it has been suggested that of higher levels of CM-sIgE, greater wheal diameter and a high basophil activity decrease the likelihood of reaching tolerance [28]. Evaluation of these factors before initiating therapeutic therapy can help predict the success of CM-OIT [29].

Egg used for OIT can be offered as pasteurized raw egg white, extensively heated egg, baked egg (BE) products [30] and dehydrated egg white in

powder [31]. Current evidence suggests that OIT can desensitize more than 80% of children with egg allergy [32], and elicit long-term tolerance in 50% after 4 years of treatment [33]. The most important egg allergens are Gal d 1 (ovomucoid), stable against enzymatic digestion and after extensive heating, in contrast to the unstable egg allergens Gal d 2 (ovalbumin), Gal d 3 (conalbumin), and Gal d 4 (lysozyme). Sensitization to Gal d 1 is associated with an increased risk of persistent egg allergy [34]. Polysensitization to all four egg allergens and high titre of egg white IgE are associated with poor desensitization responses [35]. A recent multicenter, randomized, open-label study compared the induction of SU in children (aged 3–16 years) who are BE-tolerant but allergic to unbaked egg after 2 years of treatment with daily BE ingestion versus egg-OIT. Authors showed that OIT was more effective to achieve SU than ingesting BE alone [36].

Peanut-OIT (POIT) usually has been performed with defatted peanut flour, crushed roasted peanuts, and boiled peanuts. In January 2020 the United States Food and Drug Administration approved AR101 (Palforzia Aimmune Therapeutics, Brisbane, CA, USA), an oral biologic drug for POIT in patients aged 4–17 years with a confirmed diagnosis of peanut allergy [37]. Two main studies investigated the safety and efficacy of AR101 in children (4–17 years), with peanut allergy in North America and Europe. At the exit DBPCOFC a significant rate of patients in the active drug group (67 and 58%) were able to ingest a single dose at least 600 mg and 1000 mg peanut protein respectively, but not in the placebo group [38,39]. Several studies have investigated POIT outcomes. A recent study showed that more than half (78%) of 40 enrolled children (9–36 months) with

peanut allergy achieved SU after stopping maintenance POIT for 4 weeks [40].

Adverse events (AEs) may occur during OIT, mainly during build-up phase. These could be mild, such as abdominal pain, or more rarely severe, such as anaphylaxis [12²²]. The development of EoE was also described [41]. Concomitant cofactors (e.g. infections, exercise, empty stomach, drugs, menses, uncontrolled asthma) may increase the risk of AEs and need to be clearly discussed with patients and their families for a proper management [12²², 42, 43].

ALTERNATIVE ROUTES OF ADMINISTRATION

Sublingual immunotherapy

SLIT is performed by administering the liquid food extract daily sublingually, then swallowed after 2–3 min. This method is currently used for environmental allergen induced allergic rhinitis; but several studies have been conducted mainly with peanut, but also milk, hazelnut, peach, and kiwi [44]. SLIT is well tolerated, main side effects were largely oropharyngeal, and were observed during both the up-dosing and maintenance phases [12²²]. A multicenter, randomized double-blind, placebo-controlled clinical trial (DBPCT) of peanut SLIT showed the safety, with 98% of doses tolerated without severe AEs, and the efficacy with the reachment of moderate level of desensitization and the achievement of SU in 10% of cases [45].

Epicutaneous immunotherapy

EPIT consists of an allergen-releasing skin patch applied on the arm or between shoulder blades. The protocols provide for the application for a few hours a day until reaching progressively 24 h a day. EPIT is well tolerated, although local side effects are common (e.g. local erythema and eczema at the application site) [46]. EPIT has been mainly investigated for the treatment of milk and peanut allergies [47]. Effectiveness has been linked to dose and younger age [48]. A recent phase III multicenter, randomized DBPCT included 356 peanut-allergic children, aged 4–11 years, treated with 250- μ g peanut-patch therapy vs placebo. After 12 months of treatment, the percentage difference in responders was statistically significant (21.7%), but did not meet prespecified criterion for a positive satisfying trial result [49].

Subcutaneous immunotherapy

SCIT is used for environmental allergy and venom allergy immunotherapy. This route has been tested

for peanut allergy, but resulted in systemic adverse reactions during build up and maintenance phases [50]. Other studies have been performed to produce hypoallergenic but effective food allergens molecules, in order to decrease the risk of systemic reactions [51, 52]. However, further studies are needed to evaluate the safety and the efficacy of this method in children.

Comparison among different routes of administration (OIT vs. SLIT vs. EPIT vs. SCIT)

In addition to different immunological mechanisms, the main differences among routes, relate to efficacy and safety [Table 1]. Two studies suggest that in pediatric patients with FA to CM and peanut, OIT is more effective than SLIT, even in achieving SU [53, 54]. An important limitation of SLIT is related to the small volume that can be held under the tongue, which could reduce efficacy [55]. EPIT appears a promising modality, especially for peanut allergy [56]. Despite the safety and the good tolerability, the adequacy of its desensitization is under investigation and its long-term tolerance is unknown, compared to OIT [19]. Moreover, EPIT in murine models seems to induce more significant immunological changes than SLIT [57]. Furthermore, another study on murine models showed that OIT and SCIT reduced clinical manifestations of FA and resulted in comparable changes in serum levels of allergen-specific IgE and IgG subtypes [58]. About the safety profile, OIT showed a significantly higher incidence of systemic reaction compared to SLIT and EPIT, mainly responsible of local reactions [19]. SCIT has proven unsafe for the treatment of FA, due to the high rate of local and systemic adverse reactions [59].

ADJUNCTIVE THERAPY

Biologics

In the last years, several studies have been conducted to evaluate the role of biologics in FA, due to their ability to inactivate the underlying proinflammatory pathways [60]. Omalizumab is an anti-IgE monoclonal antibody, approved for the treatment of moderate-to-severe allergic asthma, chronic idiopathic urticaria and nasal polyps. Omalizumab is being studied for FA treatment, as monotherapy or in addition to OIT [61–63].

Omalizumab reduced the risk of severe reactions during dose-escalation phase and promoted a rapid build-up phase [64–66]. Indeed, according to EAACI guidelines, in patients with systemic reactions, the use of Omalizumab may be considered [12²²].

Table 1. Comparison between OIT vs. SLIT vs. EPIT vs. SCIT regarding immunological mechanisms, benefits and side effects.

	Immunological mechanism	Benefits	Side effects
OIT	Activates dendritic cells in the gut mucosa, increases function of CD4+FOXP3+ Treg and production of INF γ , shifts cytokine profile from Th2 to Th1 and decrease IL-4 and IL-13	Mostly achievement of desensitization Possible 'Sustained unresponsiveness' Improvement of quality of life	Common Oropharyngeal reaction Abdominal pain Vomiting Wheezing Urticaria Anaphylaxis Eosinophilic Esophagitis
SLIT	Activates Langerhans cells in the oral mucosa, induces production of IL-10 e TGF β , activates FOXP3- positive Tregs and Th2 cytokines downregulation.	Well tolerated Modest desensitization effectiveness Improvement of quality of life	Uncommon Mainly Oropharyngeal reaction Rare systemic reactions
EPIT	Activates Langerhans cells in the epidermis and a subpopulation of dendritic cells expressing Cytotoxic T-lymphocyte Antigen 4 (CTLA-4), induces Tregs and Th2 response downregulation, decreases eosinophil recruitment to the skin	Better safety profile than OIT and SLIT No ingestion of allergen Home application Decreased frequency of medical follow- up	Uncommon Local erythema or eczema at the site application
SCIT	Activates immature subcutaneous dendritic cells, which migrate to local lymph nodes, inducing development of Tregs and suppression of Th2 response	Possible administration every 1-2 weeks Possible good efficacy profile	Common Local reaction at the application site Severe systemic reactions, such as anaphylaxis

CTLA-4, cytotoxic T-lymphocyte antigen 4; EPIT, epicutaneous immunotherapy; OIT, oral immunotherapy; SLIT, sublingual immunotherapy; SCIT, subcutaneous immunotherapy.

Ligelizumab, a new more potent anti-IgE monoclonal antibody, is currently being developed for FA indication.

Dupilumab is an anti-IL4 alpha receptor, human monoclonal antibody, approved for the treatment of asthma, atopic dermatitis and nasal polyposis. A single case report describes achievement clinical tolerance to corn and nuts in a woman, who previously experienced anaphylaxis, and passed the OFC at the third month of treatment with Dupilumab [67]. At least two trials are ongoing to evaluate the safety and efficacy of Dupilumab, either adjuncted to OIT or as a monotherapy in peanut allergy [68,69]. Other biologic agents are being studied and may have a role in the treatment of FA, including additional monoclonal antibodies and Toll-like receptors (TLR) agonists [70].

Probiotics

A clinical trial adding the probiotic *Lactobacillus rhamnosus* to POIT or placebo was conducted. The primary endpoint was the achievement of SU 2–5 week after stopping OIT, which was reached in 82.1% of those receiving OIT and 3.6% of those receiving placebo. Despite the short period of treatment, the percentage of patients achieving SU was higher than in other studies, thus raising the

possibility that probiotics may truly improve this effect [71]. In children with egg allergy, the first randomised DPBC trial is ongoing to evaluate the effectiveness of probiotic and egg-OIT in inducing desensitisation or SU [72]

However, to date, there is no recommendation to use probiotics for the treatment or prevention of FA [73]. Further studies are awaited.

FUTURE PERSPECTIVES AND CONCLUSION

Research in the field of FA therapy is constantly growing, as evidenced by the relevance of ongoing clinical trials [74]. To minimize/overcome including the safety risks and health-care costs of emerging treatments, patients with a higher risk of persistent allergy should be correctly identified, using validated predictive factors and a proper assessment of severity of FA disease [75]. The future of FA therapy should lie in a personalized method, in which different immunotherapy approach, with/without adjunctive therapies, may be more optimised and suitable for the specific patient's profile and desires. Clinicians must have an exhaustive conversation with families, providing a detailed action plan and clarifying both the risks and benefits of treatments for a shared decision-making and

optimal adherence, in the holistic perspective of improving the quality of life of patients and their families. Despite all current advancements, further studies are needed to elucidate the mechanisms of desensitization or tolerance achievement, in order to improve AIT approach and provide a precision therapy and a definitive cure for FA.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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