

Allergen immunotherapy for IgE-mediated food allergy: There is a measure in everything to a proper proportion of therapy

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Abstract

IgE-mediated food allergy (FA) is a potentially life-threatening condition with a negative impact on quality of life and an increasing prevalence in westernized countries in the recent two decades. A strict avoidance of the triggering food(s) represents the current standard approach. However, an elimination diet may be difficult and frustrating, in particular for common foods, (eg, milk, egg, and peanut). Food allergy immunotherapy (FA-AIT) may provide an active treatment that enables to increase the amount of food that the patient can intake without reaction during treatment (ie, desensitization), and reduces the risk of potential life-threatening allergic reaction in the event of accidental ingestion. However, several gaps need still to be filled. A memorable Latin orator stated: "Est modus in rebus" (Horace, Sermones I, 1, 106-07). This sentence remembers that there is a measure in everything to a proper proportion of therapy. The common sense of measure should find application in each stage of treatment. A personalized approaching should consider the specific willing and features of each patient. Efforts are devoted to improve the efficacy, the safety but also the quality of life of patients suffering from FA. In the near future, it will be important to clarify immunologic pathways of FA-AIT, and to identify reliable biomarkers in order to recognize the most suitable candidates to FA-AIT and algorithms for treatments tailored on well-characterized subpopulations of patients.

KEYWORDS

biologics, children, desensitization, food allergy, immunotherapy, precision medicine, quality of life, tolerance

1 | INTRODUCTION

The epidemic of food allergy represents a major public health problem with an important individual and social burden.^{1,2} There are extensive data to suggest that food allergies are common with up to 10% of the population affected in industrialized countries.³⁻⁵ The

greatest burden is in childhood when rapidly rising rates of food allergies are most evident. Although a large number of foods have been reported to cause IgE-mediated food allergy (FA), more than 90% of allergic reactions in children have been related to eight items: milk, egg, peanuts, tree nuts, fish, crustacean shellfish, wheat, and soy.⁶ The new current view for treatment of FA is represented by

Abbreviations: B reg, B regulatory cells; DC, dendritic cells; EPIT, epicutaneous immunotherapy; FA, IgE-mediated food allergy; FA-AIT, allergen immunotherapy for food allergy; FoxP3⁺, forkhead box protein 3; GID/OIT, Gastro-Intestinal Delivery Oral Immunotherapy; IgA, immunoglobulin A; IgE, immunoglobulin E; IgG, immunoglobulin G; IgG4, immunoglobulin G4; IL, interleukin; ILC, innate lymphoid cells; OFC, oral food challenge; OIT, oral immunotherapy; SLIT, sublingual immunotherapy; Thf, T follicular helper; T_{reg}, regulatory T cells; Th, T helper; Thf, T follicular helper; TSLP, thymic stromal lymphopoietin.

allergen immunotherapy (AIT). It represents a potentially curative therapy for FA. There is strong evidence for the effectiveness during active treatment. This is also referred as “desensitization,” and indicates the ability to safely assume the food antigen(s), while regularly consuming the AIT doses.^{7,8} However, a more desirable goal for FA-AIT lies on the effectiveness after the discontinuation of the treatment. The latter is also known as “tolerance” or “post-discontinuation effectiveness” or “sustained unresponsiveness” and refers to the absence of symptoms after ingestion of a normal serving of the culprit food despite a period of absence of exposure; it remains still one of the major issue to be clarified.^{7,9} Notwithstanding, after build-up phase, and having achieved the maintenance dose, it is overall recommended to consume the allergenic food in order to maintain the beneficial effects of desensitization. There is no agreement on a standardized post-desensitization strategy. However, it is usually recommended to daily consume maintenance doses of allergenic food(s).¹⁰ This recommendation is usually considered highly demanding by patients. Data support the efficacy and the preference by patients of a scheme of at least three regular services per week in patients suffering from allergy to one¹¹ or multiple foods.^{12,13}

Overall, this new vision (ie, active treatment of persistent IgE-mediated food allergy) is reinforced by the encouraging results of recent studies.¹⁴

2 | A HISTORICAL OVERVIEW

Despite anecdotal reports, modern allergen immunotherapy was initially studied with regard to respiratory allergy and relatively ignored for FA until the beginning of the last century. The first medical application of FA-AIT has been reported in 1908 in a teenage boy with allergy to hen's egg, who was successfully desensitized with raw egg white.¹⁵ Following a long period characterized by a number of small, uncontrolled studies, the interest ensued in the 1990s. In 1997, Nelson et al¹⁶ reported the first double-blind, placebo-controlled trial using subcutaneous injections of aqueous peanut extract; despite the efficacy in inducing desensitization, severe systemic reactions, including anaphylaxis, were common, and this therapeutic approach has been replaced by a more dedicated modality to studying AIT delivered by other route(s) of administration. The promising results from the first oral immunotherapy (OIT) and sublingual immunotherapy (SLIT) trials¹⁷⁻¹⁹ provided a proof of concept for larger controlled clinical trials. OIT and SLIT trials to date have primarily utilized single-allergen preparations, with the majority focused on peanut,^{20,21} cow's milk,²²⁻²⁴ and hen's egg,^{25,26} although treatment of FA with other allergens is under investigation.²¹ So far, native or fresh foods have been mainly used, because of the lack of standardized OIT products. Recently, the first multicenter, randomized, placebo-controlled, phase 3 trial on a novel oral drug product containing a well-characterized and standardized peanut protein profile has been carried out and its results have met both the safety and the effectiveness outcomes.²⁷ In order to reduce the risk of adverse allergic reactions while on AIT, biologicals (eg, omalizumab,

Key Message

Food allergy immunotherapy is currently the only active treatment for IgE-mediated food allergy. It is able to increase the amount of food that the patient can intake without reaction during treatment, and reduce the risk of potential life-threatening allergic reactions. This rostrum provides an updated critical insight in this field with a pragmatic approach and a future outlook.

a humanized monoclonal anti-IgE antibody) have been investigated with promising results.²⁸

3 | PUTATIVE MECHANISMS OF ACTION

During immune system development, the establishment and maintenance of oral tolerance to food antigens depends on articulated mechanisms that involve the integrity and functionality of the intestinal barrier and the interplay between systemic and gut immune cells.^{29,30} In addition, tonsils may play a role in induction of allergen-specific T-cell tolerance as demonstrated by *in vivo* existence of Bet v 1-specific Treg cells in human tonsils.³¹ Recent studies shed light on the importance of microbiota composition in the prevention of food sensitization.³²⁻³⁴ The microbiota, in particular segmented filamentous bacteria, induces the expansion of Th17 cells in lamina propria³⁵ that, after converting to T follicular helper (Tfh) cells in Peyer's patches, may promote B-cell production of secretory IgA.³⁶ Luminal food antigens are taken up by intestinal dendritic cells, directly or through the mediation of macrophages,³⁷ and presented to naïve CD4⁺ T cells in draining lymph nodes.³⁸ TGFβ- and retinoic acid-producing dendritic cells favor the production of antigen-specific, forkhead box protein 3⁺ (FoxP3⁺) regulatory T cells (T_{reg}) that play a pivotal role in gut immune tolerance, mainly through the production of IL-10 and TGFβ.³⁹

Regarding the mechanisms of FA induction, the exposure to food allergens through a damaged skin barrier may cause allergic sensitization.^{39,40} Epithelial disruption in the gastrointestinal tract may interfere with the above-mentioned tolerance pathways and induce the release of damage-driven cytokines, such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), thus favoring a skewing to Th2 immune response.⁴¹ These epithelium-derived cytokines are pivotal in stimulating T helper 2 cells (Th2) and type 2 innate lymphoid cells (ILC2) and dendritic cells.⁴² An imbalance in the direction of FA-specific T cells in the direction of Th2 profile is the main pathogenetic mechanism.⁴³ In addition, IL-25 and TSLP induce the development of T helper 9 cells (Th9) which produce IL-9, causing the proliferation and activation of mast cells.⁴⁴ Both ILC2 and Th2 cells produce IL-4, IL-5, and IL-13^{44,45} that inhibit Treg function and favor Treg skewing into Th2 cells,⁴⁶ promote the expansion of mast cells and eosinophils

and stimulate DCs to induce the transformation of naïve $CD4^+$ T cells into Th2.⁴⁷

On the contrary, during FA-AIT multiple suppressor factors are involved to establish oral tolerance to allergens.⁴⁸ Over the course of FA-AIT, allergen-specific T cells can now be characterized by the novel mass cytometry techniques.⁴⁹ It has been demonstrated that Th2 cells become anergic and apoptotic,⁵⁰ and mast cell and basophil activation is inhibited.⁵¹ Moreover, food-specific Treg function and FOXP3 gene demethylation increase both in patients successfully desensitized during OIT and in those who spontaneously outgrow their allergy.⁵² Tregs secrete IL-10, suppressing antigen-specific IgE levels and inducing IgG₄ production,⁵³ and inhibit DCs required for

the activation of effector T cells.⁵⁴ Similarly to Treg cells, B regulatory cells (Breg) show an increasing production of IL-10 during FA-AIT, contributing to IgG₄ production⁵⁵ and inhibiting IgE-dependent mast cell activation.⁵⁶ IgG₄ can inhibit antigen-induced mast cell and basophil activation itself. However, further studies on the mechanisms of action of different immune cell subsets, affinities of FA-specific IgE and IgG₄ antibodies, and tissue responses, particularly mucosal epithelial cells during short- and long-term courses of OIT, are awaited in order to better understand the complex interplay that promotes immune tolerance and to try to discover new potential therapeutic targets for FA. A graphical overview of the main known mechanisms involved in FA and immune tolerance is provided in Figure 1.

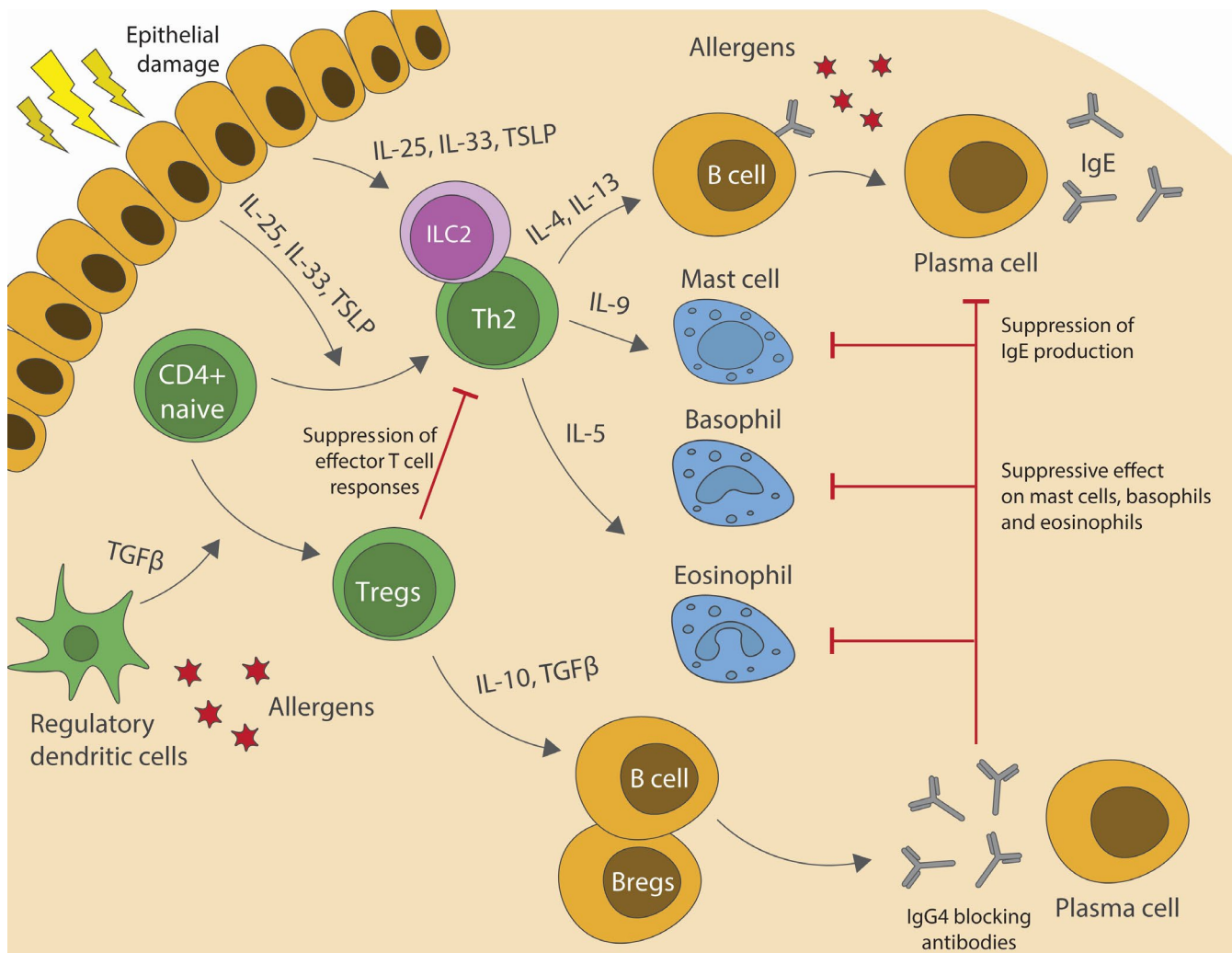


FIGURE 1 Putative immune mechanisms in food allergy and immune tolerance. In the scenario of food allergy, impaired epithelial barrier (eg, eczema) promotes inflammation and foreign antigen (eg, food allergens) penetration and activation of innate and specific immune responses. Epithelial cell-derived cytokines (such as TSLP, IL-33, and IL-25) drive type 2 immune responses and stimulate several cell types (including basophils, eosinophils, and mast cells) to start and maintain allergic inflammation also in regional draining lymph nodes (eg, B-cell IgE skewing). In the scenario of immune tolerance, an allergen is internalized and processed by dendritic cells, then presented to T cells and antigen-specific naïve T cells are polarized. Regulatory T cells suppress the excess allergic responses through several mechanisms, including the following: (a) suppression of effector T cells; (b) suppression of allergen-specific IgE and induction of IgG₄ from B cells; (c) suppressive effects on mast cells, basophils and eosinophils; and (d) suppression of inflammatory cell migration to tissues and tissue inflammation. B regs, B regulatory cells; DC, dendritic cells; Ig, immunoglobulin; IL, interleukin; ILC, innate lymphoid cells; T regs, T regulatory cells; TSLP, thymic stromal lymphopoietin

4 | METHODS

There are and have been many studies on FA-AIT, but the wide variability among them makes it difficult to compare properly its results. The differences of study design, selection of patients, methods and routes, type of food and possible modified forms, schedules during the initial and maintenance phase, the target maintenance dose, grading and reporting of adverse reactions, and some other factors make evaluation challenging.¹⁰

4.1 | Routes

The three most frequent methods and routes are as follows: OIT (oral), SLIT (sublingual), and epicutaneous immunotherapy (EPIT). OIT consists of the immediate swallowing of the food allergen,^{7,8} with the administration of increasing amount until it is tolerated at usual doses.^{7,57} OIT has the largest body of evidence among emerging therapies for FA.^{7,58} The excellent results, although in small populations, have been, however, hampered, in some patients, by adverse events. In SLIT, patients take increased drops of food allergen extract that are placed under the tongue for 2 minutes and then spit or swallow. SLIT doses are limited by the concentration of available extracts and the volume of liquid that can be held under the tongue. Thus, typical doses of administered allergen are smaller compared to OIT⁵⁸. The initial doses are usually in the order of micrograms (range 0.1–0.4 µg) in SLIT vs a few milligrams of allergenic protein in OIT (range 0.1–4 mg), and similarly, the maintenance doses are bigger in OIT (125–4000 mg/d) than in SLIT (1–13 mg/d).^{10,59} Adverse events are less frequent in SLIT than in OIT.¹⁰ However, the rate of desensitization is not as good as with OIT. In EPIT, an allergen-containing patch is applied to the skin surface.⁵⁸ Daily doses range usually between 100 and 500 µg.⁶⁰ It has been proposed that the food protein allergen is absorbed from the patch through the epidermis and dermis, where it is processed by dendritic cells.⁶¹ The latter migrate to local draining lymph nodes where regulatory T cells are produced. Some preclinical studies in animals indicated a potential application in therapeutics leading to the clinical development of peanut EPIT.⁶² Few studies in children with cow's milk allergy⁵⁷ have been conducted in Europe. Results from a multicenter, double-blind, randomized, placebo-controlled study conducted in 74 US participants with peanut allergy (aged 4–25 years) are quite encouraging⁶³. The safety profile was optimal, though the short-term efficacy resulted modest after 52 weeks, with the highest responses among younger children (age, 4–11 vs >11 years). Overall, current data show that efficacy of EPIT in inducing desensitization depends on longer duration of treatment and still is lower than what is achieved with OIT. However, EPIT offers a more favorable safety profile compared with OIT, with only local reactions at the application site and no instances of anaphylaxis.⁶⁰ Additional data from an ongoing phase 3 efficacy study in toddlers (REALISE)⁶⁴ are awaited to better clarify optimal patients to candidate for treatment with EPIT, duration of treatment and hopefully elucidate adequate biomarkers of efficacy.

Lately, peanut in sealed capsules (Gastro-Intestinal Delivery Oral Immunotherapy—GIDOIT-) has been used to reduce the adverse events without affecting efficacy⁶⁵ with encouraging results.

4.2 | Type of food in OIT

Milk,^{11,22,24} egg,^{23,66} and peanut^{20,21,67} are the more frequently studied food allergens in OIT, although there have been some studies on peach (SLIT),⁶⁸ hazelnut (SLIT),¹⁹ wheat,⁶⁹ and kiwi.⁷⁰ Some investigations have also been performed with multiple foods.⁷¹

There have also been differences in the form the food is given. Milk—the most frequently consumed and preferred is liquid milk subjected to upperization/UHT. Depending on the brand and fat content, the amount of proteins ranges between 2.9 and 3.3 g/100 mL, so it is advised to use the same type and brand, if possible. In addition, commercial powdered milk for adults can be used taking in account the higher protein content. 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.^{72,73} Also fermented dairy products are being used for OIT, mainly when the child can have big amounts of milk as these products are better accepted.

Egg used for OIT can be given (depending on the aim) as pasteurized raw egg white (many adverse events reported),⁶⁷ extensively heated egg (boiled white and yolk and/or well-cooked omelette), and baked egg products.^{74–76} Dehydrated egg white in powder is another possibility.⁷⁴

OIT with peanut has been performed with defatted peanut flour,^{20,21} crushed roasted peanuts,⁷⁷ and boiled peanuts.⁷⁸

4.3 | Schedules

Before starting AIT, an oral food challenge (OFC) should be performed to assure that the child is still allergic and set up her/his threshold of reaction to the specific food. The usual OIT schedule starts with a build-up phase in which small amounts of the diluted food are given to the patient at hospital. The maximum tolerated dose is that to be administered at home daily. The doses are increased weekly at the outpatient clinic, until a usual amount of the food is reached and the maintenance phase starts. From then on, the food should be taken daily.

Currently, OIT and SLIT are being evaluated in clinical trials in tertiary hospital or in academic centers. A global drug product development is being conducted for OIT and EPIT for peanut. The launch of commercial products for immunotherapy for peanut is therefore expected in the next 2 years.

5 | DESENSITIZATION AND POST-DESENSITIZATION EFFECTIVENESS

FA-AIT in all forms and particularly with the oral route (OIT) involves ingesting gradually increasing doses of allergenic foods. Currently,

the possibility to achieve desensitization is quite high, as estimated up to 90%.⁵⁸ Thus far, different schedules are being used for clinical trials: rush, cluster, or slow up-dosing regimen. Altogether, the amount of tolerated dose(s) is marginally affected by the different regimens.¹⁰ So far, the use of fresh material or native foods for OIT is advisable to achieve the goal of desensitization for cow's milk, hen's egg, and peanuts allergy. Since desensitization is defined as increase in reaction threshold to food allergen(s), while receiving active therapy, it protects patients from the occurrence of severe reaction in the event of an accidental ingestion of the culprit food. However, the pivotal clinical issue is represented by the post-desensitization strategy. The development of both immunologic tolerance and clinical effectiveness after successful desensitization has not been defined to date.^{58,79}

Accordingly, the understanding of the characteristic(s) of post-desensitization strategy is crucial: the definition "*post-desensitization effectiveness*" represents in our opinion either a clear semantic definition and a worthwhile goal of FA active therapy.⁷ In this context, the so-called "*ad libitum*" consumption of known food allergens to achieve post-desensitization effectiveness does not appear to be required in all cases. Therefore, more flexible maintenance regimen(s) is possible at least for children who have been desensitized to cow's milk^{11,24} and even to multiple foods.¹³ It is reasonable to assert that in developed countries the frequent ingestion of foods such as cow's milk and hen's egg usually present in the daily diet drives patient(s) in "*modus in rebus*" (ie, "in proportion"), that is, to a proper proportion of therapy.

6 | ISSUES FOR CLINICAL PRACTICE

There is more and more attention to the concept of precision medicine, tailored on specific patient's profile. In this concept, FA-AIT represents the best candidate for the treatment of FA.^{80,81} However, there are still several issues for clinical practice. A few of them have been assessed above in the respective paragraphs, such as the need of improving the post-discontinuation treatment effectiveness (please see "Desensitization and post desensitization effectiveness") and a deep understanding of the FA-AIT mechanisms of action (discussed in "Putative mechanisms of action"). A better knowledge in how FA-AIT works might allow to overcome the current clinical gaps and to identify sensitive biomarkers⁸² to recognize, who could take advantage of FA-AIT, in which measure and through which specific procedure ("Precision medicine" algorithms).

In addition, FA-AIT is currently logistically demanding and time-consuming, and many patients are affected by side effects though often mild. Thus far, no fatality has been reported in literature, but systemic reactions are consistently described as quite common.¹⁰ Some risk factors (ie, physical exercise, infection, non-steroidal anti-inflammatory drugs, and menses) are known to increase the risk of reactions, especially during the maintenance phase(s) of OIT, when patients continue treatment at home and a specific counseling can improve the management.⁸³ However, safety issues are still

unsolved. In this perspective, adjunctive therapies such as omalizumab have been investigated with quite promising results.^{28,84} Nevertheless, a shared grading and homogenous reporting system of adverse reactions is currently missing. This makes it difficult to compare the real occurrence and severity of specific type of adverse reactions among trials. There is a wide heterogeneity among studies also in terms of study design, age of patients, number and typology of FA, evaluated outcomes, procedures, schedules, and route of administrations. All of this variability affects the comparability among study results and therefore the robustness of synthetic quantitative data when meta-analyses are performed.¹⁰

Standardized products and vehicles are lacking. The constellations of products so far used in the different trials are enormously heterogeneous. Typically, the natural-raw form is used.¹⁰ However, the use of different types of processed foods could be an alternative treatment.⁶⁶ The allergenic potential of food allergenicity may vary on the basis of duration and type of processing and may be influenced by the food matrix.⁸⁵ A recent phase 3 trial evaluating an OIT with 300 mg peanut protein AR101 for treatment of peanut allergy showed that 67.2% of AR101 treated children were desensitized to 600 mg peanut protein and 50.3% were desensitized to 1000 mg peanut protein after 12 months of OIT vs. 4.0% and 2.4% of placebo treated children respectively.²⁷ However, as far as safety is concerned, it appears that 59.7% of AR101 treated children experienced moderate adverse events and 4.3% experienced serious adverse events vs. 44.4% and 0.8% of placebo treated children respectively. 14.2% of AR101 treated children experienced systemic allergic reactions (one event of which was severe grade 3 anaphylaxis, the rest being mild or moderate) vs. 3.2% in the placebo treated children. The frequency and severity of adverse events were higher during build-up than maintenance phase. During the maintenance phase, the proportion of children who experienced moderate or severe adverse events was comparable in both treatment arms; however, children in the AR101 group were five times more likely to experience systemic allergic reactions than the placebo group. During the course of the trial, epinephrine was administered twice as often in the AR101 group than in the placebo group, raising the question as to whether being desensitized with OIT is indeed better than pursuing allergen avoidance. In addition, as efficacy was not shown in adult patients it might be considered that starting at a younger age can predict a more favourable outcome.²⁷

Similarly, validated and shared protocols are needed. Furthermore, the impact on quality of life needs to be better elucidated.⁸⁶ FA is associated with a negative impact on the quality of life of patients and their families.^{87,88} To buy special foods, to limit social encounters, to lose time from work, to change careers, and to visit emergency room have been reported to play a predominant role in the total annual economic burden of FA.^{87,88}

On the other side, OIT, though logistically demanding and with side effects, might lead to significant and long-term improvements in health-related quality of life of patients and their caregivers.⁸⁸

Evidence on this regard is limited. Validated measures of quality of life should be included in future FA clinical trials to recognize the baseline

TABLE 1 Milestones of allergen immunotherapy for IgE-mediated food allergy

Confirmed diagnosis of persistent systemic IgE-mediated food allergy
Goal of desensitization in affected children; in future, expected also in adults
Adherence and motivation of patients and their families to the treatment
Clinical centers with expertise and facilities to emergency treatment
Provision of emergency kit with copy of emergency action plan and adrenaline auto-injector for treatment of anaphylaxis

characteristics that could potentially help identify the most suitable candidates for FA-AIT. In terms of health economics, cost-effectiveness of OIT needs to be assessed in well-designed large studies.⁸⁹

For all these reasons, FA-AIT is usually relegated to experimental trials in a few specialized centers able to provide local facilities and organization of care of patients experiencing severe anaphylaxis. However, individuals with persistent IgE-mediated FA deserve better treatment methods than a strict allergen avoidance. Currently, the specific active treatment of FA is poised in clinically important advance, and the immunomodulatory treatment of FA has found a new tool in FA-AIT (Table 1).

7 | THE CHOICE FOR FUTURE DEVELOPMENTS

FA represents both a promising and intriguing field of application for allergen immunotherapy especially in its oral form (OIT).⁷⁻⁹ Currently, the use of fresh material or native food(s) is suggested to achieve the goal of desensitization.²⁵ On the other hand, there is a race to develop commercial treatment for FA fueled by increasing prevalence and severity of FA in children. Further, multicenter phase III clinical trial (OIT) with standardized products containing major allergen of peanut is required.²⁷ We need, in the future, to establish the effective and safe maintenance dose, duration of FA-AIT, and frequency of maintenance dosing for long-term therapy. In this context, in order to avoid extensive dropout of patients, it is reasonable to attempt reducing the "ad libitum diet" during maintenance phase of OIT. Considering that some patients with persistent IgE-mediated FA, are allergic to multiple foods (e.g. milk, egg, peanut, tree nuts, seeds), an effective approach for combining multiple foods is desirable. Patients with the most severe phenotype of life-threatening anaphylaxis and those with concomitant bronchial asthma represent the difficult cases in clinical practice. In all probability, the appropriate use of anti-IgE monoclonal antibody (omalizumab) could be an important therapeutic tool to treat patients with persistent severe FA and asthma.^{28,90}

CONFLICT OF INTERESTS

Nothing to disclose for all authors.

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