International Journal of
Allergy Medications

Mini Review: Open Access

State of the Art on Food Allergy Immunotherapy

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Abstract

Food allergy is increasing in prevalence in westernized countries, leading to significant morbidity including nutritional deficiencies and the potential for fatal anaphylaxis during accidental exposure to the allergen. The current treatment remains strict avoidance, although the disease is not cured. Allergen specific immunotherapy for food allergy is currently being actively evaluated, but is still experimental. Nevertheless, it is the only disease-modifying therapy for IgE-mediated food allergy and appears to be a promising method of desensitization and tolerance achievement. Despite the success of different protocols studied in clinical trials (oral, sublingual and epicutaneous immunotherapy), the main drawback is the appearance of adverse reactions, which impacts in the patient adherence to the treatment. The mechanisms underlying successful food desensitization are also unclear, in part because there is no standard immunotherapy protocol and different mechanisms have been proposed. The treatment variations currently being investigated increases the likelihood of finding novel or modified therapies for food allergy. In this regard, mouse models of experimental allergy constitute a valuable biological tool to elucidate and understand these mechanisms, and to evaluate novel therapeutic strategies.

Keywords

Immunotherapy, Food allergy, Tolerance, Desensitization, IgE

Review

Food allergy, along with other allergic diseases, has increased in prevalence in westernized countries in the last decade and results from the interaction of different factors such as age, genetic load, immunogenicity and conformational features of food proteins and composition of the microbiota, among others. Food allergies are immune-mediated adverse reactions to food proteins and they can be IgE-mediated (causing immediate symptoms and potential anaphylaxis), non-IgE mediated (causing delayed reactions), or a combination of both. Food allergies involve different target organs and hence clinical presentation is variable and heterogeneous. It is not a unique clinical entity.

Emerging studies show that a loss of oral tolerance or a failure to induce tolerance is implicated in its immune-pathogenesis. The critical role of regulatory T cells (Treg) in tolerance development have been demonstrated in humans and mice [1,2]. The genetic deficiency of FoxP3 (transcription factor involved in the induction of the regulatory functions of T lymphocytes) or IPEX syndrome (Immunodeficiency, Polyendocrinopathy and Enteropathy, X-Linked Syndrome) produces a severe autoimmunity and food allergy in patients. A similar clinical picture is observed in Foxp3-null mice [3].

There is no treatment approved for food allergy and the currently accepted standard of care is allergen avoidance, accompanied by nutritional counseling [4]. Nevertheless, patients are prone to potential accidental exposure to the offending allergen with significant morbidity as well as mortality if anaphylaxis is produced in IgE-mediated allergic patients. This means that patients should be prepared for an eventual anaphylactic reaction with anti-histamines or injectable epinephrine. There is therefore much effort being made to *develop* disease-modifying therapies for IgE-mediated food allergy. In the context of treating allergic diseases, immunotherapy has been widely and empirically used during the last century. However, in the last years, results are by large showing that mucosal-based immunotherapy can mitigate the disease progress and it is nowadays the only disease-modifying treatment that could potentially cure allergy [5,6]. The step-wise administration of small amounts of the allergen through different mucosa, followed by maintenance dosing, induces specific tolerance mechanisms that restore the impaired immune-regulation observed in these patients [7,8]. In addition, the clinical therapeutic effect achieved with allergen-specific immunotherapy made restriction diet a currently controversial and debatable decision. Furthermore, there is emerging evidence showing that in high-risk patient with severe symptoms, prevention should contemplate the administration of the allergen even in patients with less than 1 year old [9]. In this prospective and randomized trial authors revealed that the early administration of peanut in infants with positive markers of sensitization reduced the risk of peanut allergy up to 80% compared with infants that avoided the allergen. Then a 12-month avoidance period did not reverted the clinical tolerance achieved [10]. However, there is no evidence to decide whether prevention strategies including allergen intervention should be performed in the general population, irrespective of the allergen-containing food consumption of the population, environmental exposure to the allergen, an allergen-free diet followed by mothers during pregnancy and lactation, etc. [11].

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Citation: Smaldini PL, Docena GH (2016) State of the Art on Food Allergy Immunotherapy. Int J Aller Medications 2:015

Received: January 01, 2016: **Accepted:** March 28, 2016: **Published:** March 31, 2016

The mechanisms by which immunotherapy works in allergic rhinitis, asthma, allergic conjunctivitis and bee venom allergy are mostly based on complex mechanisms that induce allergen tolerance. By contrast, the mechanisms by which allergen-specific immunotherapy works in food allergy are poorly understood. It is widely known that the main mechanism that is induced during the controlled mucosal administration of the offending allergen is the induction of T cell tolerance. The term tolerance is defined as a lack of adaptive immunity response to harmless antigens, which does not mean lack of response, but induction of several regulatory circuits that control both innate and adaptive immune responses involved in inflammation. Regulatory T cells have attracted the attention since its resurgence decades after they were discovered in the 70's [12], and were described as key cells in immune-modulation. Nevertheless, special subsets of dendritic cells, NK cells or innate lymphocytes, macrophages and B cells have been involved in the regulation of the allergic reaction. While IgG4 and/or IgA are responsible to block the access of the allergen to antigen presenting cells and sensitized mast cells/basophils/eosinophils, induced-specific Treg can modulate the threshold for mast cell/basophil activation, control memory T cells, differentiation and tissue homing of Th2 cells, suppression of IgE-producing plasma cells, and induction of regulatory B cells and regulatory dendritic cells [13].

Despite the significant progress made in identifying the underlying mechanisms that govern the subcutaneous immunotherapy (SCIT), the high rate of systemic reactions elicited during treatment of food allergic patients, made these protocols inadequate for these patients [14]. More recently, and based on the better *knowledge* of human intestinal immune system and tolerance induction against oral antigens, oral immunotherapy (OIT), sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT) have been evaluated as novel therapeutic options for food allergy. The mechanisms by which these immunotherapies might work are less studied [15]. These therapies rely on the administration (ingestion for OIT, held under the tongue for SLIT and skin contact for EPIT) of small and increasing amounts of the allergen, followed with a maintenance dose for a currently undefined duration of time. Although promising results were achieved, adverse reactions have been the main drawback in clinical trials, which in many cases affects therapeutic adherence. Therefore, and notwithstanding the great advances made in understanding the basis for these therapies, efforts are needed for optimization safety and efficacy.

Currently, *clinical trials* for *several* candidate immunotherapy protocols for food allergy are in *various* phases, with significant successes noted in clinical outcomes and modulation of immune mechanisms [6]. Two possible states of *unresponsiveness* against the allergen can be accomplished during the different investigational approaches: *desensitization* or *tolerance*. The former refers to the lack of reaction to allergen during the regular daily exposure to allergen on the maintenance dosing, which is achieved in most cases (patients regain sensitization after the treatment). True tolerance is the permanent absence of symptoms after the therapeutic exposure to allergen. This is the decisive goal of immunotherapy: patients can resume symptom-free consumption of the previously allergenic food. Although desensitization is the desired outcome of the interventional strategy, tolerance is the state considered for the onset of disease resolution. It is not clear which cells and mechanisms govern both states, and, mainly, which are the factors that affect the outcome of the treatment. Currently, oral food challenge (OFC) is performed at the end of the protocol to evaluate the dose of allergen that provokes symptoms. However, biomarkers that monitor the progress of the treatment (peripheral cells, peripheral cellular responses, antibodies, cytokines, etc), not currently available, will help to predict the effectiveness of immunotherapy.

Although there are inconsistencies between studies, in terms of protocol definitions and OFC implementation, a continuous success in amelioration of symptoms, increase of the threshold to have a positive OFC and reduction of adverse reaction with increased adherence has been observed for more than a decade in clinical trials. The protocolization of a controlled administration of the allergen and better-designed clinical trials rendered apparently more effective regulatory mechanisms, as shown by 20- to 100-fold or even greater improvement of OFC performance from baseline after treatment [16-18], with a decrease in SPT size and reduction of adverse effects up to 10% of patients involved in the trial [16]. Nevertheless, several trials have demonstrated that tolerance induction is transient and symptoms relapse in weeks or months if exposure to the food is resumed [19-21]. The IMPACT clinical trial (The Immune Tolerance Network), a randomized 3-year OIT (134 weeks of OIT followed by 26 weeks of allergen avoidance), was launched in 2013 to investigate long-term tolerance in 144 peanut-allergic children.

Unfortunately the term tolerance has a wide meaning and probably several and complex mechanisms that involve soluble factors (IL-10, TGF-β, IL-35, IL-25, IL-27, etc), cell-cell contacts (CTLA-4, PD-1, etc), and different cell subsets of innate (innate lymphocytes, dendritic cells and macrophages) and adaptive immunity (B and T cells) are implicated in the control of the Th2-mediated allergic immune response and outgrown of allergy. This emphasizes the need for further studies to identify which are the most powerful mechanisms that can address a long-term protection. In this sense, two approaches can be proposed to achieve tolerance: immunomodulation through the induction of the contra-regulatory Th1 cells, and tolerance through the Treg-mediated regulatory mechanisms that control innate and adaptive immune response.

In this regard, mouse models that resemble allergic diseases in human provide an essential tool for studying the pathogenesis of these inflammatory disorders, and the development of novel therapies. In order to elicit an allergic sensitization in mice, species that does not spontaneously develop allergy due to its genetic background, a pro-Th2 mucosal adjuvant should be used. Cholera toxin or Staphylococcus enterotoxin B are the most widely employed adjuvants to breakdown oral tolerance to the co-administered antigens. Several protocols of oral sensitization to food antigens have proved to induce secretion of antigen-specific IgE and a cellular immune response skewed to Th2 profile that promotes the induction of immediate hypersensitivity reactions upon challenge with the allergen [22,23]. Considering this parallel with human food allergy, animal models of experimental allergy that lead to mucosal allergic sensitization have shown to be useful biological tools to optimize and validate existing treatments as well as to develop novel specific and safer therapies [24].

Mouse models were used to optimize OIT in terms of reducing adverse side effects. The use of different anti-IgE monoclonal antibodies has shown promise to block soluble IgE or membrane-bound IgE (BCR on memory IgE-switched B cells). In humans, a large body of research demonstrated that the anti-IgE therapy with Omalizumab, a humanized monoclonal antibody that blocks the binding of IgE to the high-affinity receptor, has shown to be effective at reducing circulating IgE antibodies and IgE-receptors (FcεRI) on sensitized cells (mainly mast cells and basophils), alongside the induction of histamine-specific inhibitory receptors (H4) in mast cells, [25] in asthma and rhinitis, while the new generation of humanized antibodies with 400-fold higher affinity for the inhibitory receptor FcγRIIb on B cells suppresses the generation of IgE-producing plasma cells [26]. In food allergy, although Omalizumab showed promising results in combination with oral immunotherapy for peanut allergy [27], the long-term efficacy is controversial. In addition, a humanized mouse model of asthma was successfully treated with an anti-IgE monoclonal antibody that reduced the frequency of IgE-switched B cells and the level of soluble IgE. Since it was demonstrated that apoptosis of IgE-memory B cells was induced it could be proposed as a long-lasting treatment for IgE-mediated diseases [28]. Another therapeutic strategy assessed in mice has been the use of peptides containing T epitopes or a single B epitope through the oral route. This approach has showed to be safe and effective in animal models of asthma to mites [29] and food allergy to egg [30].

Sublingual immunotherapy also shows promising since very low doses of the allergen are administered under the tongue to activate the local immune system [31]. Although most of the SLIT studies have focused on inhalant allergies, emerging clinical trials with SLIT have shown hopeful results at inducing desensitization in food allergy [32]. However, only few studies have been done in hazelnut, peanut, kiwi, peach and cow's milk allergy [33-38], and yet SLIT is not recommended for treatment of food allergy [5]. Despite the debatable efficacy of SLIT, lower frequencies of adverse reactions have been reported in SLIT compared to OIT [39]. Additionally, the end SLIT dose used in clinical trials is much lower than OIT dose. Considering that the induction of Treg is the key mechanism underlying desensitization and tolerance, it has been reported that the current protocols of SLIT have a lower efficiency to induce Treg in the mouth mucosa compared with OIT. At present, neither OIT nor SLIT provides optimal safety and efficacy for treatment of food allergy. Literature shows scarce reports exploring SLIT in mouse models of rhinitis and asthma. Pre-clinical studies in animals may provide useful and novel information regarding the uptake of allergen by the Langerhans cells of the oral cavity and how Tregs are induced in the sublingual mucosa or in the regional lymph nodes [40]. The use of nanoparticles composed of carbohydrates may enhance safety of SLIT through protecting and directing allergen towards antigen presenting cells [31,41]. Therefore, it is a tempting field to speculate on novel SLIT protocols for therapeutic induction of mucosal tolerance in food allergy.

Finally, *epicutaneous immunotherapy* or EPIT, the most recent mucosal therapy, delivers the antigen on the skin surface. Although limited studies are published in food allergic patients, pre-clinical [42,43] and clinical trials using an allergen-embedded patch (milk and peanut) showed and acceptable safety profile, with positive clinical effects and mostly local adverse reactions ([44] and VIPES Study at https://clinicaltrials.gov/ct2/show/record/NCT01955109]). It has been shown that different skin dendritic cell subsets internalize allergens and traffic to draining lymph nodes to generate specific Tregs that control the systemic allergic immune response in mice [43].

In conclusion, immunotherapy appears to be a promising option for a disease-modifying therapy for IgE-mediated food allergy. Since anaphylaxis is a major drawback, and protocols show a lack of consistency, none of the current therapies are ready for wide-spread clinical use. In this scenario a*nimal models hold great* potential as powerful biological tools to assess new therapeutic strategies and for pre-clinical studies, to provide more safety and efficacy to current immunotherapies. Long-term and sustained tolerance should then be explored in clinical trials, based on developments made on molecular mechanisms of immune regulation that promotes allergen-tolerance.

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