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Review Article

New Insights in Immunotherapies for Food Allergies. A Path between the Mouse Model and the Allergic Patient

Paola L Smaldini and Guillermo H Docena*
Instituto de Estudios Inmunológicos y Fisiopatológicos – IIFP, Facultad de Ciencias Exactas, Departamento de Ciencias Biológicas, Universidad de La Plata, La Plata, Argentina

***Corresponding author:** Guillermo H Docena, Instituto de Estudios Inmunológicos y Fisiopatológicos – IIFP, Facultad de Ciencias Exactas, Departamento de Ciencias Biológicas, Universidad de La Plata, La Plata, Argentina, E-mail: guidoc@biol.unlp.edu; guillermo.docena@gmail.com

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Abstract

Allergic diseases are the most prevalent immunopathologies worldwide. Nowadays, allergen avoidance is the unique effective treatment for allergic patients. Pre-clinical studies and clinical trials have been successful to prove that immunotherapies may accomplish mucosal mechanisms of allergen-specific tolerance, which are able to revoke the allergic sensitization.

Although more than 100 years have elapsed since the first reported procedure achieved in patients sensitive to pollen, the main obstacle in these therapies still remains adverse reactions induced during treatment. The need for further studies is required to explore safe and effective therapeutic protocols. More recently, immunotherapy appears to be an attractive option for patients with food allergy, although it is still experimental. Different strategies were proposed to overcome the concerning adverse effects that compromise safety, effectiveness and compliance with treatments. At this point, translational medicine is a flourish field in the arenas of basic science, applied science, and clinical research. The use of experimental animals may provide new insights to unravel mechanisms that play key roles in desensitization and tolerance induction, and to modify existing protocols or design new therapeutic approaches. The present reviews describes the different immunotherapies that are used in allergic patients, the promising immune interventions that are currently evaluated in clinical trials and the contributions that animal models may provide to improve the quality of treatments.

Introduction

Allergic diseases are a global health concerning and result from a complex interaction between environmental factors and genes. Food allergy is an immune-mediated adverse reaction against antigenic foods and constitutes a growing clinical problem. As incidence of allergy escalated during the last decades in some highly industrialized regions, the prevalence of food allergy has raised at the same time mainly in infancy [1,2] and is becoming a growing issue in adults [3].

Despite the great progress made to elucidate the molecular basis of allergic disorders, it is not completely understood why some individuals develop allergic sensitization to some foods, while the majority of individuals are immunologically tolerant. In this regard evidence suggests that environmental factors are key inducers [4]. Although any food is potentially capable of causing an allergic reaction, a group of eight major allergenic foods, referred to as the "Big 8", account for 90 % of all food allergic reactions in The United States. These are: peanut, tree nuts, cow's milk, egg, soybean, wheat, fish and shellfish and its derivatives. Recent evidences may explain why certain foods are inherently allergenic [5,6].

A variety of symptoms involving the skin, gastrointestinal and respiratory tracts can be evidenced in allergic patients upon exposure to the offending food; these symptoms can be attributed to IgE-mediated and/or non-IgE mediated mechanisms. Genetic predisposition, environmental factors, route of exposure and maturity of the mucosal immune system may play a role in sensitization rather than oral tolerance to foods, leading to a Th2-biased food specific T cell-mediated immune response underlying the detrimental reaction to the innocuous food.

Diagnosis of food allergy is complicated. It is a heterogeneous disorder involving several clinical entities with no single immunologic mechanism involved. Once food allergy is suspected the first clinical or even familial indication is avoidance of the suspicious food. Currently, there is no accepted form of therapy for food allergies. Patient and family should be educated to avoid exposure to the responsible allergen, and they should have immediate access to epinephrine in case of anaphylaxis when accidental ingestion occurred. In addition, there are no therapies proven to accelerate the development of oral tolerance or provide effective protection from accidental exposures. However, novel allergen specific and allergen non-specific approaches to food allergy therapy are under study [7].

Immunotherapy is nowadays a treatment procedure to induce, enhance or suppress an immune response in different immunological disorders (cancer, autoimmunity, allergy, etc). Although allergen specific immunotherapy has been used for the treatment of IgE-mediated allergy longer than a hundred years, the first randomized clinical trial of oral immunotherapy for food allergy was done in 2008. Of note, this therapeutic procedure has not been accepted as a routine treatment for food allergy.

The aim of food allergy immunotherapy is to step-wise induce desensitization followed with a permanent restoration of oral tolerance. The term *desensitization* accounts for a temporary hypo-responsiveness during regular ingestion of the food, as dosing is

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discontinued, the protective effect is lost. *Tolerance* is defined as a prolonged ability to ingest large amounts of food proteins with no detrimental reaction, being immunotherapy completed. Different reports describe advances made in oral, sublingual and subcutaneous food immunotherapies, with some approaches and innovations derived from animal model studies [8].

In this sense, mouse models of allergic diseases provide an essential tool for studying the pathogenesis of allergic diseases, and the development of novel or modified therapeutic strategies. As mice do not develop allergy spontaneously, it is induced artificially through the use of pro-Th2 adjuvants (aluminum hydroxide, cholera toxin, Staphylococcus enterotoxin B, etc.). The artificial sensitization method employed limited the use of these experimental animals to study the inductive phase of food allergy. During the sensitization phase, the repeated intragastric administration of food proteins in combination with a potent mucosal adjuvant, cholera toxin, abrogates oral tolerance to the co-administered antigens, and establishes the disease state, which can be easily evidenced with the clinical signs elicited minutes after the exposure to the food allergen [9,10]. A variety of *in vitro* and *in vivo* parameters can be evaluated to characterize the allergic status of sensitized mice [10-12]. These experimental models have been successfully employed to explore the effects of different immunotherapeutic strategies on the immune system. The ability to sensitize animals to a specific food through the intragastric administration of allergens, and then elicit an allergic response by activating mucosal immune cells provides clear ties to the human condition. In addition, mouse models constitute useful biological tools to study novel mucosal adjuvants, both to induce a Th2 immunoregulatory immune response for Th1-mediated immunopathologies (autoimmunity), and to modulate it (allergic disorders).

Oral immunotherapy

Oral immunotherapy (OIT) consists in a daily consumption of milligrams to grams of the selected allergen, which is incrementally raised over weeks to months with the goal of inducing desensitization and then tolerance [13-15]. In the first randomized double-blind placebo-controlled OIT trial performed by Skripak et al., 20 children with IgE-mediated cow's milk allergy were randomized given milk or placebo. The main point of this study was that patients tolerated 128 times higher amounts of milk compare with patients before treatment or with placebo-treated patients [15]. Despite no variation on serum specific IgE levels, IgG4 and titration SPT threshold were increased, and most of the patients experienced transient adverse reactions after OIT treatment. Therefore, this study did not provide a clear evidence of tolerance induction. Keet et al. showed that 40 % of subjects receiving milk OIT passed an oral food challenge when treatment was ceased for 6 weeks, however some regained reactivity within a week [16]. Similar results were observed in OIT with egg and peanut allergens [17,18]. Although data on long-term treatment are limited, Keet et al. showed that, three to five years after cow´s milk OIT was finished, only 25% of subjects were consuming normal amounts of milk without any symptoms, and that almost 20% of treated patients experienced anaphylactic reactions during the follow-up period, including children who appeared to have a good response to treatment [19].

Additionally, peanut allergy is the most common cause of fatal food allergic reactions [20] since peanut components are widely used in processed foods, and some of them were probed to be highly immunogenic [21]. This means that fatal or nearly fatal reactions to this life-threatening allergen are responsible for several deaths in the United States (thousands of hospitalizations and hundreds of fatal cases per year) following accidental exposure to this allergen [22,23]. Although, there are no immunotherapy regimens in routine use for peanut allergy, peanut OIT has showed promising results. Most peanut OIT protocols involve an initial escalation phase (days) of orally administered peanut. This is followed by administration of further build-up doses (months), and then maintenance doses (months). The maximum maintenance doses are between 300 mg and 4000 mg of peanut protein. While some studies have shown hopeful results, the risk of severe reactions during allergen administration is of concern [24,25]. Anagonostou et al. have investigated the role of peanut OIT in 99 children with peanut allergy in a phase II, randomized-controlled trial. Subjects who successfully completed the OIT protocol had a 25-fold increase of their peanut threshold [26].

Despite the number of promising OIT studies and the increasing interest of the medical community in the development of a routine OIT using native proteins, a high percentage of patients still suffer *adverse side effects*. One of the therapeutic strategies assessed to overcome it was to include modified allergenic proteins (baked or roasted) in the sequential steps of allergen administration. The addition of baked milk or egg to the diet of allergic children that tolerated such baked foods accelerated the development of tolerance to unbaked milk or egg compared with patients that did not tolerated the processed food and received a free-allergen diet [27,28]. It was observed that this procedure induced mild adverse reactions, which were easily controlled.

In summary, OIT has showed promising results in cow´s milk, peanut and egg white allergen patients, with the primarily induction of desensitization and further tolerance. However, the high rate of adverse reactions elicited during the immunotherapy, and the uncertainty of long term outcome require further studies. Furthermore, the immunological mechanisms underlying desensitization and tolerance mechanisms in OIT have not been fully investigated (Table 1). In this sense, experimental animals may provide relevant information in a way that would be nonviable in clinical trials.

A relatively new form of non-specific immunotherapy is the

Table 1: Mechanisms induced in antigen-specific immunotherapies.

Immunotherapy	Study	Antigen	Mechanism	References
OIT	Human	Peanut Milk Egg	Treg, IL-10, TFG-β	[71-73]
	Mouse	Milk Egg Peanut	Treg, IL-10, TFG-β	[37,74,75]
SLIT	Human	Milk Peanut	IL-10, Th1, IgG4	[27,76,77]
	Mouse	--	--	No ref.
SCIT	Human	Milk Peanut	Treg, IL-10, increase IgA, Igg4	[62,63]
	Mouse	--	--	No ref.

anti-IgE therapy (with humanized a-IgE monoclonal antibody-Omalizumab), which has been successfully used in asthma. Sampson et al. started a phase II clinical trial with Omalizumab in 150 patients with peanut allergy; however the study was terminated early due to the severe reactions that occurred during the peanut challenge [29]. Recently, a combination therapy was studied using the a-IgE antibody in patients undergoing OIT. It was observed that the biological was effective in reducing adverse reactions during the oral administration of the allergen (cow´s milk, wheat, peanut and egg), with a rapid oral desensitization [30-32]. Although these clinical trials were effective for mono-allergic and multi-allergic patients, reaching daily doses of 4000 mg for individual allergens during several weeks, tolerance was not demonstrated [33]. However, several potential benefits can be speculated with the combination of both therapies. An additional strategy to reduce the risk of adverse reactions is the use of modified allergens. The efficacy of this therapy was evaluated in a humanized mouse model [34]. OIT with dietary food produce a high rate of adverse side effects, due to the intact B cell epitopes in native allergenic proteins with capacity to cross-link IgE bound to mast cell and basophil membrane receptors. The use of peptides containing T epitopes has been reported to be a safe and effective option for OIT in animal models of asthma to mite allergen [35,36] and food allergy to egg [37]. Finally, food allergy mouse models were used to test mutated allergens, in which immunodominant B cell epitopes were modified by point mutation to impair allergenicity, and to develop a safer immunotherapy [38-40].

Sublingual immunotherapy

Sublingual immunotherapy (SLIT) involves frequent placement of micrograms to milligrams of allergen under the tongue. Cochrane analyses have confirmed the efficacy and safety of sublingual therapy for allergic rhinitis with long-term benefits (1-2 years) [41]. Although most of the SLIT studies have focused on inhalant allergies, emerging clinical trials with SLIT have shown promising results at inducing desensitization in food allergy [42,43]. However, SLIT is not currently recommended for treatment of food allergy [44]. Only few studies have been done in peanut, nuts, kiwi, peach and cow´s milk allergy [45-49] and they showed lower frequencies of adverse reactions compared with OIT, which is likely due to lower doses of allergen administration and the capacity of the mouth mucosa to induce intestinal tolerance. However, the efficacy of SLIT is still debated. 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 as compared to OIT (Table 1) [50,51]. Nevertheless, SLIT protocols used for egg, cow´s milk or peanut allergy [52] showed a significant increase in the threshold dose of the food allergen to induce allergic symptoms, a decrease in serum specific IgE along with a rise in serum IgG4 levels , and induction of Tregs [40]. There are only two randomized studies comparing oral and sublingual immunotherapies. Keet et al. conducted a clinical trial with 30 milk allergic patients comparing SLIT alone versus SLIT followed by OIT. It was reported that despite the similar number of total adverse food reactions between groups, the number of systemic reaction was higher in the OIT groups. Of note, the oral challenge performed after 60 weeks of maintenance doses, rendered a higher allergen threshold in SLIT followed by OIT treated patients compared with SLIT-treated patients [16]. Narisety et al. performed a similar randomized study with peanut allergic patients to compare the safety and efficacy of OIT and SLIT. They found a partial desensitization with at least a 10-fold increases in peanut challenge threshold compared with baseline. They similarly found that efficacy of OIT was greater than SLIT, although safety is still greater in patients receiving SLIT compared with OIT [18].

The literature shows scarce reports exploring SLIT in mouse models. Most of them employed mucosal adjuvants and were done in rhinitis and asthma. Lombardi et al. showed that Pam3CSK4, a known TLR2 agonist, exhibits immunomodulatory properties with the induction of $CD4^+$ T cells that secreted IL-10 and IFN-γ to control the allergic reaction [53]. Saint Lu et al. used a mucoadhesive form of chitosan to enhance allergen uptake, processing and presentation by dendritic cells. It was shown that the treatment enhances tolerance induction in mice with established asthma, with a reduction of lung inflammation [54]. Of note, there is no study with experimental animals using SLIT to show that immunomodulatory mechanisms can be induced in the sublingual mucosa, with the subsequent control of the intestinal inflammation and the systemic allergy. Based on our preliminary data showing that the sublingual administration of the allergen, or the allergen in combination with Th1 adjuvants, can control hypersensitivity symptoms upon allergen oral challenge, we consider that food allergy mouse models are indeed a valuable biological tool to study pre-clinical strategies for food allergy immunotherapy. Using a cholera toxin-driven IgE-mediated milk allergy model, we could revert an established Th2-biased intestinal immune response with the oral administration of milk proteins, and the subsequent induction of Tregs (data not published).

In summary, SLIT in humans has been clearly associated with a substantially reduced risk of adverse reactions, although efficacy and long-term effectiveness are the main drawbacks. Food allergy mouse models may provide information for new hopes to improve this disease-modifying therapy.

Subcutaneous and epicutaneous immunotherapy

The major form of allergen-specific immunotherapy is the subcutaneous immunotherapy (SCIT). Subcutaneous injections of the allergen deliver the allergen to skin Langerhans cells, with the subsequent migration of dendritic cells to lymph nodes and further regulation of effector allergic responses [55]. Although, it is widely used for treatment of allergy, it is not accepted as a routine therapy, especially for children. Recruitment of patients and then (less that 5% of all allergic patients) compliance to SCIT (less than 25% of patients drop out within the first year of treatment) are difficult to achieve [56].

Safety and effectiveness of SCIT have been reported in rhinitis and asthma [57]. Although adverse reactions have been documented, the vast majority are mild and very rarely fatal [58]. In contrast, clinical trials of SCIT in peanut allergic patients showed that anaphylactic side-effects induced during the administration of the native allergen are highly frequent [59,60]. The first attempt to improve this protocol was done by The European multicenter consortium that conducts the prospective Food Allergy Specific Immunotherapy (FAST) project to evaluate the use of alum-adsorbed hypoallergens to control fish and peach allergy. Recombinant mutated allergens, with decreased IgE-binding capacity and intact T cell-reactivity capacity, are included in

the SCIT. Patients will be enrolled for a phase I/IIA initial clinical trial, while animal models will be used to evaluate the allergenicity of the recombinant hypoallergenic proteins developed and efficacy of the immunotherapy [61].

More recently, epicutaneous immunotherapy (EPIT) with allergen-embedded patch administration has been carried out in food allergy. One of the first clinical trials for EPIT evaluated 18 children with cow´s milk allergy during three months. EPIT not showed serious systemic adverse effects. Although treatment was associated with more frequent complaints for local pruritus and discomfort than placebo, patient compliance was not compromised [62]. In addition, there is a phase I clinical trial that is conducted in the United States with 80 peanut allergic patients that received EPIT and 20 placebo-treated subjects; mild or moderate local adverse effects were experienced by 90% of patients [63]. Another clinical trial in phase IIA with 54 children with peanut allergy that underwent EPIT showed a good response. Oral food challenges conducted at 6-month intervals over a 18-month period revealed that 67 % of patients achieved desensitization, with a 10-fold increase in cumulative reactive dose from baseline [64,65].

Despite the scarce number of reports, studies of allergen patch in animal models indicate a potential application of this therapy. Pre-clinical studies in mice were carried out with peanut, ovoalbumin and some aeroallergens using a skin patch [66-68]. EPIT on intact skin down-modulated the allergic immune response through the induction of long-lasting tolerogenic Treg [69]. The protection offered by EPIT-induced Tregs was adoptively transferred to peanut sensitized animals [68,70].

Remarkably, there is no study of SCIT in animal models, thus reflecting the difficulty to immunomodulate allergic disorders through this administration route in mice.

Conclusions

Immunotherapy appears to be a promising option for the treatment of food allergy. OIT and SLIT have emerged as attractive therapies to divert the aberrant immunological mechanisms underlying these diseases. Both modalities have shown to induce desensitization through different mechanisms (Table 1). Although it has been demonstrated that a sustained unresponsiveness can be achieved with OIT, several clinical trials support that safety, feasibility, compliance, and economic profile is mainly found with the sublingual immunotherapy. However, further research is needed to improve its efficacy and long-term effectiveness. In this scenario, mouse models represent a valuable tool for evaluating novel or modified forms of immunotherapy and also for dissecting the mechanism of action. The combination of specific methods or even both specific and non-specific methods may enhance desensitization with a rapid onset of tolerance.

References

1. Gupta RS, Dyer AA, Jain N, Greenhawt MJ. Childhood food allergies: current diagnosis, treatment, and management strategies. Mayo Clinic proceedings 2013; 88: 512-26.
2. Venter C, Arshad SH. Epidemiology of food allergy. Pediatric clinics of North America 2011; 58: 327-49, ix.
3. Röckmann H, van Geel MJ, Knulst AC, Huiskes J, Bruijnzeel-Koomen CA, et al. Food allergen sensitization pattern in adults in relation to severity of atopic dermatitis. Clin Transl Allergy 2014; 4: 9.
4. Kim BJ, Lee SY, Kim HB, Lee E, Hong SJ. Environmental changes, microbiota, and allergic diseases. Allergy Asthma Immunol Res 2014; 6: 389-400.
5. Ladics GS, Knippels LMJ, Penninks AH, Bannon GA, Goodman RE, et al. Review of animal models designed to predict the potential allergenicity of novel proteins in genetically modified crops. Regul Toxicol Pharmacol 2010; 56: 212-24.
6. Mills ENC, Sancho AI, Rigby NM, Jenkins JA, Mackie AR Impact of food processing on the structural and allergenic properties of food allergens. Mol Nutr Food Res 2009; 53: 963-9.
7. Calvani M, Giorgio V, Miceli Sopo S. Specific oral tolerance induction for food. A systematic review. Eur Ann Allergy Clin Immunol 2010; 42: 11-9.
8. Oyoshi MK, Oettgen HC, Chatila TA, Geha RS, Bryce PJ. Food allergy: Insights into etiology, prevention, and treatment provided by murine models. J Allergy Clin Immunol 2014; 133: 309-17.
9. Li XM, Schofield BH, Huang CK, Kleiner GI, Sampson HA. A murine model of IgE-mediated cow's milk hypersensitivity. J Allergy Clin Immunol 1999; 103: 206-14.
10. Smaldini PL, Ibañez AE, Fossati CA, Cassataro J, Docena GH. Oral delivery of Brucella spp. recombinant protein U-Omp16 abrogates the IgE-mediated milk allergy. Hum Vaccin Immunother 2014; 10: 1-9.
11. Smaldini P, Curciarello R, Candreva A, Rey MA, Fossati CA, et al. *In vivo* evidence of cross-reactivity between cow's milk and soybean proteins in a mouse model of food allergy. Int Arch Allergy Immunol 2012; 158: 335-46.
12. Curciarello R, Smaldini PL, Candreva AM, González V, Parisi G, et al. Targeting a cross-reactive Gly m 5 soy peptide as responsible for hypersensitivity reactions in a milk allergy mouse model. PloS one 2014; 9: e82341.
13. Meglio P, Bartone E, Plantamura M, Arabito E, Giampietro PG. A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. Allergy 2004; 59: 980-7.
14. Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. J Allergy Clin Immunol 2008; 121: 343-7.
15. Skripak JM, Nash SD, Rowley H, Brereton NH, Oh S, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol 2008; 122: 1154-60.
16. Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, Schroeder JT, Hamilton RG, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol 2012; 129: 448-55.
17. Burks AW, Jones SM. Egg oral immunotherapy in non-anaphylactic children with egg allergy: follow-up. J Allergy Clin Immunol 2008; 121: 270-1.
18. Narisety SD, Frischmeyer-Guerrerio PA, Keet CA, Gorelik M, Schroeder J, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. J Allergy Clin Immunol 2014; [Epub ahead of print].
19. Keet CA, Seopaul S, Knorr S, Skripak JM, Wood R. Long-Term Follow-up of Oral Immunotherapy for Cow's Milk Allergy. J Allergy Clin Immunol 2014; 132: 737-9.
20. Sampson H. P EANUT A LLERGY. N Engl J Med 2002; 346: 1294-9.
21. Zhao X, Chen J, Du F. Potential use of peanut by-products in food processing: a review. J Food Sci Technol 2012; 49: 521-9.
22. Nguyen-Luu NU, Ben-Shoshan M, Alizadehfar R, Joseph L, Harada L, et al. Inadvertent exposures in children with peanut allergy. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 2012; 23:133-9.
23. Fleischer DM, Perry TT, Atkins D, Wood RA, Burks AW, et al. Allergic reactions to foods in preschool-aged children in a prospective observational food allergy study. Pediatrics 2012; 130: e25–32.

24. Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschorner J, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. J Allergy Clin Immunol 2010; 126: 83-91.e1.

25. Hofmann AM, Scurlock AM, Jones SM, Palmer KP, Lokhnygina Y, et al. NIH Public Access. 124: 286-91.

26. Anagnostou K, Clark A (2014) The management of peanut allergy. Archives of disease in childhood. 1-5.

27. Kim JS, Nowak-węgrzyn A, Sicherer SH, Noone S, Moshier EL, et al. Dietary baked-milk accelerates resolution of cow's milk allergy in children. J Allergy Clin Immunol 2012; 128: 125-31.

28. Leonard SA, Martos G, Wang W, Nowak-Węgrzyn A, Berin MC. Oral immunotherapy induces local protective mechanisms in the gastrointestinal mucosa. J Allergy Clin Immunol 2012; 129: 1579-1587.e1.

29. Sampson HA, Leung DYM, Burks AW, Lack G, Bahna SL, et al. A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. J Allergy Clin Immunol 2011; 127: 1309-10.e1.

30. Nadeau KC, Schneider LC, Hoyte L, Borras I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. J Allergy Clin Immunol 2012; 127: 1622-4.

31. Schneider LC, Rachid R, LeBovidge J, Blood E, Mittal M, et al. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. J Allergy Clin Immunol 2013; 132: 1368-74.

32. Lafuente I, Mazon A, Nieto M, Uixera S, Pina R, et al. Possible recurrence of symptoms after discontinuation of omalizumab in anti-IgE-assisted desensitization to egg. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 2014.

33. Bégin P, Dominguez T, Wilson SP, Bacal L, Mehrotra A, et al. Phase 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using Omalizumab. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology 2014; 10: 7.

34. Brightbill HD, Jeet S, Lin Z, Yan D, Zhou M, et al. Antibodies specific for a segment of human membrane IgE deplete IgE-producing B cells in humanized mice. J Clin Invest 2010; 120: 2218-29.

35. Suzuki K, Kaminuma O, Yang L, Motoi Y, Takai T, et al. Development of transgenic rice expressing mite antigen for a new concept of immunotherapy. Int Arch Allergy Immunol 2009; 149: 21-24.

36. Suzuki K, Kaminuma O, Yang L, Takai T, Mori A, et al. Prevention of allergic asthma by vaccination with transgenic rice seed expressing mite allergen: induction of allergen-specific oral tolerance without bystander suppression. Plant Biotechnol J 2011; 9: 982-90.

37. Rupa P, Mine Y. Oral immunotherapy with immunodominant T-cell epitope peptides alleviates allergic reactions in a Balb/c mouse model of egg allergy. Allergy 2012; 67:74-82.

38. Reese G, Viebranz J, Leong-Kee SM, Plante M, Lauer I, et al. Reduced Allergenic Potency of VR9-1, a Mutant of the Major Shrimp Allergen Pen a 1 (Tropomyosin). J Immunol 2005; 175: 8354-64.

39. Wai CYY, Leung NYH, Ho MHK, Gershwin LJ, Shu SA, et al. Immunization with Hypoallergens of Shrimp Allergen Tropomyosin Inhibits Shrimp Tropomyosin Specific IgE Reactivity. PloS one 2014; 9: e111649.

40. Rolland JM, Prickett S, Gardner LM, O'Hehir RE. T cell targeted strategies for improved efficacy and safety of specific immunotherapy for allergic disease. Antiinflamm Antiallergy Agents Med Chem 2013; 12: 201-22.

41. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. Allergy 2005; 60:4-12.

42. Larenas-Linnemann D, Blaiss M, Van Bever HP, Compalati E, et al. Pediatric sublingual immunotherapy efficacy: evidence analysis, 2009-2012. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. American College of Allergy, Asthma & Immunology 2013; 110: 402-415.e9.

43. Sun J, Hui X, Ying W, Liu D, Wang X. Efficacy of allergen-specific immunotherapy for peanut allergy: a meta-analysis of randomized controlled trials. Allergy and asthma proceedings : the official journal of regional and state allergy societies 2014; 35: 171-7.

44. Le UH, Burks A. Oral and sublingual immunotherapy for food allergy. World Allergy Organ J 2014; 7:35.

45. Kerzl R, Simonowa A, Ring J, Ollert M, Mempel M. Life-threatening anaphylaxis to kiwi fruit: protective sublingual allergen immunotherapy effect persists even after discontinuation. J Allergy Clin Immunol 2007; 119: 507-8.

46. Webber CM, England RW. Oral allergy syndrome: a clinical, diagnostic, and therapeutic challenge. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 2010; 104: 101-8.

47. Fernández-Rivas M, Garrido Fernández S, Nadal JA, Díaz de Durana MDA, García BE, et al. Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. Allergy 2009; 64: 876-83.

48. Patriarca G, Nucera E, Pollastrini E, Roncallo C, De Pasquale T, et al. Oral specific desensitization in food-allergic children. Dig Dis Sci 2007; 52: 1662-72.

49. de Boissieu D, Dupont C. Sublingual immunotherapy for cow's milk protein allergy: a preliminary report. Allergy 2006; 61: 1238-9.

50. Bonvalet M, Moussu H, Wambre E, Ricarte C, Horiot S, et al. Allergen-specific CD4+ T cell responses in peripheral blood do not predict the early onset of clinical efficacy during grass pollen sublingual immunotherapy. Clinical and experimental allergy : Journal of the British Society for Allergy and Clinical Immunology 2012; 42: 1745-55.

51. Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, et al. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter tria. J Allergy Clin Immunol 2014; 131: 119-27.

52. Wang J, Sampson HA. Review article Oral and sublingual immunotherapy for food allergy. Asian Pac J Allergy Immunol 2013; 31: 198-209.

53. Lombardi V, Van Overtvelt L, Horiot S, Moussu H, Chabre H, et al. Toll-like receptor 2 agonist Pam3CSK4 enhances the induction of antigen-specific tolerance via the sublingual route. Clinical and experimental allergy : Journal of the British Society for Allergy and Clinical Immunology. 2008; 38: 1819-29.

54. Saint-Lu N, Tourdot S, Razafindratsita A, Mascarell L, Berjont N, et al. Targeting the allergen to oral dendritic cells with mucoadhesive chitosan particles enhances tolerance induction. Allergy 2009; 64: 1003-13.

55. Novak N, Bieber T, Allam J. Immunological mechanisms of sublingual allergen-specific immunotherapy. Allergy 2011; 66: 733-9.

56. Brown D, Hankin C, Scott D, Henry M, Anderson K, et al. Characteristics Associated with Premature Discontinuation of Allergen Immunotherapy among Children and Adults: Findings from a Large, Single-Specialty Allergy Practice in the United States. Journal of Allergy and Clinical Immunology. Elsevier; 2009; 123: 728.

57. Erekosima N, Suarez-Cuervo C, Ramanathan M, Kim JM, Chelladurai Y, et al. Effectiveness of subcutaneous immunotherapy for allergic rhinoconjunctivitis and asthma: a systematic review. The Laryngoscope 2014; 124: 616-27.

58. Osguthorpe JD. Immunotherapy. Current opinion in otolaryngology & head and neck surgery. 2010; 18: 206-12.

59. Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. J Allergy Clin Immunol 1992; 90: 256-62.

60. Mempel M, Rakoski J, Ring J, Ollert M. Severe anaphylaxis to kiwi fruit: Immunologic changes related to successful sublingual allergen immunotherapy. J Allergy Clin Immunol 2003; 111: 1406-9.

61. Zuidmeer-Jongejan L, Fernandez-Rivas M, Poulsen LK, Neubauer A, Asturias J, et al. FAST: towards safe and effective subcutaneous immunotherapy of persistent life-threatening food allergies. Clin Transl Allergy. BioMed Central Ltd; 2012; 2: 5.

62. Dupont C, Kalach N, Soulaines P, Legoué-Morillon S, Piloquet H, et al. Cow's milk epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivity. J Allergy Clin Immunol 2010; 125: 1165-7.

63. Agbotounou W, Martin L, Dupont B, Pascal I, Vauléon C, Benhamou PH. Epicutaneous Immunotherapy (EPIT) Is Safe for the Treatment of Peanut Allergy in Allergic Patients. Journal of Allergy and Clinical Immunology. Elsevier 2013; 131: AB91.

64. Dupont C, Bourrier T, de Blay F, Guénard-Bilbault L, Sauvage C, et al. Peanut Epicutaneous Immunotherapy (EPIT) In Peanut-Allergic Children: 18 Months Treatment In The Arachild Study. Journal of Allergy and Clinical Immunology. Elsevier 2014; 133: AB102.

65. Jones SM, Burks AW, Dupont C. State of the art on food allergen immunotherapy: oral, sublingual, and epicutaneous. J Allergy Clin Immunol 2014; 133: 318-23.

66. Mondoulet L, Dioszeghy V, Ligouis M, Dhelft V, Dupont C, et al. Epicutaneous immunotherapy on intact skin using a new delivery system in a murine model of allergy. Clinical and experimental allergy : Journal of the British Society for Allergy and Clinical Immunology. 2010; 40: 659-67.

67. Mondoulet L, Dioszeghy V, Vanoirbeek JAJ, Nemery B, Dupont C, et al. Epicutaneous immunotherapy using a new epicutaneous delivery system in mice sensitized to peanuts. Int Arch Allergy Immunol 2011; 154: 299-309.

68. Dioszeghy V, Mondoulet L, Dhelft V, Ligouis M, Puteaux E, et al. Epicutaneous immunotherapy results in rapid allergen uptake by dendritic cells through intact skin and downregulates the allergen-specific response in sensitized mice. J Immunol (Baltimore, Md. : 1950) 2011; 186: 5629-37.

69. Mondoulet L, Dioszeghy V, Puteaux E, Ligouis M, Dhelft V, et al. Intact skin and not stripped skin is crucial for the safety and efficacy of peanut epicutaneous immunotherapy (EPIT) in mice. Clin Transl Allergy 2012; 2: 22.

70. Dioszeghy V, Mondoulet L, Dhelft V, Ligouis M, Puteaux E, et al. The regulatory T cells induction by epicutaneous immunotherapy is sustained and mediates long-term protection from eosinophilic disorders in peanut-sensitized mice. Clinical and experimental allergy : Journal of the British Society for Allergy and Clinical Immunology. 2014; 44: 867-81.

71. Syed A, Garcia MA, Lyu SC, Bucayu R, Kohli A, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). J Allergy Clin Immunol. 2014; 133: 500-10.

72. Shreffler WG, Wanich N, Moloney M, Nowak-wegrzyn A. Association of allergen-specific regulatory T cells with the onset of clinical tolerance to milk protein. J Allergy Clin Immunol. American Academy of Allergy, Asthma & Immunology 2009; 123: 43-52.e7.

73. Fuentes-Aparicio V, Alonso-Lebrero E, Zapatero L, Infante S, Lorente R, et al. Induction of Treg cells after oral immunotherapy in hen's egg-allergic children. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2014; 25: 103-6.

74. Adel-Patient K, Wavrin S, Bernard H, Meziti N, Ah-Leung S, et al. Oral tolerance and Treg cells are induced in BALB/c mice after gavage with bovine β-lactoglobulin. Allergy 2011; 66: 1312-21.

75. van Wijk F, Wehrens EJM, Nierkens S, Boon L, Kasran A, et al. CD4+ CD25+ T cells regulate the intensity of hypersensitivity responses to peanut , but are not decisive in the induction of oral sensitization Clinical and Experimental Allergy. Clin Exp Allergy 2007; 37: 572-81.

76. Frischmeyer-Guerrerio PA, Keet CA, Guerrerio AL, Chichester KL, Bieneman AP, et al. Modulation of dendritic cell innate and adaptive immune functions by oral and sublingual immunotherapy. Clin Immunol 2014;155: 47-59.

77. Chin SJ, Vickery BP, Kulis MD, Kim EH, Varshney P, et al. Sublingual versus oral immunotherapy for peanut-allergic children: A retrospective comparison. J Allergy Clin Immunol. American Academy of Allergy, Asthma & Immunology; 2013; 132: 476-478.e2.

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