

Evidence Gaps in Oral Immunotherapy for Food Allergy

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Abstract

Purpose of review IgE-mediated food allergy (FA) is a potentially life-threatening condition with negative impact on the quality of life of patients and their family. It has been emerging as a public health priority in westernized countries in the recent two decades. The current standard approach to FA consists of the strict avoidance of the triggering food and keeping rescue medication readily available in the event an allergic reaction occurs. However, an elimination diet may be difficult and frustrating, above all for those foods (e.g., milk and egg) that are pivotal in the common diet.

Recent findings Oral immunotherapy (OIT) may increase the amount of food that the patient can intake without reaction, and reduce the risk of potential life-threatening allergic reactions. As its enormous potential, OIT is currently considered the most promising treatment for FA. However, many gaps are still unsolved. OIT is logistically demanding, time-consuming, and most patients are affected by side effects though often mild.

Summary The aim of this review is to shed light on the main needs in OIT that are currently unmet in order to stimulate in the near future the development of longitudinal, prospective, well-designed studies with the final goal of a “precision medicine”, tailored on each single patient suffering from FA.

Introduction

IgE-mediated food allergy (FA) is a potentially life-threatening condition [1, 2]. Its incidence has increased significantly over the past two decades, affecting currently around 6–8% of children and 2–3% of adults in westernized countries [1, 3]. It has been emerging as a public health priority, also for the negative impact on the quality of life (QoL) of patients and their family, as anxiety, fear of accidental exposures, requiring changes in dietary habits and social interactions [4, 5].

Most children with allergy to cow's milk (CM), hen's egg (HE), soy, and wheat naturally overgrow their allergies over time [6–11]. On the contrary, less than 20% of peanut- or tree nut-allergic patients spontaneously develop tolerance to these foods [12, 13]. The latter are responsible for the majority of fatal or near-fatal food allergic reactions [14, 15].

Nevertheless, the current standard approach to FA consists of the strict avoidance of the triggering food and keeping epinephrine, corticosteroids, and antihistamines readily available as rescue medication in the event an allergic reaction occurs [16••, 17]. However, an elimination diet may be difficult and frustrating in patients

with persistent FA, above all for those foods (such as CM and HE) that are pivotal in the common diet and, therefore, ubiquitous in store-bought foods, and in home and restaurant recipes [18]. Nevertheless, despite efforts to comply with this diet, accidental exposures leading to adverse reactions are frequent [19].

Oral immunotherapy (OIT) is a potential curative treatment in food allergies. Since the first case described in 1908 [20], it has gained momentum above all over the last decade. Recently, the European Academy of Allergy and Clinical Immunology (EAACI) has developed a systematic review and meta-analysis [21••] in order to assess the current evidence base in relation to evaluating allergen immunotherapy (AIT) for the treatment of FA and, therefore, provide clinical recommendations.

The aim of this review is to shed light on the main needs in OIT that are currently unmet in order to stimulate in the near future the development of longitudinal, prospective, well-designed studies with the final goal of a "precision medicine" tailored on each single patient suffering from FA.

Oral immunotherapy

OIT is an active treatment for IgE-mediated food allergies. It implies the reiterated administration of the culprit food. Most protocols consist of three successive phases: initial escalation, up-dosing, and maintenance. Usually, the initial dose escalation starts with incremental administration of small amounts of food allergen, below the threshold of reactivity, usually over 1–2 days. The up-dosing begins with daily ingestion of the highest dose tolerated during escalation phase, with doses increased usually weekly or biweekly until the maintenance dose is reached. In the maintenance phase, patients consume the food regularly (usually daily) for months or years. However, protocols are widely heterogeneous among OIT studies. There are some rush protocols and slow up-dosing regimens with or without an initial dose escalation day. Therefore, their results are to some extent not comparable [21••].

OIT may increase the amount of food that the patient can intake without reaction, and reduce the risk of potential life-threatening allergic reactions [21••]. There is strong evidence for the effectiveness during treatment, also referred as "desensitization" [21••], defined as the ability to safely assume the food antigen, while consuming the OIT doses regularly. The ideal goal of FA-AIT lies on the post-discontinuation effectiveness, also known as "tolerance" or "sustained unresponsiveness", referred to the absence of symptoms after ingestion of a normal serving of the culprit despite a period of absence of exposure.

However, this is one of the major issues to be clarified [21••].

As its enormous potential, OIT is currently considered the most promising treatment for FA. However, many gaps are still unsolved. OIT is logistically demanding, time-consuming, and most patients are affected by side effects though often mild. The main gaps are summarized in Table 1 and assessed below through the manuscript.

Standardized products and vehicles

The availability of medicinal products is pivotal in order to provide both a reliable diagnosis of clinical allergy (e.g., IgE assays, skin prick testing, and oral food challenge) and an effective treatment (OIT). To our best knowledge, currently, there are no authorized medicinal products in the field of food allergy. The landscape of products used in the different trials is enormously heterogeneous ranging from natural-raw form [22] to different processed foods [23]. It is known that not only the presence of the allergens can vary inside a food (e.g., egg white and yolk) but also the duration and type of processing (such as homogenization, dry and moist thermal processing, fermentation, hydrolysis, irradiation) and the food matrix may impact on the allergenic potential and, therefore, on the ability of foods to elicit allergic reactions [24]. For instance, an extensive heating diminishes the allergenicity of egg white proteins, and the majority (50–85%) of egg allergic patients are tolerant to baked egg products [25]; the boiling could reduce and, on the contrary, the roasting aggravate the allergenicity of peanut proteins [26]. Furthermore, most studies have focused on peanut, milk, or egg. Other foods should be investigated.

The availability of standard product results is urgent. To fill this gap, a collaboration among clinical investigators, pharmaceutical companies, and regulators is needed.

Table 1. Gaps in the evidence of FA-AIT

Gaps in the evidence of FA-AIT

- ❖ Standardized products and vehicles
- ❖ Validated and shared protocols
- ❖ Definition of clinically relevant outcomes of effectiveness
- ❖ Improvement of post-discontinuation treatment effectiveness
- ❖ Safety
- ❖ Adjunctive treatment(s)
- ❖ Impact on quality of life
- ❖ Cost-effectiveness
- ❖ Mechanisms of action
- ❖ Markers of response
- ❖ Identification of the most suitable candidates
- ❖ “Precision medicine” algorithms

Validated and shared protocols

Many questions remain in optimizing OIT with respect to the optimal dose of the culprit food allergen to be used for maintenance, the length of the maintenance period, and the sustainability of the desensitization process.

OIT studies are widely heterogeneous. First, the study design may be different (open label versus double blinded, placebo-controlled; randomized controlled trials versus controlled clinical trial; multi-site versus single-site; and so on). Inclusion and exclusion criteria for enrollment differ as well. Some studies excluded patients with severe allergies [27] and vice versa; others included only patients with severe FA [28]. There is lack of evidence in adult population. Most studies have been conducted in children, some of them in preschool age [29] and other in mixed population (children plus adults) [21••]. As the natural history of allergies differs among the foods [6–11], it should be useful to perform subgroup analyses based on different ranges of age in childhood in order to better understand the best timing/time window to start OIT for each culprit food. However, most studies pool data from wide age range and subgroup analyses are not feasible [21••].

Duration and dosing in each OIT phase differ among the studies: some regimens have a “rush” phase [30], others a slower schedule with smaller increasing doses and/or interval-length in between [31]. The target maintenance dose ranges widely also for the same food. For example, the study from Anagnostou et al. considered as target maintenance dose a minimum of 800 mg of peanut [32], Tang et al. 2 g [33], and Varshney et al. refer to 4 g of peanut [34]. This variability should be considered in the analyses.

Among the main needs still unanswered, to establish validated protocols with optimal dosing and duration of therapy has a high priority. Furthermore, this point relates to the requirements to define clinically relevant outcomes of effectiveness. It is yet unclear which duration and frequency of ingestion of the allergic food(s) are required to maintain desensitization. We are lacking criteria with which to evaluate and diagnose permanent tolerance, too. To meet these needs, a careful analysis of existing data, but above all, new well-designed observation and controlled trials, and a consensus discussion involving patients, clinicians, pharmaceutical companies, and regulatory agencies are demanded.

Improvement of post-discontinuation treatment effectiveness

In comparison to desensitization (effectiveness during treatment), post-discontinuation treatment effectiveness (also referred as “tolerance” and “sustained unresponsiveness”) has been evaluated in far fewer trials. Furthermore, there has also been heterogeneity in the approach to evaluating it, as different studies have varied both the duration of maintenance and the abstinence period (2 weeks to few months), sometimes within the same trial [22, 23, 27, 35–38]. Re-challenge after varying periods of avoidance has shown rates of non-reactivity to a food challenge ranging from 18–78% [22, 23, 27, 35–38]. Most subjects still maintained a state of desensitization to a threshold level higher than their screening challenge. To establish validated protocols with optimal dosing and duration of therapy has high priority in order to assess the

acquisition of the ability to safely consume a normal serving of foods containing the trigger allergen despite a period of absence of exposure.

Improvement of safety

Besides efficacy, safety is underpinning in any treatment. Furthermore, in AIT, safety is particularly important, as it is typically a pediatric condition, and potential adverse events are mostly immediate onset, food-induced IgE-mediated reactions, which can lead to anaphylaxis. Thus far, no fatality has been reported in literature, but systemic reactions are consistently described as common. Patients in the OIT-active arm have a 9% higher risk of systemic reaction than those in the placebo groups (RR 1.16, 95% CI 1.03–1.30) [21••]. However, the rate of adverse events (AEs) during OIT largely varies in published studies, but mild AEs are predominant, and only a few dropped out for this reason [21••]. Reporting, description, and grading of AEs are less than ideal, and this makes it difficult to compare the real occurrence and severity of specific type of AEs among studies [39•]. This drawback also affects the identification of risk factors and their avoidance. Known risk factors include exercise, infection, and menses which may increase the risk of reactions [40], especially during the maintenance phase(s) of OIT, when patients continue treatment at home. However, in OIT studies, most adverse reactions have been reported in the absence of these risk factors [21••].

Patients with higher serum specific IgE levels (> 8.85 kU/L to ovomucoid in HE-OIT and > 50 kU/L to CM in CM-OIT), higher skin tests (> 9 mm to milk in CM-OIT), low threshold of reactivity and/or severe reactions in the entry food challenge or upon accidental exposure, and underlying asthma seem to be at high risk for repeated reactions and early FA-AIT failure [41]. However, further larger observational and controlled trials and the establishment of a common registry of systemic adverse events are needed for a precise identification of biomarkers and predictors of severe AEs and, therefore, the necessity of safety measures (such as longer and slower up-dosing phase, premedication with H1-antihistamines, chromones, or even monoclonal anti-IgE antibody).

Adjunctive therapies to OIT

Novel therapeutic approaches are being developed to improve FA-AIT, most of them in preclinical or early clinical trials. Among the adjunctive therapies to OIT so far evaluated, the most promising seems to be omalizumab. The latter is a humanized monoclonal IgG antibody, binding the freely circulating human IgE but not mast cell- or basophil-bound IgE. Once circulating IgE is bound by anti-IgE, it is unable to bind to its specific high-affinity receptor (FcεRI) on mast cells and basophils. These antigen-antibody complexes are then cleared from the circulation. Pretreatment with anti-IgE could potentially prevent the systemic reactions experienced with OIT while achieving the beneficial effects of desensitization. Although anti-IgE therapy is expensive and requires frequent administration to maintain low the concentration of freely circulating IgE, it could theoretically be used quite effectively in conjunction with OIT. There is already evidence that omalizumab may markedly reduce adverse reactions due to OIT compared to placebo [39•, 42, 43]. However, further studies are waited to better clarify

optimal doses and schedule of this combined treatment. Additionally, OIT is an allergen-specific therapy and, therefore, treating multiple allergies results in complex, long, and expensive therapy. Theoretically, one such combined approach could be the best therapeutic option in patients with allergies to multiple foods and/or having failed a previous treatment with OIT alone [44].

As bacteria are potent stimulants of Th1 immune responses, modified bacterial products are under investigation as adjuvants for FA-AIT [33, 45].

Impact on quality of life and cost-effectiveness

Food allergy is associated with a negative impact on the quality of life of patients and their families, even more so than other chronic childhood diseases [4, 5, 46]. The burden of FA on caregivers (buying special foods, limiting social encounters, time lost from work, changing careers, and emergency room visits) has been reported to play a predominant role in the total annual economic burden of FA [4, 5, 47, 48]. On the other side, OIT, though a promising therapy for food allergy [21••], can be linked to anxiety. OIT is logistically demanding, time-consuming, and most patients are affected by side effects, mostly mild but sometimes severe and/or repeated to induce OIT drop-out [21••]. OIT could possibly lead to significant and long-term improvements in caregiving [21••, 32, 48]. Evidence on this regard is limited. Validated measures of quality of life should be included in future food allergy clinical trials and baseline characteristics that could potentially help identify patients who would benefit the most from OIT should be better identified [32, 48].

In terms of health economics, there is lack of evidence on cost-effectiveness of OIT in FA and studies are needed [21••].

Mechanisms of action of OIT and markers of response

Mechanisms of action in allergen-specific immunotherapy have been explored for allergic diseases such as allergic rhinitis and insect venom allergy and are likely to be similar in food allergy immunotherapy. Protection from reactions in the early stages of immunotherapy is due to decreased activation of mast cells and basophils, which has been seen as early as in the first 3–4 months of OIT [27, 49–51]. In addition, many other cell types might contribute to early immunotherapy responses but this needs further investigations. The induction of peripheral T cell tolerance is a pivotal step induced by immunotherapy, and in different models, various changes in antigen specific T cell populations correlated with tolerance, including increased T regulatory cells, decreased Th2 cells, and increased anergic T cells [52–54]. The proportion of antigen-specific T cell subsets and the change in the dominant subset may skew towards allergy vs. tolerance [52]. OIT can induce changes in immunoglobulin subsets. Patients undergoing peanut OIT for a median of 41 months had serum increased levels of peanut-specific IgG4 with de novo specificities associated with reduced serum levels of peanut-specific IgE. [55] Although increasing evidence supports a role for antigen-specific IgG4 in directly inducing tolerance, IgG4 levels may also correlate with other mechanisms promoting tolerance.

There is still a long way to go to determine the extent to which the mechanisms underlying “desensitization” vs. “long-term tolerance” are similar or different and to develop tests that can reliably determine the immune status of food-allergic subjects.

Precision medicine

There is growing interest towards the concept of “Precision Medicine” in different medical fields, including allergy. As the National Research Council explains, “Precision Medicine refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology or prognosis of those diseases they may develop, or in their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not. Although the term ‘personalized medicine’ is also used to convey this meaning, that term is sometimes misinterpreted as implying that unique treatments can be designed for each individual.”

To identify the most suitable candidates to OIT and algorithms for treatments tailored on individual patients are still needed. Analysis of existing data and biological samples, new controlled trials, and consensus discussion are requested.

Conclusions

OIT represents an emerging reality as an active treatment for IgE-mediated food allergies. However, currently, many issues remain unanswered. Clinical trials for OIT so far conducted are extremely heterogeneous. Differences encompass dosage, amount and frequency, duration of build-up and maintenance phases, type of allergen used, patient characteristics, reporting in adverse events, and adjuvant therapies.

Consequently, studies have also shown variation in results. Much larger, longitudinal and well-designed studies using more homogenous protocols are needed in order to standardize products and to validate protocols (optimal doses and schedule); to assess the sustainability of the desensitization process; to improve the post-discontinuation effectiveness, the safety, and the impact on quality of life; and to identify the role of adjunctive therapies (such as omalizumab and probiotics).

Although there is still a long way towards a precision medicine, tailored on each patient, OIT is poised for clinically important advances.

Compliance with ethics standards

Conflict of interest

Stefania Arasi declares that she has no conflict of interest.

Giovanni Pajno declares that he has no conflict of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011;128:e9–17.
 2. Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. *J Allergy Clin Immunol*. 2014;133:291–307.
 3. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol*. 2007;120:638–46.
 4. Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. *Allergy*. 2010;65:933–45.
 5. Lieberman JA, Sicherer SH. Quality of life in food allergy. *Curr Opin Allergy Clin Immunol*. 2011;11:236–42.
 6. Savage JH, et al. The natural history of egg allergy. *J Allergy Clin Immunol*. 2007;120:1413–7.
 7. Skripak JM, Matsui EC, Mudd K, Wood RA. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol*. 2007;120:1172–7.
 8. Wood RA, Sicherer SH, Vickery BP, Jones SM, Liu AH, Fleischer DA, et al. The natural history of milk allergy in an observational cohort. *J Allergy Clin Immunol*. 2013;131:805–12.
 9. Sicherer SH, Wood RA, Vickery BP, Jones SM, Liu AH, Fleischer DM, et al. The natural history of egg allergy in an observational cohort. *J Allergy Clin Immunol*. 2014;133:492–9.
 10. Keet CA, Matsui EC, Dhillon G, Lenehan P, Paterakis M, Wood RA. The natural history of wheat allergy. *Ann Allergy Asthma Immunol*. 2009;102:410–5.
 11. Savage JH, Kaeding AJ, Matsui EC, Wood RA. The natural history of soy allergy. *J Allergy Clin Immunol*. 2010;125:683–6.
 12. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. *J Allergy Clin Immunol*. 2001;107:367–74.
 13. Fleischer DM, Conover-Walker MK, Matsui EC, Wood RA. The natural history of tree nut allergy. *J Allergy Clin Immunol*. 2005;116:1087–93.
 14. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol*. 2001;107:191–3.
 15. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001–2006. *J Allergy Clin Immunol*. 2007;119:1016–8.
 - 16.•• Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al., EAACI Food Allergy and Anaphylaxis Guidelines Group. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy*. 2014;69:1008–25.
- The guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) on the recognition, assessment, and management of food allergy and anaphylaxis.
17. Sampson HA, Aceves S, Bock SA, James J, Jones S, Lang D, et al. Food allergy: a practice parameter update—2014. *J Allergy Clin Immunol*. 2014;134:1016–25. e43.
 18. Ford LS, Taylor SL, Pacenza R, Niemann LM, Lambrecht DM, Sicherer SH. Food allergen advisory labeling and product contamination with egg, milk, and peanut. *J Allergy Clin Immunol*. 2010;126:384–5.
 19. Boyano-Martínez T, García-Ara C, Pedrosa M, Díaz-Pena JM, Quirce S. Accidental allergic reactions in children allergic to cow's milk proteins. *J Allergy Clin Immunol*. 2009;123:883–8.
 20. Schofield AT. A case of egg poisoning. *Lancet*. 1908;1:716.
 - 21.•• Nurmatov U, Dhimi S, Arasi S, Pajno GB, Fernandez-Rivas M, Muraro A, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy*. 2017. <https://doi.org/10.1111/all.13124>.
- Updated systematic review and meta-analysis conducted by EAACI and assessing the current evidence base in relation to evaluating food allergen immunotherapy for the treatment of food allergy.
22. Caminiti L, Pajno GB, Crisafulli G, Chiera F, Collura M, Panasci G, et al. Oral immunotherapy for egg allergy: a double blind placebo controlled study, with postdesensitization follow-up. *J Allergy Clin Immunol Pract*. 2015;3:532–9.
 23. Leonard SA. Baked egg and milk exposure as immunotherapy in food allergy. *Curr Allergy Asthma Rep*. 2016;16:32.
 24. Calvani M, Arasi S, Bianchi A, Caimmi D, Cuomo B, Dondi A, et al. Is it possible to make a diagnosis of raw, heated, and baked egg allergy in children using cutoffs? A systematic review. *Pediatr Allergy Immunol*. 2015;26:509–21.

25. Escudero C, del Rio PR, Sanchez-Garcia S, Perez-Rangel I, Perez-Farinos N, Garcia-Fernandez C, et al. Early sustained unresponsiveness after short-course egg oral immunotherapy: a randomized controlled study in egg-allergic children. *Clin Exp Allergy*. 2015;45:1833–43.
 26. Verhoeckx KC, Vissers YM, Baumert JL, Faludi R, Feys M, Flanagan S, et al. Food processing and allergenicity. *Food Chem Toxicol*. 2015;80:223–40.
 27. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, et al. Oral immunotherapy for treatment of egg allergy in children. *N Engl J Med*. 2012;367:233–43.
 28. Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *J Allergy Clin Immunol*. 2008;121:343–7.
 29. Vickery BP, Berglund JP, Burk CM, Fine JP, Kim EH, Kim JJ, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol*. 2017;139:173–81.
 30. Barbi E, Longo G, Berti I, Neri E, Saccari A, Rubert L, et al. Adverse effects during specific oral tolerance induction: in-hospital "rush" phase. *Eur Ann Allergy Clin Immunol*. 2012;44:18–25.
 31. Pajno GB, Caminiti L, Salzano G, Crisafulli G, Aversa T, Messina MF, et al. Comparison between two maintenance feeding regimens after successful cow's milk oral desensitization. *Pediatr Allergy Immunol*. 2013;24:376–81.
 32. Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. *Lancet*. 2014;383:1297–304.
 33. Tang MLK, Ponsonby AL, Orsini F, Tey D, Robinson M, Su EL, et al. Administration of a probiotic with peanut oral immunotherapy: a randomized trial. *J Allergy Clin Immunol*. 2015;135:737–44.
 34. Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol*. 2011;127:654–60.
 35. Narisety SD, Frischmeyer-Guerrero PA, Keet CA, Gorelik M, Schroeder J, Hamilton RG, 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*. 2015;135:1275–82.e1–6.
 36. Staden U, Rolinck-Werninghaus C, Brewe F, Wahn U, Niggemann B, Beyer K. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. *Allergy*. 2007;62:1261–9.
 37. Vickery BP, Scurlock AM, Kulis M, Steele PH, Kamilaris J, Berglund JP, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *J Allergy Clin Immunol*. 2014;133:468–75.
 38. Jones SM, Burks AW, Keet C, Vickery BP, Scurlock AM, Wood RA, et al. Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy. *J Allergy Clin Immunol*. 2016;137:1117–27.
 39. Pajno GB, Nadeau KC, Passalacqua G, Caminiti L, Hobson B, Jay DC, et al. The evolution of allergen and non-specific immunotherapy: past achievements, current applications and future outlook. *Expert Rev Clin Immunol*. 2015;11:141–54.
- This is a detailed report describing the evolution of allergen and non-specific immunotherapy over time, looking at the future perspectives in the treatment of allergic diseases.
40. Pajno GB, Caminiti L, Chiera F, Crisafulli G, Salzano G, Arasi S, et al. Safety profile of oral immunotherapy with cow's milk and hen egg: a 10-year experience in controlled trials. *Allergy Asthma Proc*. 2016;37:400–3.
 41. Vázquez-Ortiz M, Alvaro-Lozano M, Alsina L, García-Paba MB, Piquer-Gibert M, Giner-Muñoz MT, et al. Safety and predictors of adverse events during oral immunotherapy for milk allergy: severity of reaction at oral challenge, specific IgE and prick test. *Clin Exp Allergy*. 2013;43:92–102.
 42. Wood RA, Kim JS, Lindblad R, Nadeau K, Henning AK, Dawson P, et al. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. *J Allergy Clin Immunol*. 2016;137:1103–10.
 43. MacGinnitie AJ, Rachid R, Gragg H, Little SV, Lakin P, Cianferoni A, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. *J Allergy Clin Immunol*. 2016;137(2):AB194.
 44. Bégin P, Dominguez T, Wilson SP, Bacal L, Mehrotra A, Kausch B, et al. Phase 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using omalizumab. *Allergy Asthma Clin Immunol*. 2014;10:7.
 45. Wood RA, Sicherer SH, Burks AW, Grishin A, Henning AK, Lindblad R, et al. A phase 1 study of heat/phenol-killed, *E. coli*-encapsulated, recombinant modified peanut proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) for the treatment of peanut allergy. *Allergy*. 2013;68:803–8.
 46. Gupta RS, Springston EE, Smith B, Kim JS, Pongratic JA, Wang X, et al. Food allergy knowledge, attitudes, and beliefs of parents with food-allergic children in the United States. *Pediatr Allergy Immunol*. 2010;21:927–34.
 47. Gupta R, Holdford D, Bilaver L, Dyer A, Holl JL, Meltzer D. The economic impact of childhood food allergy in the United States. *JAMA Pediatr*. 2013;167:1026–31.
 48. Arasi S, Otani IM, Klingbeil E, Bégin P, Kearney C, Dominguez TL, et al. Two year effects of food allergen immunotherapy on quality of life in caregivers of children with food allergies. *Allergy Asthma Clin Immunol*. 2014;10:57.
 49. Keet CA, Frischmeyer-Guerrero PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S, et al. The safety

- and efficacy of sublingual and oral immunotherapy for milk allergy. *J Allergy Clin Immunol.* 2012;129:448–55. 55, e1–5
50. Syed A, Garcia MA, Lyu SC, Bucayu R, Kohli A, Ishida S, 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. e11.
51. Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. *J Allergy Clin Immunol.* 2009;124:292–300. e1–97
52. Akdis M, Verhagen J, Taylor A, Karamloo F, Karagiannidis C, Cramer R, et al. Immune responses in healthy and allergic individuals are characterized by a fine balance between allergen-specific T regulatory 1 and T helper 2 cells. *J Exp Med.* 2004;199:1567–75.
53. Smaldini PL, Delgado MLO, Fossati CA, Docena GH. Orally-induced intestinal CD4+ CD25+ FoxP3+ Treg controlled undesired responses towards oral antigens and effectively dampened food allergic reactions. *PLoS One.* 2015;10:e0141116.
54. Aslam A, Chan H, Warrell DA, Misbah S, Ogg GS. Tracking antigen-specific T-cells during clinical tolerance induction in humans. *PLoS One.* 2010;5:e11028.
55. Vickery BP, Lin J, Kulis M, Fu Z, Steele PH, Jones SM, et al. Peanut oral immunotherapy modifies IgE and IgG 4 responses to major peanut allergens. *J Allergy Clin Immunol.* 2013;131:128–34. e3.