

REVIEW

Food allergy—From food avoidance to active treatment

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Abstract

The prevalence of food allergy (FA) has increased too rapidly, possibly due to environmental factors. The guidelines recommend strict allergen avoidance, but FA is still the main cause of anaphylaxis in all age groups. Immunotherapy is the only treatment able to change the course of allergic disease, and oral immunotherapy (OIT) is the more effective route in FA. However, it carries the risk of adverse reactions, including anaphylaxis. To improve OIT safety, adjuvant therapy with the immunoglobulin E (IgE) monoclonal antibody omalizumab has been extensively used. Results suggest particular benefit in patients with high risk of fatal anaphylaxis. An alternative approach is to use omalizumab instead of OIT to prevent severe allergic reactions upon accidental exposure. This paper reviews current evidence regarding IgE-mediated FA, focusing on natural tolerance and food sensitization acquisition, and on avoidance measures and their limitations.

1 | INTRODUCTION

The prevalence of food allergy has been increasing over the past few decades in line with other allergic diseases,¹ currently affecting approximately 5% of the population in Western countries.² This increase has occurred too rapidly to be explained by genetics alone. Although still today the knowledge of the pathogenesis of food allergy remains to be fully elucidated,¹ it is known that host genetics, epigenetics and environmental exposures^{1,3} play a role in determining food allergy risk. It has also been hypothesized that the increase in food allergy may relate to the simultaneous rise in vitamin D insufficiency and/or vitamin A sufficiency.⁴

Once the allergen is identified, all guidelines recommend strict allergen avoidance.^{5–10} In fact, this is the most effective form of preventing a reaction that can range from a non-serious skin reaction to a potential life-threatening anaphylactic reaction.¹¹ However, guaranteeing strict avoidance may be troublesome. There is the potential for nutritional deficiencies,^{5,8–11} accidental exposure, cross-contamination or even mislabelling of processed foods, despite existing labelling legislation.^{5,6,8,9,11–15} Currently, precautionary allergen labelling (PAL; ‘may contain traces’)^{6,9,12,14} is an emerging issue due to excessive PAL by food processing companies, in order to avoid liability. This restricts patients to a diet very difficult to comply with, restricting the food-allergic

patients to extremely limited food choices and leading to PAL disregard.

Food allergies impair quality of life (QoL) and are still the main cause of anaphylaxis in all age groups. Forty to 100% of fatal anaphylaxis occur due to foods consumed or prepared outside the home.¹¹ Patient education is crucial. In the case of infants and children, families, close relatives, friends and caregivers should be properly informed^{5,14} of how to intervene when an anaphylactic reaction occurs, given these are potentially fatal.^{8,11,16} Due to all the aforementioned, active therapy should be considered. Immunotherapy with allergens is the only treatment that can change the course of allergic disease. This is achieved by inducing allergen-specific immune tolerance in a subset of patients. Such induced tolerance^{11,17} or sustained unresponsiveness,^{17,18} defined as the ability to ingest a previously allergenic food without symptoms regardless of long avoidance periods or irregular consumption, is the goal of immunotherapy with food allergens. However, and due to the risk of adverse reactions, including anaphylaxis,² immunotherapy with food allergens is not recommended for routine clinical use. The procedure should be performed only in highly specialized centres with expert staff and adequate equipment.^{2,17,19} Immunotherapy has several routes of administration and has been performed subcutaneously, sublingually, epicutaneously and orally. Oral immunotherapy (OIT) is more effective for food allergy than the other routes, in part because much larger doses can be administered. However, safety has been a major limitation.²⁰

Currently, and in order to improve the safety profile of OIT and maintain or increase its efficacy, adjuvant therapy with the IgE monoclonal antibody omalizumab has been extensively used in severe peanut allergy, milk allergy, egg allergy and multiple food allergy, with significant clinical improvement both in adults and children.^{2,11,20-47} Moreover, omalizumab has the ability to prevent systemic reactions to OIT, thus enabling completion of treatment in patients who otherwise would have to stop it prematurely.^{17,24,28,31-33,37,42,43,45,46,48-53} Taken together these results suggest that omalizumab may be particularly beneficial in the most severe patients, at high risk of fatal anaphylaxis. Omalizumab also allows a more rapid desensitization^{2,11,20,26,40,42,45,53} and has been shown to reduce the time to achieve maintenance dose.^{20,45,52,53} An alternative approach to OIT is to use omalizumab as monotherapy, to prevent severe reactions upon allergen exposure. This approach seems effective, as reported in pilot experiences designed to establish proof of concept of the effectiveness of omalizumab monotherapy in food-allergic patients.⁴⁶

This paper will review current evidence regarding IgE-mediated food allergies, focusing on acquisition of natural tolerance and food sensitization, avoidance measures and their limitations, immunotherapy with food allergens and the usefulness of omalizumab in food allergies.

2 | ACQUISITION OF NATURAL TOLERANCE AND FOOD SENSITIZATION

Acquisition of natural tolerance and food sensitization depends on genetic, hereditary, environmental, socio-economic and cultural factors.⁵⁴ The diet in the first year of life influences the development of food allergy.^{54,55}

Infant feeding guidelines aim to prevent allergy. However, existing guidelines, although mainly consensual, are vague. The European guidelines recommend exclusive breastfeeding for all infants for at least the first 4-6 months of life. If breastfeeding is insufficient or not possible, infants at high risk can be recommended a hypoallergenic formula with a documented preventive effect for the first 4 months. However, this practice has been challenged recently.⁵⁶ There seems to be no need to avoid introducing complementary foods beyond 4 months. Currently, the evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic foods after 4 months once weaning has commenced, irrespective of atopic heredity. There is also no evidence supporting the use of prebiotics or probiotics for food allergy prevention.⁵⁷ A review of the American and Canadian Guidelines similarly concluded that delayed introduction of allergenic foods does not prevent allergic disease.⁵⁸ Concerning breastfeeding, this review does not differ much from the European Guidelines, recommending exclusive breastfeeding for 6 months. However, there is no evidence that exclusive breastfeeding helps to prevent food allergy in infants.

With few exceptions, allergenic foods may be introduced into children's diets between the ages of 4 and 6 months. Once introduced, regular exposure to the food is important to maintain tolerance, although the optimal frequency is not known.⁵⁸ Earlier Western recommendations promoted food avoidance and delayed introduction of several foods, but these were later withdrawn as studies failed to show beneficial effects of these avoidance measures.^{3,59-62} A consensus statement from several academies concerning specifically peanut allergy recommends that peanut-containing products should be introduced early in life (4-11 months old) in high-risk populations and in countries where peanut allergy is prevalent. In fact, delaying the introduction of peanuts may be associated with a higher risk of developing peanut allergy.⁶³ This active prevention recommendation is based on two recent RCTs.^{64,65}

All these recommendations are based on the current knowledge regarding the immune mechanisms responsible for natural tolerance and food sensitization, represented in Figure 1. Food antigens present in the gut lumen are captured by dendritic cells and carried to the mesenteric lymph node.

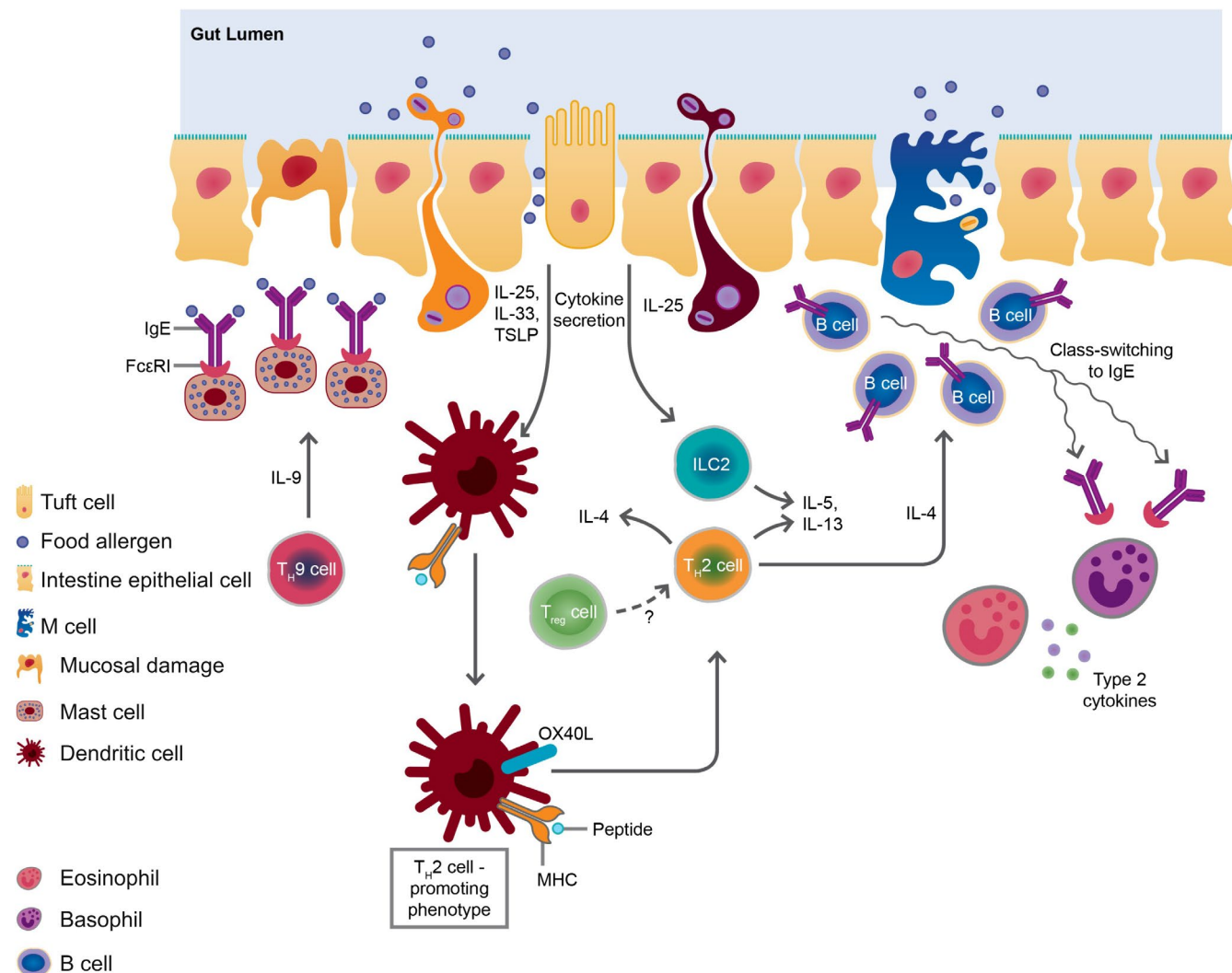


FIGURE 1 Food antigens present in the gut lumen are captured by extending dendrites from dendritic cells CX3CR1 (1) between the intestinal epithelial cells, via M cells localized in Payer's patches and via paracellular or transcellular routes and carried by CD11c + CD103 + DC (2) to the mesenteric lymph node. Epithelial cells damage or inflammation may contribute to antigen sampling. Intestinal tuft cells constitutively express IL-25 and have an essential role in the initiation of immune response. IL-33 and thymic stromal lymphopoietin (TSLP) are also released from epithelial cells, driving Th2 responses via OX40L on DCs and inducing allergic sensitization. Th2 cells and innate type 2 lymphoid cells (ILC2) that produce interleukin-4 (IL-4), IL-5 and IL-13 are involved in type 2 immunity. These cells promote basophil, mast cell and eosinophil activation and food-specific immunoglobulin E (IgE) production. Besides Th2 cells, newly described CD4 + T helper subsets, including Th9 that may play a role in allergic diseases by increasing tissue mast cell accumulation. IgE produced by plasma cells binds to high-affinity IgE receptors on mast cells and basophils. During a second exposure, the allergen binds to and cross-links IgE antibodies present on the surface of basophils and mast cells promoting the release of inflammatory mediators. Mast cells are central to both local and systemic manifestations of food allergy. Antigen can trigger distal reactions, such as urticaria and gastrointestinal manifestations

Intestinal tuft cells have an essential role in the initiation of immune response. Th2 cells and innate type 2 lymphoid cells, involved in type 2 immunity, promote basophil, mast cell and eosinophil activation and food-specific immunoglobulin E (IgE) production. IgE produced by plasma cells binds to high-affinity IgE receptors on mast cells and basophils. During a second exposure, the allergen binds to and cross-links IgE antibodies present on the surface of basophils and

mast cells promoting the release of inflammatory mediators. Mast cells are central to both local and systemic manifestations of food allergy.

Over the last 10-15 years, an approach termed 'baby-led weaning' has grown in popularity. This approach involves allowing infants to self-feed family foods, encouraging the infant to set the pace and intake of the meal. Despite significant interest in this approach, there is limited evidence suggesting

that it may lead to positive outcomes, namely in food allergy. Further research is needed, particularly to understand baby-led weaning across different populations.⁶⁶

The authors agree that breastfeeding should be encouraged. The introduction of potentially allergenic foods should not be delayed although further studies are necessary to define optimal timing for specific foods.

The majority of the population does acquire natural tolerance to all types of foods. However, 5%-6% of adults and 8% of children develop food allergy,¹¹ although these prevalences vary by region.^{5,7,67} What should be done when these food allergies occur?

3 | AVOIDANCE MEASURES AND THEIR LIMITATIONS

Once the allergen is identified, all guidelines recommend strict allergen avoidance.⁵⁻¹⁰ However, and although being the most effective form of preventing a reaction, guaranteeing avoidance is not simple, for several reasons. Depending on the allergen, extensive and long-term avoidance can result in nutritional deficiencies, which are especially important in infants and children, and should therefore be monitored by a dietician with specific competences in food allergy.^{5,8-11} On the other hand, accidental exposure is relatively common,^{5,6,8,9,11-15} since some ubiquitous allergens exist in pharmaceutical agents, probiotics,⁹ sweets, cold meats, pasta, beer, wine, cosmetic products⁸ and vaccines.¹⁴

One study in peanut-allergic children found that by 3 years 50% had been accidentally exposed and by 5 years 75% had been exposed. Another study in peanut-allergic children found inadvertent peanut ingestion rates of 14% per year.¹³ Younger children were particularly at risk whilst at children's parties and in the care of extended family or friends.¹³ Moreover, an annualized reaction rate of 0.81 per year for all foods, with 56% of children having more than 1 reaction, has been reported in infants receiving care in food allergy centres.¹⁴ Most reactions were attributed to lack of vigilance (e.g. label checking errors and unintentional ingestion), with additional errors including cross-contact in meal preparation and food not provided by the parents. The severity of these unpredictable and sudden reactions may be exacerbated by the presence of cofactors.⁶⁸ However, approximately 11% of reactions were attributed to non-accidental exposure, indicating that in some cases, families might have reintroduced the allergenic food without medical supervision, to explore whether it would be tolerated.⁶⁹

Importantly, avoidance diets impair QoL^{5,8,11,69,70} and carry significant social, psychological^{11,64,69,71} and economic^{11,64} burdens to patients and families. Another problem in implementing a strict avoidance diet is intentional risky behaviour, especially in teenagers/young adults,^{12,13} due to peer

pressure, shame or even fear. Indeed, it has been reported that 45% of children with food allergies are bullied, consequently lowering their QoL and increasing anxiety.⁶⁹

Finally, and due to all the above reasons, it is of the utmost importance that patients, families, close relatives, friends and caregivers are aware of the course of action to take when an anaphylactic reaction occurs.^{8,11,16} One study reported that of 11.4% anaphylactic reactions, only 29% were treated with epinephrine due to one of the following reasons: the caregiver did not recognize the severity, epinephrine was unavailable, or the caregiver was afraid to administer it.⁶⁹ In fact, risk factors for fatal anaphylaxis are delay or failure in using epinephrine, teenager/young adult and failure to recognize symptoms as anaphylaxis.¹³ Finally, food allergies are still the main cause of anaphylaxis in all age groups, with 40%-100% of fatal anaphylaxis occurring due to foods consumed or prepared outside the home.¹¹ Some guidelines and reviews propose measures to avoid these situations.^{7,72}

Children should be re-evaluated at regular intervals for assessment of tolerance and to avoid inappropriate or unnecessarily lengthy avoidance diets.^{5,9,10} The most common outgrown food allergies include cow's milk and egg allergies, whilst allergy to shellfish and peanuts/tree nuts are seldom outgrown.⁷³

Given the limitations of avoidance measures, and especially in patients with severe reactions to ubiquitous allergens, active therapy, namely tolerance induction, should be considered. However, it should be noticed that there are no active therapies currently approved by the Food and Drug Administration (FDA) or the European Medicines Agency (EMA).²⁰

The authors reinforce the numerous limitations of strict avoidance measures in the management of these patients.

4 | IMMUNOTHERAPY WITH FOOD ALLERGENS

Immunotherapy with allergens is the only treatment that can change the course of allergic disease by inducing allergen-specific immune tolerance. This induced tolerance^{11,17} or sustained unresponsiveness,^{17,18} defined as the ability to ingest the previously allergenic food without symptoms, regardless of long avoidance periods or irregular consumption, is the goal of immunotherapy with food allergens. In order to achieve tolerance, the patient first has to reach desensitization, which is dependent on the regular ingestion of the allergenic food.¹¹ This is achieved by administering increasing doses of the food allergen in order to modify the IgE-mediated immune response. One mechanism is the immune deviation from allergen-specific Th2 to Th1 responses and a shift in allergen-specific antibody production from IgE to immunoglobulin G4 (IgG4).⁷⁴ Consequently, there will be a decrease in serum food-specific IgE antibodies, an increase

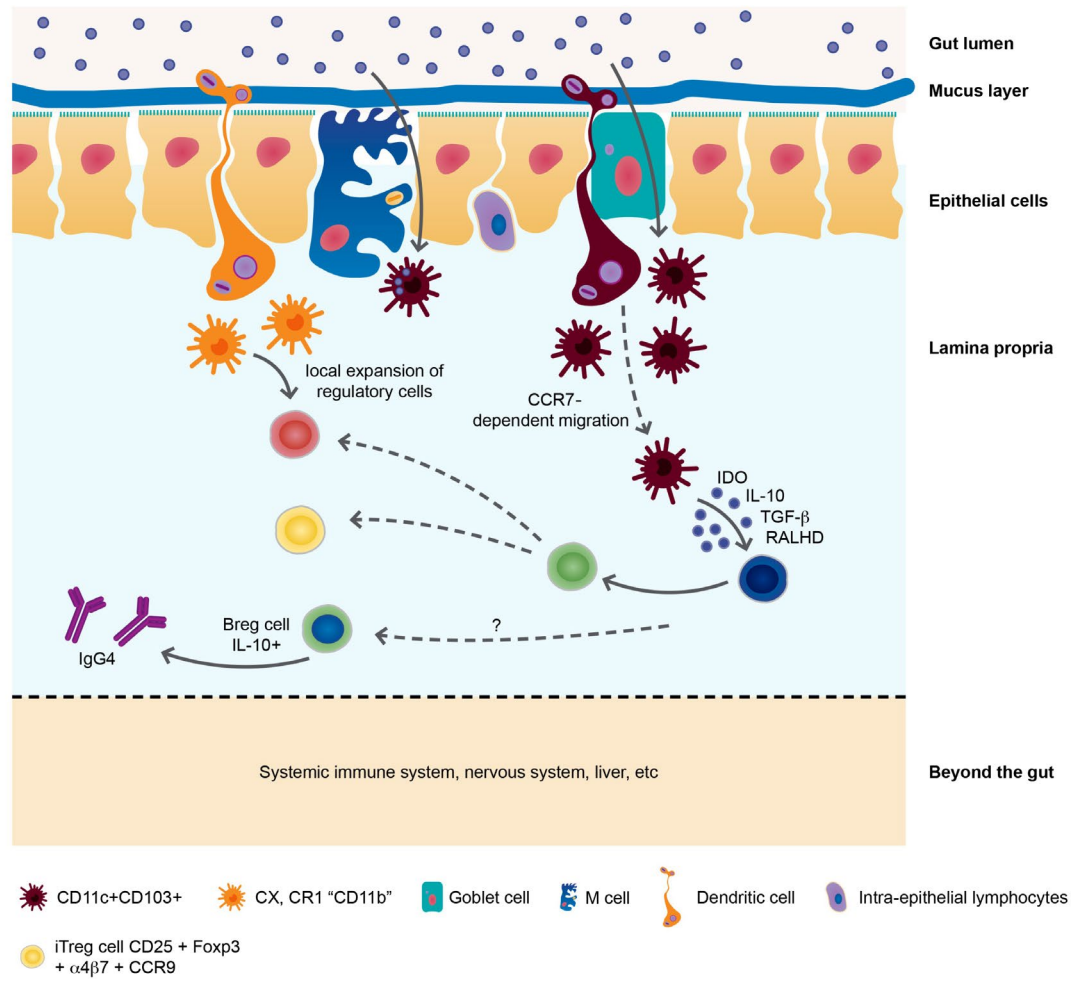


FIGURE 2 Induction of tolerance to food allergens occurs in the gut and gut-associated lymphoid tissue (GALT), mainly in mesenteric lymph nodes (MLN) and Peyer's patches. DC expressing CD11c and CD103 that coexpress CCR7 migrate to MLN. In the MLN, they express high levels of transforming growth factor- β (TGF β), IL-10, retinoic acid synthesizing (RALDH) and indoleamine 2,3-dioxygenase (IDO) contributing to the promotion and active development of Treg and Breg cells. Dendritic cells (DC) expressing CD11b and CX3CR1, which express high levels of IL-10, contribute mainly to local expansion of specific antigen regulatory cells. In the lamina propria, forkhead box P3 (FOXP3) + Treg cells, IL-10-secreting Tr1 cells and TGF β -secreting T helper 3 (TH3) cells; iTreg CD25 + Foxp3 + $\alpha 4\beta 7$ + CCR9 + cells and IL-10 + Breg IgG4 + cells repress the allergic dependent inflammation of Th2, decreasing mast cell activation, IL-4/ IL-5/ IL-13 production from ILC2 and Th2 cells, and IgE production from plasma cells

in food-specific serum and salivary IgG4 and IgA antibodies, and a decreased reactivity of mast cells and basophils. Additionally, the development of regulatory T cells followed by anergy and/or deletion of effector T cells allows for the achievement of sustained unresponsiveness.⁷⁵ Figure 2 schematically represents these mechanisms underlying immunotherapy.

An international consensus stated that the indications for immunotherapy in food allergy are poorly defined. However, the same consensus recognized that there is practically no controversy regarding the use of immunotherapy in the treatment of allergic rhinitis or allergic asthma. Some studies show clinical improvement of cross-reacting food allergy in patients submitted to pollen extracts immunotherapy.⁷⁶ Nevertheless, and due to the risk of adverse

reactions, immunotherapy with food allergens is not recommended for routine clinical use. It should be performed only in highly specialized centres with expert staff and adequate equipment.^{6,21,23} It is important to consider that, despite the promising results of immunotherapy with food allergens,^{15,18,77-103} there are no standardized protocols. In fact, those currently existing vary regarding initial dose, maintenance dose, time period between dose increments, induction (rapid increase in dose) and maintenance (daily fixed dose) periods.^{11,17,20,104} This between-protocol difference may account for the different results obtained from various studies. Also, significant concerns regarding safety and long-term consequences still exist.²⁰ Strategies for improving safety during either up-dosing protocol or maintenance regimen need to be standardized.¹⁰⁵

Important aspects that should be taken into account when performing food immunotherapy are the various cofactors, such as menstruation, exercise, alcohol, NSAIDs, stress and infections, that may decrease the threshold and increase the probability of serious adverse reactions.⁷⁵

Immunotherapy has several routes of administration and has been performed subcutaneously, sublingually, epicutaneously and orally. The subcutaneous approach was abandoned many years ago due to safety concerns. The sublingual and epicutaneous approaches have both been shown to be safe, but efficacy is limited by a restricted dose capacity, that is the amount that can be absorbed through the skin or under the tongue. Oral immunotherapy (OIT) is more effective than the other routes, in part because much larger doses can be administered. However, safety has been a major limitation.²⁰

4.1 | Sublingual allergen immunotherapy (SLIT)

In SLIT, the food protein is delivered sublingually in a liquid form, held for 2 minutes and then swallowed.^{11,17} SLIT has been tested with milk, peanut, hazelnut and peach.^{11,102} Although effective, SLIT is less effective than OIT,^{17,104,106} perhaps due to the doses at maintenance, which typically range from micrograms to milligrams in SLIT and from milligrams to grams in OIT. Also, SLIT has a lower chance of achieving sustained unresponsiveness, but has an excellent safety profile.^{11,40,80,88,89,91,94,99,102,107} SLIT may be useful for patients with severe allergy who cannot tolerate OIT,^{17,104,107} or as a stepwise approach (SLIT followed by OIT) to increase safety of OIT dosing.^{17,94,107} SLIT with native foods may never be the most effective method to induce clinically significant desensitization or sustained unresponsiveness given the lower daily maintenance doses used.¹⁰⁷ However, the recent development of quantified food extract-isolated proteins may alter these responses.^{108,109}

4.2 | Epicutaneous immunotherapy (EPIT)

EPIT is performed by repeated application of an allergen to intact skin.^{11,110} It is relatively well tolerated with very few systemic reactions and no reports of anaphylaxis.^{17,110,111} Reactions are primarily mild, cutaneous symptoms, including local erythema or eczema at application sites, pruritus and flares of atopic dermatitis.^{17,40,91,99,107,110,111} Allergen doses vary from 100 µg to 500 µg daily, depending on the food allergy.^{2,51,111} Some studies have failed to show a statistically significant increase in the amount of food tolerated by milk- and peanut-allergic subjects treated with EPIT,^{91,99,107} whilst others have reported that EPIT modestly induced tolerance in 28%-50% of patients but no sustained unresponsiveness has been demonstrated.^{40,111} A review from 2015 concluded that the efficacy of EPIT is in the range of that induced by SLIT, and further suggested that, as in SLIT,

EPIT may be useful as a stepwise approach (EPIT followed by OIT) to increase safety of OIT dosing.⁹⁴

4.3 | OIT

Different studies on peanut,^{18,77,78,80,83,86,87,91,94,97-99,101-103} egg^{15,43,81,82,85,91,94-96,98-102} and cow's milk allergies,^{43,79,84,91,94,95,98,99,101,102} the latter two using either fresh or baked egg or milk products, have shown varied levels of efficacy and safety. These different results are probably due to the fact that there are no standardized protocols for OIT,^{17,96,104} neither in terms of dosing schedule nor in timing of the doses.²⁰ Although further studies are required, some evidence suggests that the use of processed egg or milk products may accelerate tolerance induction and reduce the risk for severe adverse events even in those patients who would naturally develop tolerance.¹¹² Patients who have reactions to baked egg or milk products are the most severe cases and should therefore be particularly considered for OIT. Strict avoidance should be the first step, followed by a very slow OIT protocol.

OIT has shown effectiveness in terms of desensitization induction but its ability to induce permanent tolerance once ongoing exposure has stopped remains unclear.^{46,96,99,101} Safety is also a concern^{96,99,100,106} and, although AEs have been reported to be generally mild, severe reactions such as anaphylaxis have occurred.^{20,96,99}

Another issue regarding OIT is the patients' age, since OIT can be a source of anxiety and decreased QoL as it carries the risk for allergic reactions.¹¹³ Therefore, some physicians do not consider OIT to be appropriate for children under 6 years of age, whilst others have the opinion that for some foods such as milk, avoidance measures will increase anxiety and decrease QoL even more than OIT.

It is authors' opinion that food immunotherapy should be used for the management of food allergy. However, its use is still limited, and new approaches to enhance efficacy and reduce risks are needed.

In order to improve the safety profile of OIT and maintain or increase its efficacy, adjuvant therapy with the IgE monoclonal antibody omalizumab has been extensively used with significant clinical improvement both in adults and children.^{2,11,20-47}

4.4 | Omalizumab

Begin et al³⁸ proposed pretreatment with omalizumab before OIT in order to prevent systemic reactions. Figure 3 represents an adaptation of their proposal. Generalized treatment with omalizumab does not exist and is not incorporated in the most recent EAACI guidelines,¹⁷ where a case-by-case evaluation is proposed. Treatment should be individualized and monitored, depending on the allergy and the severity.¹¹⁴

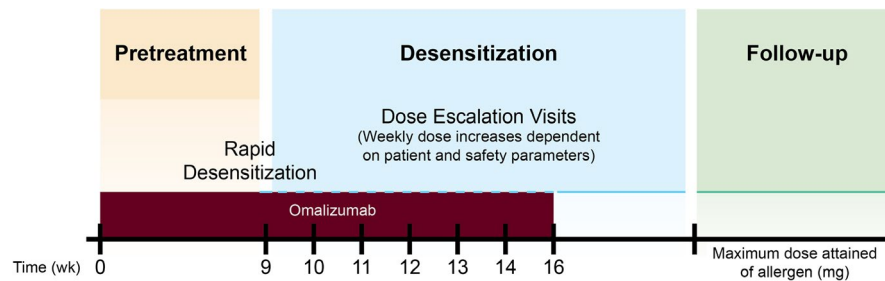


FIGURE 3 Oral Immunotherapy with previous treatment with Omalizumab. We propose the pretreatment of Omalizumab before OIT in order to prevent systemic reactions (adapted from Begin et al³⁸). OIT trial design including (A) screening and trial flow chart and (B) immunotherapy protocol timeline. Amount of maintenance dose depends on number of allergen in mix (4000 mg per allergen). Importantly, generalized treatment with omalizumab does not exist, there are no standard protocols, and treatment should be individualized and monitored, depending on the food allergy and its severity. Optimal duration of treatment, when should it be stopped or even if it should be stopped, are currently unanswered questions

Omalizumab is a recombinant DNA-derived fully humanized monoclonal antibody that selectively binds to IgE. It is currently approved by EMA for children >6 years as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and frequent day-time symptoms or night-time awakenings, and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids plus a long-acting inhaled beta2-agonist. It is also approved as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment.¹¹⁵

Omalizumab has been the most studied drug in the context of severe food allergies.⁴⁶ In 2010, Rafi et al described that in patients receiving omalizumab for their asthma symptoms, there was a reduction in their concomitant IgE-mediated food allergy symptoms. Based on these results, the authors concluded that in patients who are at significant risk of severe or fatal food anaphylaxis, omalizumab may be a therapeutic option.⁷³

Currently, and in order to improve the safety profile of OIT and maintain or increase its efficacy, adjuvant therapy with omalizumab has been extensively used in severe peanut allergy, milk allergy, egg allergy and multiple food allergy, with significant clinical improvements observed in both adults and children.^{2,11,20-47,116} The ability of omalizumab to prevent systemic reactions to OIT enables completion of treatment in patients who otherwise would have to stop it prematurely.^{17,24,28,31-33,37,42,43,45,46,48-53} Taken together, these results suggest that omalizumab may be particularly beneficial in the most severe patients, at high risk of fatal anaphylaxis. Omalizumab also allows a more rapid desensitization^{2,11,20,26,40,42,45,53} and has been shown to reduce the time to achieve maintenance dose.^{20,45,52,53} Nevertheless, a percentage of patients relapse, with a decrease in the clinical reactivity threshold, at 2-4 months after suspending

omalizumab, suggesting the need for longer maintenance therapy with omalizumab.^{39,43,52}

Considering all the above, optimal duration of treatment with omalizumab, when should it be stopped or even if it should be stopped, are currently unanswered questions. There are no standard protocols, as they vary according to the food allergy and its severity.¹¹⁴ Further studies are needed to determine whether the initial benefit provided by omalizumab translates to improved long-term outcomes,⁵² and to fully evaluate the efficacy of therapy with omalizumab versus the cost and the optimal duration of combined treatment.⁵¹

An alternative approach is to use omalizumab not simultaneously, but instead of OIT.²⁹ In fact, several reports suggest that omalizumab as monotherapy may allow food-allergic patients to tolerate higher amounts of the allergenic before reacting, providing protection to accidental ingestions.¹¹⁷ One of those reports showed that IgE immunoadsorption, used to establish the starting basis for omalizumab monotherapy, was able to increase the tolerance threshold to foods in a 6-year-old boy with anaphylaxis to multiple foods.³⁴ Nilsson et al²⁸ treated five children, 6-16 years of age, with severe milk allergy including episodes of anaphylaxis, with omalizumab, using CD-sens monitoring to decide whether or not an oral milk challenge would be safe. CD-sens is a basophil allergen threshold sensitivity test that measures CD 63% expression after in vitro stimulation of basophils with serial dilutions of the allergen. After 4 months of omalizumab monotherapy, all children had a negative milk challenge, although one child required doubling of the omalizumab dose. A very similar study on 23 severely peanut-allergic adolescents with history of peanut-induced anaphylaxis, also showed that after individually dosed omalizumab monotherapy, all adolescents had a successful peanut challenge after 8-32 weeks of treatment.²² Given these promising results, omalizumab monotherapy in food allergies is worth further exploring.^{29,46,118}

The authors propose that in cases with severe or multiple food allergies omalizumab is useful as an adjuvant to food immunotherapy.

5 | FUTURE PERSPECTIVES

There is still a lack of consensus on the use of immunotherapy with food allergens. Despite being considered a promising approach, there is a clear need to standardize evidence-based protocols in order to ascertain its real clinical effectiveness. The role of omalizumab as monotherapy for food allergy is still debatable and further studies are warranted. Nonetheless, it may be considered in very severe patients with multiple food allergies who frequently present accidental exposure, to reduce reactions to allergens, since it has proven to be effective and safe, with virtually no adverse events as adjuvant therapy. Future molecules that could be explored include anti-IL4, anti-IL5, anti-IL13, PG-D2 and tailor-made recombinant immunotherapy.

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CONFLICT OF INTEREST

The authors declare the absence of economic or other types of conflicts of interests.

AUTHOR CONTRIBUTIONS

All Authors contributed concerning data collection, analysis and interpretation, and preparation and revision of the manuscript. All Authors approved the final version of the manuscript.

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