

The use of biologics in food allergy

Alessandro Fiocchi¹, Brian P Vickery², Robert A Wood³

¹ Allergy Unit, Bambino Gesù Children's Hospital, IRCCS, Piazza Sant'Onofrio 4, 00165, Rome, Italy

² Emory University School of Medicine, Atlanta GA – U.S.A.

³ Johns Hopkins University School of Medicine, Baltimore MD – U.S.A.

E-mails:

Alessandro Fiocchi: alessandro.fiocchi@allegriallergia.net

Brian P Vickery: brian.p.vickery@emory.edu

Robert A Wood: rwood@jhmi.edu

Author Contribution

AF initiated the concept and contributed made the first draft

BPV and RAW participated to the development of the document

All authors reviewed and approved the final manuscript.

Ethics approval and consent to participate:

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/CEA.13897](https://doi.org/10.1111/CEA.13897)

This article is protected by copyright. All rights reserved

Not applicable; the manuscript does not report on or involve the use of any animal or human data or tissue.

Consent for publication: Not applicable; the manuscript does not contain any individual persons' data.

Availability of data and materials: This is a review article

Competing Interests: CoI forms have been uploaded with the manuscript

Funding: This is a review article that did not need or receive any funding

Data availability statement: The data that support the findings of this study are freely available in Pubmed at <https://pubmed.ncbi.nlm.nih.gov/>, in the University of Nebraska Food Allergy Research and Resource Program, available at <https://farrp.unl.edu>, and in the US National Library of Medicine Clinical Trials register, available at <https://clinicaltrials.gov>.

Corresponding Author

Alessandro Fiocchi

Allergy Unit, Bambino Gesù Children's Hospital, IRCCS

Piazza Sant'Onofrio 4, 00165, Rome, Italy

Tel: +39-06-68593570; fax: +39-06-68592218.

The use of biologics in food allergy - Abstract.

Background. Food allergy continues to pose problems due to its increased frequency and its increasingly high severity. In this context, alongside the traditional avoidance strategies of allergenic foods and desensitization through the cautious progression of exposure to foods in the context of oral immunotherapy (OIT), alternative strategies have made their way in the last decades. We review the possibilities of intervention in food allergy with the use of biological drugs capable of interfering with the synthesis of IgE, with their mechanisms of action, or with the complex of biological mechanisms that lead to the establishment of a food allergy.

Methods. Repeated Entrez PubMed searches using the template algorithm “Food allergy” and “biologics” or “Omalizumab” or “Dupilumab” or “milk desensitization” or “oral tolerance induction” or “oral immunotherapy” or “Etokimab” or “Tezepelumab” or “Quilizumab” or “Ligelizumab” or “Tralokinumab” or “Nemolizumab” or “Mepolizumab” or “Reslizumab” or “Benralizumab”. The authors’ clinical experience in pediatric allergy units of University hospitals was also drawn upon.

Results. The landscape in this context has changed dramatically over the past 10 years. We have acquired knowledge mainly on the effect of different types of anti-IgE treatments in poliallergic patients with food allergy, and in patients treated with OIT. However, other mediators are being targeted by specific biologic treatments. Among them, the alarmins IL-33 and TSLP, IL-4 and IL-13, eosinophil-related molecules as IL-6, IL-8, IL-10, IL-12, and mostly IL-5, and integrins involved in the pathogenesis of eosinophilic gastrointestinal diseases (EGIDs), as SIGLEC-8.

Conclusions. The ever better knowledge of the mechanisms of food allergy allowing these developments will improve not only the perspective of patients with the most serious immediate food allergies such as anaphylaxis, but also those of patients with related diseases such as atopic dermatitis, eosinophilic esophagitis, and EGIDs. Biologics are also intended to complement OIT strategies that have developed over the years.

Introduction

In the last twenty years epidemiological studies, reviews, and meta-analyses suggest that food allergy is on the rise worldwide by frequency and severity^{1,2,3}.

The incidence of IgE-mediated forms, typically rapid in onset⁴, range from 1% to 10% in infants and preschool-aged children, from 1% to 5% in school age, and about 4.5% in adults⁵. The non IgE-mediated forms, mainly affecting the gastrointestinal tract and the skin, appear with reactions 24-72 hours after ingesting the culprit food^{6,7} (Table). Their frequency is ill-defined⁸.

Most of the allergic reactions to food are mild or moderate, but some become severe and potentially life-threatening, culminating in IgE-mediated anaphylaxis⁹. Death from anaphylaxis is a rare occurrence¹⁰, which most probably happen among patients with severe food allergy (SFA)¹¹, but is a public health concern¹². To reduce the risk of allergic reactions, strict avoidance of the offending food is advised.

The limits of food avoidance

The patient who has been prescribed to avoid one or more food allergens must be extremely careful on what she eats. Some foods are easily identifiable, others require extra attention. To safeguard the health of food allergic consumers, the health authorities of 66 countries over the five continents require by law that allergenic ingredients must be declared when used in prepackaged foods^{13,14,15}. Despite scrupulous observance of this prescription, accidental reactions to food may occur in greater proportion with the multiplicity of sensitizations. While infants and young children with allergy to milk or egg may experience less than one accidental reactions per year¹⁶, teens with severe food allergy have been described with reactions once a month¹⁷. Other factors linked to the probability of severe reactions include the dose of antigen, a timely effective treatment, and allergic comorbidities (in particular asthma)¹⁸. Reactions to undeclared ingredients are also not

unusual¹⁹.

The difficulties in observing the avoidance prescription affects the quality of life of those suffering from food allergy²⁰. SFA in particular reduces the quality of life and increases costs of living in patients and their families^{9,21,22}. Hence, different approaches to the management of food allergy, aimed to reach some degree of tolerance to the offending food, have been developed.

The limits of Oral Immunotherapy

Food Oral Immunotherapy (OIT) was developed on the model of allergen immunotherapy (AIT) for allergic rhinitis, in the hope that it could increase tolerance and modify the natural history of the disease. The mechanisms of AIT are manifold²³. Among them, the only mechanism unanimously recognized in OIT is the continuous allergenic stimulation of basophils and mast cells, which are thus deprived of their preformed mediators through continuous degranulation. This prevents the development of the allergic reaction to accidental contact with the allergen by disarming the effector cells²⁴. Numerous studies have shown that, unlike the AIT, in OIT the desensitization process does not go hand in hand with a stable inhibition of specific IgE for the food subject to desensitization. While it is able to increase the food threshold²⁵, the suspension of OIT most often leads to the reappearance of symptoms unless the sensitivity decreased in the meantime due to the natural history of the disease^{26,27}. For peanut, the discontinuation or reduction to 300 mg daily of OIT after two years of treatment increases the likelihood of regaining clinical reactivity²⁸. Thus, from a clinical point of view, the most precise word to define the effect of current versions of OIT is "mithridatization".

The search for mechanisms that can transform this practice into etiological therapy has been and still is frantic, but the immunologic variations associated with a possible sustained unresponsiveness remain inhomogeneous across studies (Figure 1)^{29,30,31}. OIT surely induces immunological changes due to allergen exposure. Among these, the most uniquely observed are the increase in IgE during the initial phase of therapy, followed by their stabilization and gradual reduction, and the rapid increase in IgG4 levels³². However, many years after the beginning of the OIT studies, we are still groping in the dark on the long-term immunological effects of this practice²⁵.

The side effects of OIT are higher than those of AIT, and may appear at any stage in its

execution³³. For this reason there is no certainty about the opportunity to propose OIT to all patients with food allergy, while the need to reduce side effects is strongly felt³⁴. This is one of the purposes for which the use of biologicals, aimed at contrasting the pathogenetic traits of the disease, has become plausible.

Mediators involved in food allergy

The development of biologics for food allergy stems from the understanding of the mechanisms that lead to the food allergic reaction: they are increasingly better known, and -whatever the severity - different forms of food allergy share common biologic mechanisms³⁵.

In IgE-mediated food allergy, specific IgE are only the last link in a long chain. The sensitization process involves the activation of allergen-specific T-cells and develops with their proliferation, cytokine production, and the generation of memory cells³⁶. On a genetically predisposed terrain³⁷, the inception of the disease depends substantially by environmental factors which determine the transcription or not of genes leading towards the creation of specific IgE³⁸. In this, an increasingly important role is recognized to the components of exposome including allergen contacts, environmental pollution, intestinal and skin microbiome^{39,40}.

In most people, the ingestion of a food determines the development of immunological tolerance. This process, particularly active in the first months of life, depends on amount of foods reaching the bowel, the intestinal permeability, the endocytic capacity of the enterocytes, and the immune response of intestinal cells and of the whole organism⁴¹.

Breaking the food tolerance determines a food sensitization and paves the way to food allergy. The importance of the intestinal environment in determining sensitization is evidenced by the fact that alterations in gastric pH⁴², intestinal microbiome⁴³, and intestinal length⁴⁴ are associated with an increased risk of food allergy. Alongside this pathway, the possibility of sensitization by cutaneous penetration of antigens through a permeable cutaneous barrier has also been hypothesized, especially in children with atopic dermatitis (AD)⁴⁵. Irritant biological and chemical molecules may challenge the physical integrity of the cutaneous barrier by degrading the intercellular barrier proteins at tight and adherence junctions. Environmental factors responsible for such damage may include protease enzymes of allergens, detergents, tobacco, ozone, particulate matter, diesel exhaust,

nanoparticles, and microplastic⁴⁶. In reaction to the exposure to intact food allergens that have eluded the cleavage mechanisms, the organism activates a group of cytokines leading to the inception of Th2 immunity (Figure 2). These are primarily epithelial derived cytokines, in particular interleukin 25 (IL-25), thymic stromal lymphopoietin (TSLP), and interleukin 33 (IL-33)⁴⁷. Such mediators stimulate innate lymphoid cells to release IL-13 and IL-5⁴⁸, and induce T-Helper 9 cells to produce IL-9, a mast cell growth factor able to promote their IgE-mediated activation⁴⁹. The alarmin IL-33 can activate lymphoid type 2 interstitial cells (ILC2) which in turn induce the production of IL-13 and IL-4^{50,51,52}. It also promotes the IgE-mediated activation of mast cells. These cytokines determine the release of IL-25 which, by exerting a positive feedback on ILC2, increases the production of IL-13 and IL-4. IL-4 in particular can subvert allergen specific regulatory T cells into Th2-like cells, resulting in the breakdown of immunological tolerance for the specific antigen⁵³.

The activation of epithelial derived cytokines induce IgE synthesis, both for their direct action and through ILC2. Furthermore, TSLP promotes the differentiation of CD4 + cells towards the Th2 line. As a whole, therefore, the epithelial derived cytokines strongly stimulate Th2 to the disadvantage of Th1 immunity, resulting in a powerful induction of the allergic response⁵⁴.

In this context, a protagonist role is played by IL-4⁵⁵, IL-5, and IL-13. These cytokines are produced by mast cells, basophils, dendritic cells (DC), Th2 lymphocytes, and ILC2. They are able to directly stimulate B-cells to produce IgE, to activate eosinophils to secrete IL-6, IL-8, IL-10, IL-13 and leukotrienes, and to promote macrophage differentiation into the alternatively activated M2 subtype⁵⁶. In the eosinophil activation they are assisted by GM-CSF and eotaxins.

Phenomena of this kind are also implicated in the pathogenesis of non-IgE mediated forms of food allergy. In this case the mechanisms are more obscure, and at times very distant from those of the genesis of IgE-mediated food allergy. Just think of the case of Food Protein-Induced Enterocolitis Syndrome (FPIES), where it is above all the cells of natural immunity that are indicted to trigger the reaction^{57,58,59}. Despite the fact that between FPIES and IgE-mediated food allergy there is a whole range of clinical conditions with mainly cutaneous or gastrointestinal expression, the similarity of some mechanisms is documented by epidemiological and pathogenetic affinities⁶⁰. For instance in AD, a disease often associated with food allergy⁶¹, alterations of the DCs have been identified in response to

altered fibroblasts producing CCL2 and CCL19 chemokines⁶². The lesioned skin is rich in inflammatory DCs and tissue-resident memory T cells producing IL-22 and IL-26⁶³. The cytokines involved in the process include the epithelial derived cytokines IL-33⁶⁴ and TSLP⁶⁵, together with the inflammatory cytokines IL-17, produced by Th-17 and ILC3⁶⁶, and IL-19⁶⁷. These mechanisms also lead to a high production of IgE in AD.

The eosinophilic gastrointestinal diseases (EGIDs), including Eosinophilic Esophagitis (EoE), eosinophilic gastritis, eosinophilic enteritis, eosinophilic colitis, and allergic proctocolitis, share common pathogenetic mechanisms and mechanisms specific to each of the conditions. Among them, the best studied is certainly the EoE, in which the importance of food allergens is underlined by the efficacy of elimination diets⁶⁸ and the association with immediate food reactions⁶⁹. In EoE, complex genetic and epigenetic alterations, modulated by environmental risk factors, translate in an overexpression of Th2 cells with increased production of their cytokines including IL-4, IL-5 and IL-13^{70,71}. These cells can be activated by an overproduction of thymic stromal lymphopoietin (TSLP)⁷². In the development of eosinophils, in their activation and in their circulation, IL-5 plays a fundamental role⁷³. All of these interleukins have been shown to be overrepresented in the tissues of EoE⁷⁴.

In other eosinophilic gastrointestinal pathologies, a role of IL-4 and IL-13 has also been reported. Together with eotaxin-3 and chemoattractant receptor expressed on Th2 cells (CRTH2), IL-4 and IL-13 may be involved in the abnormal activation of the eosinophilic system⁷⁵. Among the integrins involved in the pathogenesis of EGIDs SIGLEC-8, lectin receptors binding sialic acid, are playing an increasingly recognized role⁷⁶. IL-13 also mediates epithelial damage through the activation of genes such as CAPN14 and SPINK7⁷⁷. It generates a weakening of the epithelium by reducing the production of filaggrin and desmoglein-1. It is possible that the reduced integrity is responsible for the transepithelial passage of antigenic proteins leading to the development of sensitization. On the other hand, it has been well demonstrated in experimental models, including *experimentalis naturae* as the short bowel syndrome, that an increase in the allergenic load is connected with the development of food allergy⁴⁴. The final effect of this abnormal eosinophilic inflammation may be intestinal remodeling, in which a role is played by TGF- β ⁷⁸.

These pathogenetic observations, with the increasing availability of monoclonal antibodies targeted against a wide range of these mediators, open a range of possibilities for new treatments of IgE-mediated and non-IgE-mediated food allergies⁷⁹.

Monoclonal antibodies showing promise in clinical trials for IgE-mediated food allergy

Alarmin-targeted treatments

An exploratory study evaluated the effect of a single administration of **Etokimab**, an antagonist of IL-33, on IgE-mediated peanut allergy. In this protocol, a single administration of Etokimab was performed in patients with a positive Double-Blind Placebo-Controlled Food Challenge (DBPCFC) to peanut at baseline. A DBPCFC to peanut 14 and 45 days post-administration was programmed to explore changes in tolerance threshold, together with skin prick tests and immunologic evaluations⁸⁰. The drug induced an increase of the proportion of peanut-tolerating patients: 73% tolerated 275 mg of peanut protein – corresponding to two peanuts - after 14 days, 57% after 45 days. The tolerance to higher doses was inferior: 47% tolerated three peanuts after 14 days, 29% after 45 days. This clinical result was paralleled by a reduction in IL-4, IL-5, IL-9, and IL-13 in CD4⁺ T cells. SPT wheal size and peanut-specific IgE were reduced only at time 14 days. No side effects were recorded. The low sample size of this study (20 patients randomized 3:1) resulted in an imbalance in baseline characteristics. The active group [n=15] tolerated a median of 175 mg at baseline but the placebo group [n=5] tolerated only a median of 25 mg at food challenge. The median [range] peanut IgE in the active group was 39.5 [12-100] vs placebo 55[45-103]. With a very high drop out rate (3 out of 5 drop out in placebo group; 8 of 15 drop out in active group; 11 out of 20 overall dropped out), the study's findings were not significant at their longest time point, day 45. None of the study findings were significant to passing a 375 mg challenge, as opposed to a 275 mg challenge. Much larger studies are required to definitively know whether il-33 actually plays a role in human anaphylaxis or not.

Another drug potentially useful in this area is **Tezepelumab**, a TSLP antagonist used for asthma and AD^{81,82}, but no clinical trials on this drug in food allergy are being conducted at the moment.

Targeting IL-4 and IL-13

Dupilumab is a well-known monoclonal, available in the U.S. and in Europe for the indications of AD⁸³, asthma⁸⁴, and nasal polyposis⁸⁵. It targets the α -chain of the IL-4

receptor (IL-4R α), which is also common to IL-13. This binding results in a blockade of the downstream signaling initiated by both IL-4 and IL-13. As these cytokines are key players in the Th2 cell differentiation, Dupilumab inhibits several Th2-dependent immune ways, including the signaling pathway of IgE class switching, the macrophage polarization into the pro-inflammatory (M2) phenotype, and peripheral eosinophilia⁸⁶. The molecule exerts effects on B lymphocytes, eosinophils, DCs, monocytes/macrophages, basophils, keratinocytes, bronchial epithelial cells, endothelial cells, fibroblasts, and airway smooth muscle cells⁸⁷. In anecdotal observations, Dupilumab used for severe AD showed efficacy in getting tolerance to concomitant food allergy eliciting anaphylactic shock⁸⁸. Two studies are underway to evaluate the effectiveness of this biological in food allergy. The first aims to evaluate how much it increases the proportion of allergic subjects who, treated with OIT for peanut allergy AR101, pass a food challenge after 4 months⁸⁹. The second aims to assess how many peanut allergic subjects can achieve full tolerance to the food challenge after 24 weeks without any immunotherapy treatment⁹⁰. The results are expected in 2021.

Anti-IgE treatments

Immunoglobulin E is an obvious target for biological therapy, and the one most widely studied. Several strategies are possible in this context:

- a. Inhibition of IgE⁺ B cells, an important step in the control of IgE production⁹¹. This is possible by Quilizumab, a monoclonal antibody targeted against the C ϵ mX fragment on IgE⁺ B cells able to induce IgE⁺ B cell apoptosis. In animal studies, Quilizumab proved able to reduce free IgE levels and to inhibit the generation of IgE⁺ B cells⁹². Another possibility is offered by AIMab7195, a Fc-engineered antibody with similar activity to suppress B cells through interaction with Fc γ RIIb as well as sequestering free IgE⁹³. There are animal data and human trials are planned⁹⁴.
- b. Serum IgE neutralization. This is possible by Immunoabsorption plasmapheresis, anti-IgE monoclonal antibodies as Omalizumab, Ligelizumab, or their biosimilars CMAB007 and MEDI4212, and single-chain variable fragment (a single-chain antibody targeting IgE, IgE-bound cells, and IgE-secreting cells)⁹⁵
- c. Inhibition of IgE-effector cells. This has been studied using polymeric Anti-Fc ϵ RI Fab-conjugated celastrol-loaded micelles aimed to prevent IgE interaction with mast cells⁹⁶ and kill mast cells. Another strategy is the use of the CTLA4Fc ϵ fusion protein,

targeting IgE receptors, FcεRI and FcεRII/CD23⁹⁷.

In practice, the most studied strategy is IgE neutralization. Almost 20 years ago the first anti-IgE antibody, **Tazilumab** (TNX-901), was shown to be able to increase the reactivity threshold to peanut after 2 to 4 weeks of treatment⁹⁸. Although that molecule was then no longer developed, but was replaced by **Omalizumab** and recently by **Ligelizumab**, this remains a basilar proof-of-principle study.

Omalizumab is the most widely studied molecule for the treatment of food allergy .

Omalizumab instead of OIT

Omalizumab is known to reduce the basophil histamine release in peanut allergy⁹⁹. In 2010 a four-week, double-blind, placebo-controlled trial aimed to evaluate the peanut threshold at DBPCFC before and after Omalizumab was terminated early for procedural reasons due to severe reactions occurring during the screening DBPCFCs. Still, the data obtained were sufficient to indicate an 80.9-fold improvement in the peanut threshold after 24 weeks¹⁰⁰.

In a real-life study, 15 patients treated with Omalizumab at the standard dose for asthma were evaluated for their concomitant severe food allergy. The thresholds for egg, milk, baked milk, and wheat increased by 17.8 times (Figure 3), the rate of food reactions decreased by 15.6 times, the quality of life (measured by of the generic PedsQL instrument) was remarkably increased¹⁶. Nine patients were able to introduce without symptoms a full serving size amount of all the foods tested without necessity of OIT procedures. Of the remaining six patients, two were able to reintroduce at least one of the tested foods tested, and four partially improved.

These data indicate that Omalizumab could be considered in place of OIT treatment at least for a slice of patients; cost-efficacy, safety and applicability to different clinical situations should be explored before this indication can be provided.

A trial currently underway will shed further light on data in this field. The NIAID-sponsored OutMATCH (Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen Oral Immunotherapy in Food Allergic Children and Adults) study aims to evaluate the effectiveness of Omalizumab alongside with multifoood OIT¹⁰¹. In its phase 1, an Omalizumab/placebo comparison will assess among patients allergic to peanuts and other foods the ability to reach a full-serving size threshold at DBPCFC after 16-20 weeks of

treatment. A further 24-weeks extension will evaluate if a prolonged Omalizumab treatment increases the probability of patients to introduce foods¹⁰².

Omalizumab alongside OIT

Other, more substantial data evaluated the use of Omalizumab as an adjuvant during OIT procedures¹⁰³.

In **milk** OIT, a first study indicated ten years ago that the addition of Omalizumab allowed a faster build-up phase, without preventing totally the OIT adverse reactions¹⁰⁴. A second trial shown a reduction of milk-induced CD4⁺ T-cell proliferation, markers of milk-specific T cell anergy, and a reduction of milk-specific basophil activation in CMA treated with Omalizumab-protected OIT¹⁰⁵. Such immunological modifications were possibly associated with sustained unresponsiveness. In a third prospective trial, Omalizumab was shown to accelerate milk OIT with increased safety. In this study, after a 4-month course of Omalizumab or placebo patients were treated with milk OIT for 24 months. During this period, Omalizumab reduced the number of adverse events and their severity. OIT in the Omalizumab group could go on faster, but no effect was found on the final effectiveness of OIT and the duration of the benefit¹⁰⁶. In other words, the treatment could speed up the execution time of milk OIT but it did not change its final results.

Further data on the effect of Omalizumab on the acceleration of OIT maneuvers, and on their safety, were provided by a Japanese study in the context of milk allergy¹⁰⁷ and by a Spanish study in the context of milk and egg allergy¹⁰⁸. In none of these studies did Omalizumab prove able to modify the natural history of cow's milk allergy.

For **peanut** OIT, several studies document the facilitating effect of Omalizumab.

In an pilot experience, Omalizumab was able to enhance oral desensitization in peanut allergic patients at high risk for developing significant reactions on exposure to even small amounts of peanut. Ninety percent of the patients in this study were able to reach the maximal peanut dose of 8g/day. Few reactions, mostly mild, predominantly during the dose escalation phase occurred. On discontinuation of Omalizumab, its benefits were maintained for 4 weeks¹⁰⁹. These patients were also studied for an extended follow-up, demonstrating that continuing peanut OIT allows them to safely continue to consume free amounts of the

food on a regular basis in about 50% of cases¹¹⁰.

Another experience, again with an unblinded design, was conducted with individualized doses of Omalizumab based on sensitivity to basophil activation test. In the Treatment of Severe Peanut Allergy with Omalizumab and Oral Immunotherapy (FASTX) study¹¹¹, it was shown that all 23 enrolled patients with severe peanut allergy were able to reach the target dose of 2800 mg of peanut in about ten weeks. After Omalizumab discontinuation, symptoms recurred in approximately 50% of patients, some of whom had to restart Omalizumab and some had to stop OIT¹¹². In this study there was also a case of OIT-associated EoE¹¹³.

The PRROTECT study (Peanut Reactivity Reduced by Oral Tolerance in an Anti-IgE Clinical Trial) evaluated in a prospective, controlled manner about forty high-risk subjects with peanut allergy between 7 and 18 years of age. Those treated with Omalizumab were able to get a rapid OIT and to tolerate doses of peanut 10 times higher than those treated with placebo. They were more likely to tolerate the target dose of 2000 mg of peanut protein after discontinuing Omalizumab for six weeks. Seventy-five percent of them were able to tolerate a double dose of peanut after another 6 weeks. In this experience, it is documented again that once peanut immunotherapy is started, it can be continued in a large proportion of cases²⁸. Reasons for discontinuations are mainly gastrointestinal symptoms, in particular nausea. Also in this study, OIT-treated patients developed EoE with a frequency of about 10%¹¹⁴.

At least two ongoing studies are evaluating the effect of Omalizumab on the performance of peanut OIT.

The stage two of the already cited OUTMATCH study¹⁰⁵ will compare treatment with Omalizumab with placebo OIT to placebo for Omalizumab plus multi-allergen OIT. This will provide information on the ability to consume foods without symptoms at DBPCFC after treatment with either Omalizumab-facilitated OIT or Omalizumab alone. Based on their end of treatment food challenges, the OUTMATCH stage three will assign patients into three arms:

- o Long-term follow-up with dietary consumption of a food;
- o Long-term follow-up with avoidance of a food; or
- o Rescue OIT for a food.

The number of participants who, after stopping both treatments, will be able to eat peanut

and the two other foods in a dietary form will provide information on the effectiveness of these treatment approaches.

Probably the use of Omalizumab finds its greatest sense in the population of **multi-food** allergic patients. In these patients, it has been reported that a rush OIT protocol to multiple food allergens using adjunct Omalizumab can be performed safely in a hospital setting¹¹⁵. In a blinded trial, Omalizumab has been tested able to improve the efficacy of multi-food OIT and to enable safe and rapid desensitization¹¹⁶. To this end, children with 2+ food allergies were randomized to multi-food OIT with two to five foods, together with Omalizumab or placebo. The proportion of participants who passed DBPCFC to at least two of their offending foods was significantly higher in the monoclonal-treated group. In a follow-up study, food tolerance after Omalizumab-facilitated multi-OIT was shown to best occur through continued maintenance of OIT (either 300mg or 1 g) as opposed to discontinuation of multi-OIT¹¹⁷.

For multi-food allergy, at least two other studies are evaluating the effect of Omalizumab on the performance of OIT

The 'Protection from Food Induced Anaphylaxis by Reducing the Serum Level of Specific IgE' (Protana) study is specifically addressing children with very high IgE levels. In these children, the previous reduction of the total IgE level by serum IgE immunoabsorption has been anecdotally reported to overcome the usual limit of 1500 kUI/L, allowing the introduction of Omalizumab in conditions of safety¹¹⁸. The Protana study is aimed at understanding whether preventive immunoabsorption allows for safe administration of Omalizumab in a prospective caseload¹¹⁹.

The Omalizumab to Accelerate a Symptom-driven Multi-food OIT (BOOM) study is evaluating how to maximize treatment speed within patient safety using a flexible pragmatic approach¹²⁰. This is the first study to address the question of whether Omalizumab doses can be individualized for patients with food allergy, regardless of the standard dose used for respiratory allergy.

The E-B-FAHF-2, multi OIT and Omalizumab for food allergy trial is centered on the adjuvant effect of a Chinese herbal therapy in combination with multi-food OIT and Omalizumab on food tolerance¹²¹.

Another study assessing the possible synergy with Omalizumab in food allergy is the 44-

weeks NCT03679676 trial¹²²: Omalizumab is compared to placebo and Dupilumab in their ability to get tolerance to two or more food allergens at Week 38. The use of Omalizumab as OIT adjuvant still retains many points to be clarified. While it can accelerate the build-up phase of OIT, adverse effects during maintenance are similar with or without Omalizumab acceleration of build-up. No studies have so far compared the opportunity of dosing Omalizumab as a fixed dose (as in chronic urticaria) versus weight and IgE-based (as in asthma). However, a recently published study indicates that in food allergy OIT it should be adjusted for body weight alone, independently of total IgE level¹²³. The costs associated with combining Omalizumab and OIT, particularly commercial forms of OIT, should be highlighted.

Taken together, the published data on Omalizumab suggest that it is close to entering the clinic with an indication of food allergy, though we eagerly anticipate the availability of further data from trials that are ongoing. For this threatening pathology, orphan of effective and safe treatments, it is our opinion that obtaining an indication for this biological would be a robust step forward in patient management. The enthusiasms, however, must be tempered by the awareness of the lack of data on quality of life and number of anaphylactic reactions under treatment with Omalizumab. Only if the preliminary real life data¹⁷ are confirmed in prospective studies, it will be reasonable to proceed in this direction¹²⁴. Furthermore, the practical use of this molecule opens up a number of issues that are currently not completely addressed. Among these, the appropriateness of the dosage for this indication: in all probability it is different from that of the dosage for asthma¹²⁰. After initial encouraging findings¹⁰⁹, real life experiences indicate that food allergy symptoms may return upon discontinuation of Omalizumab^{108,125}. In this sense, we cannot expect more from omalizumab than what we got from immunotherapy.

Monoclonal antibodies showing promise in clinical trials for food allergy-related conditions.

As long as it is not directly part of the "food allergy" topic, we believe useful to mention some of the forms with non-IgE-mediated food allergy that can be treated with biologicals.

Atopic dermatitis

AD has an IgE-mediated component, and may be responsive to elimination diets in its severe pediatric forms¹²⁶. The use of anti IgE antibodies has not proved particularly useful in AD^{127,128}, but a trial found significant efficacy in severe pediatric cases, begging the question if **Omalizumab** may be part of therapeutic strategies in combination with other drugs¹²⁹.

The best studied biologic for AD is **Dupilumab**, able to suppress molecular markers of skin and systemic type 2 inflammation. Dupilumab reduces the clinical symptoms of AD in adult patients with moderate to severe disease^{130,131,132}. Dupilumab is able to reduce the EASI score, the Pruritus Rating Scale, the percentage of affected body surface area (BSA), the Patient Oriented Eczema Measure (POEM) score, and to increase the quality of life. The only significant side effect was conjunctivitis¹³³. In a Cochrane review, Dupilumab has been indicated as the most effective biological treatment for eczema¹³⁴. With such credentials, the drug has been approved both in America and Europe for treating AD over 12 years. A trial is also ongoing to evaluate a possible synergy between Dupilumab and anti-IL-33 (REGN3500)¹³⁵.

Tralokinumab, a monoclonal antibody targeted against IL-13 but not IL-4, has been evaluated in a phase-2 study in adults with moderate to severe AD with concomitant topical steroids¹³⁶. The study reports promising results, although the safety profile seems rather less favorable than that of Dupilumab: respiratory infections and conjunctivitis are associated with this drug to a greater extent¹³⁷.

Another anti-IL-13 antibody, **Lebrikizumab**, showed promise in reduction of clinical symptoms in adults with severe AD, both in concomitance with steroids¹³⁸ and alone¹³⁹.

Nemolizumab, an anti-IL-31RA monoclonal antibody, is targeted against the pruritus pathways of AD. In a phase 2 study, the drug proved effective in reducing symptoms and signs of AD¹⁴⁰. However, side-effects including asthma, abdominal pain, diarrhea, and musculoskeletal symptoms have been reported¹⁴¹.

The last monoclonal being evaluated in AD is the anti-thymic stromal lymphopoietin **Tezepelumab**. In this case, the clinical results do not appear encouraging¹⁴².

In any case, the effectiveness of many of these treatments document how important immunological mechanisms, including food allergy, are in the determinism of AD.

EoE.

In the therapy of EoE, the elimination diet for 4 or 6 foods has a well-recognized place, being able to obtain significant reductions in eosinophilic infiltrations and symptoms^{143,144}. In its It is therefore not surprising that drugs used for food allergy have also been tested for this condition. Biologics targeted towards IgE and IL-5, also involved in the development of food allergy¹⁴⁵, have been evaluated¹⁴⁶. Among them:

- **Omalizumab** has only been shown to be effective in a small portion of EoE patients, namely those with less intense eosinophilia¹⁴⁷.
- **Mepolizumab**, an anti-IL-5 targeted towards the main eosinophilic interleukin approved for eosinophilic asthma, proved effective in adult EoE, but the reduction in histologic eosinophils/hpf did not parallel a clinical benefit: symptoms of EoE did not improve¹⁴⁸.
- **Reslizumab**, another anti IL-5 approved for severe eosinophilic asthma, was found ineffective in EoE from a clinical and histological point of view¹⁴⁹. Better results are reported using the drug in children and adolescents over a long period of time¹⁵⁰.
- **Benralizumab**, a monoclonal antibody targeted towards the IL-5 receptor alpha-chain (IL-5R α) on eosinophils, is of potential utility in EoE¹⁵¹, but no studies have been activated to date.
- **Dupilumab** showed promising results in a phase II trial¹⁵²: a decrease in symptoms (dysphagia) was paralleled by in improvement in histologic and endoscopic features in a significant proportion of patients. These results suggest an efficacy also in the long term, since the remodeling is proportional to the eosinophilic infiltration.

Eosinophilic gastritis and duodenitis

EGIDs are defined by marked eosinophilia in the gastrointestinal (GI) tract resulting in a wide variety of GI symptoms. When accompanied by blood hypereosinophilia (HE; AEC $\geq$ 1500/mm³), EGID can occur as an isolated gastrointestinal disorder (hypereosinophilic syndrome/EGID overlap) or as part of a multisystem hypereosinophilic syndrome. In such syndromes, food allergy is frequent¹⁵³. As in EoE, food elimination diets appear to be effective in reducing clinical symptoms and tissue eosinophilia¹⁵⁴.

Among the biologics proposed for EGIDs, **Omalizumab**, **Mepolizimab** and the anti-integrin **Vedolizumab** did show reduction of tissue eosinophilia, but not symptoms^{155,156,157}. An

interesting approach, with possible future utility on food allergy, is the use of the Sialic acid-binding immunoglobulin-like lectin (Siglec)-8 blocker **Antolimab**.

Conclusions.

The advances of knowledge on the pathogenetic mechanisms of food allergy is revolutionizing the therapeutic perspectives of this disease. In this scenario, the exciting new opportunities need to be carefully weighed against their risks and their costs. Among the risks, in addition to those of the side effects of the drugs that we have outlined, we see a cultural risk: the availability and biological must not prompt the clinician to deflect from a complete diagnostic-therapeutic assessment of the food-allergic patient. The temptation to treat with a biological a patient whose food allergy has not been thoroughly investigated would be a serious therapeutic error. Biologicals are not shortcuts.

The costs of biologicals are sometimes very high, but in our opinion this should not prevent the hypothesis of using them at least in some circumstances. If an expense of thousands of dollars per month represents a remarkable investment, its value must be measured against both the direct and indirect costs faced by patients with this disease²¹. For this reason, according to the different socio-cultural and economic situations, when the indications are placed each national health system will have to foresee the appropriate cases in the specific context. To this end, the definition severity of food allergy being processed⁹ will represent a service offered by the World Allergy Organization to the community of patients, regulators, industries around the world.

References

- ¹ Sicherer SH. Food allergy. *Lancet*. 2002;360(9334):701-710
- ² Burks AW, Tang M, Sicherer S, et al. ICON: food allergy. *J Allergy Clin Immunol*. 2012;129(4):906-920
- ³ Dang AT, Chundi PK, Mousa NA, et al. The effect of age, sex, race/ethnicity, health insurance, and food specific serum immunoglobulin E on outcomes of oral food challenges. *World Allergy Organ J*. 2020;13(2):100100.
- ⁴ Ansotegui IJ, Melioli G, Canonica GW, Caraballo L, Villa E, Ebisawa M, et al. IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper. *World Allergy Organ J*. 2020;13:100080
- ⁵ Prescott SL, Fiocchi A, Beyer K, Lee BW, Sampson HA, Ebisawa M, et al. A global survey of changing patterns of food allergy burden in children. *World Allergy Organ J* 2013;6:21.
- ⁶ Fiocchi A, Ebisawa M. Non-IgE-mediated food allergies. *Curr Opin Allergy Clin Immunol*. 2020;20:290-1
- ⁷ Caubet JC, Szajewska H, Shamir R, Nowak-Węgrzyn A. Non-IgE-mediated gastrointestinal food allergies in children. *Pediatr Allergy Immunol*. 2017; 28:6–17.
- ⁸ Koletzko S, Heine RG. Non-IgE mediated cow's milk allergy in EuroPrevall. *Allergy*. 2015;70:1679-80
- ⁹ Arasi S, Nurmatov U, Dunn-Galvin A, Daher S, Roberts G, Turner PJ, Shinder SB, Gupta R, Eigenmann P, Nowak-Węgrzyn A, Sánchez Borges MA, Ansotegui IJ, Fernandez-Rivas M, Petrou S, Tanno LK, Vazquez-Ortiz M, Vickery BP, Wong GW, Ebisawa M, Fiocchi A. Consensus on DEfinition of Food Allergy SEverity (DEFASE) an integrated mixed methods systematic review. *World Allergy Organ J*. 2021;14:100503
- ¹⁰ Turner PJ, Worm M, Ansotegui IJ, El-Gamal Y, Rivas MF, Fineman S, et al. Time to revisit the definition and clinical criteria for anaphylaxis? *World Allergy Organ J*. 2019;12:100066
- ¹¹ Arasi S, Nurmatov U, Turner PJ, Ansotegui IJ, Daher S, Dunn-Galvin A, et al. Consensus on DEfinition of Food Allergy SEverity (DEFASE): protocol for a systematic review. *World Allergy Organ J*. 2020;13:100493
- ¹² Poirot E, He F, Gould LH, Hadler JL. Deaths, Hospitalizations, and Emergency Department Visits From Food-Related Anaphylaxis, New York City, 2000-2014: Implications for Fatality Prevention. *J Public Health Manag Pract*. 2020;10.1097/
- ¹³ Houben G, Burney P, Chan CH, et al. Prioritisation of allergenic foods with respect to public health relevance: Report from an ILSI Europe Food Allergy Task Force Expert Group. *Food Chem Toxicol*. 2016;89:8-18
- ¹⁴ <https://farrp.unl.edu/documents/Regulatory/FARRP-International-Regulatory-Chart-110619.pdf>, accessed April 1st, 2020
- ¹⁵ Fierro V, Di Girolamo F, Marzano V, Dahdah L, Mennini M. Food labeling issues in patients with severe food allergies: solving a hamlet-like doubt. *Curr Opin Allergy Clin Immunol*. 2017;17:204-211.
- ¹⁶ Fleischer DM. Allergic reactions to foods in preschool-aged children in a prospective observational food allergy study. *Pediatrics*. 2012;130:e25-32
- ¹⁷ Fiocchi A, Artesani MC, Riccardi C, et al. Impact of Omalizumab on food allergy in patients treated for asthma: a real-life study. *J Allergy Clin Immunol Pract*. 2019;7:1901-1909
- ¹⁸ Smith PK, Hourihane JO, Lieberman P. Risk multipliers for severe food anaphylaxis. *World Allergy Organ J*. 2015;8:30
- ¹⁹ Blom WM, Michelsen-Huisman AD, van Os-Medendorp H, et al. Accidental food allergy reactions: Products and undeclared ingredients. *J Allergy Clin Immunol*. 2018;142(3):865-875
- ²⁰ Sugunasingha N, Jones FW, Jones CJ. Interventions for caregivers of children with food allergy: A systematic review. *Pediatr Allergy Immunol*. 2020;10.1111
- ²¹ Bilaver LA, Chadha AS, Doshi P, O'Dwyer L, Gupta RS. Economic burden of food allergy: A systematic review. *Ann Allergy Asthma Immunol*. 2019;122:373-80
- ²² Wai HM, Middelveld R, Thörnqvist V, Ballardini N, Nilsson E, Strömquist J, Nilsson L, Ahlstedt S, Protudjer JLP. Pediatric food allergy-related household costs are influenced by age, but not disease severity. *World Allergy Organ J*. 2019 Oct 4;12(9):100061.
- ²³ Incorvaia C, Al-Ahmad M, Ansotegui IJ, Arasi S, Bachert C, Bos C, Bousquet J, Bozek A, Caimmi D, Calderón MA, Casale T, Custovic A, De Blay F, Demoly P, Devillier P, Didier A, Fiocchi A, Fox AT, Gevaert P, Gomez M, Heffler E, Ilina N, Irani C, Jutel M, Karagiannis E, Klimek L, Kuna P, O'Hehir R, Kurbacheva O, Matricardi PM, Morais-Almeida M, Mosges R, Novak N, Okamoto Y, Panzner P, Papadopoulos NG, Park HS, Passalacqua G, Pawankar R, Pfaar O, Schmid-Grendelmeier P, Scurati S, Tortajada-Girbés M, Vidal C, Virchow JC, Wahn U, Worm M, Ziegelmayer P, Canonica GW. Personalized medicine for allergy treatment: Allergen immunotherapy still a unique and unmatched model. *Allergy*. 2020 Sep 1. Epub ahead of print
- ²⁴ Paranjape A, Tsai M, Mukai K, Hoh RA, Joshi SA, Chinthrajah RS, Nadeau KC, Boyd SD, Galli SJ. Oral Immunotherapy and Basophil and Mast Cell Reactivity in Food Allergy. *Front Immunol*. 2020;11:602660.

- ²⁵ Nowak-Wegrzyn A, Sato S, Fiocchi A, Ebisawa M. Oral and sublingual immunotherapy for food allergy. *Curr Opin Allergy Clin Immunol*. 2019;19:606-613
- ²⁶ Loh W, Tang MLK. Debates in Allergy Medicine: Oral immunotherapy shortens the duration of milk and egg allergy - the con argument. *World Allergy Organ J*. 2018;11:12
- ²⁷ Nurmatov U, Dhami S, Arasi S, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy*. 2017;72:1133-1147
- ²⁸ Chinthrajah RS. Sustained outcomes in oral immunotherapy for peanut allergy (POISED study): a large, randomised, double-blind, placebo-controlled, phase 2 study. *The Lancet* 2019;394:1437-49
- ²⁹ Kulis MD, Patil SU, Wambre E, Vickery BP. Immune mechanisms of oral immunotherapy. *J Allergy Clin Immunol*. 2018 Feb;141:491-498
- ³⁰ Yoneyama T, Nakano N, Hara M, et al. Notch signaling contributes to the establishment of sustained unresponsiveness to food allergens by oral immunotherapy. *J Allergy Clin Immunol*. 2020; *published online ahead of print, 2020 Jul 24*
- ³¹ Orgel K, Burk C, Smeekens J, et al. Blocking antibodies induced by peanut oral and sublingual immunotherapy suppress basophil activation and are associated with sustained unresponsiveness. *Clin Exp Allergy*. 2019;49(4):461-470
- ³² Pecora V, Valluzzi RL, Mennini M, Fierro V, Dahdah L. Debates in allergy medicine: does oral immunotherapy shorten the duration of milk and egg allergy? The pro argument. *World Allergy Organ J*. 2018;11:11
- ³³ Chu DK, Wood RA, French S, et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. *Lancet*. 2019;393(10187):2222-2232
- ³⁴ Patrawala M, Shih J, Lee G, Vickery B. Peanut Oral Immunotherapy: a Current Perspective. *Curr Allergy Asthma Rep*. 2020;20(5):14
- ³⁵ Lopes JP, Sicherer S. Food allergy: epidemiology, pathogenesis, diagnosis, prevention, and treatment. *Curr Opin Immunol*. 2020;66:57-64.
- ³⁶ Long A, Borro M, Sampath V, Chinthrajah RS. New developments in non-allergen-specific therapy for the treatment of food allergy. *Curr Allergy Asthma Rep*. 2020;20:3.
- ³⁷ Hirota T, Nakayama T, Sato S, Yanagida N, Matsui T, Sugiura S et al. Association study of childhood food allergy with genome-wide association studies-discovered loci of atopic dermatitis and eosinophilic esophagitis. *J Allergy Clin Immunol* 2017; 140:1713-1716
- ³⁸ Chang C, Wu H, Lu Q. The epigenetics of food allergy. *Adv Exp Med Biol*. 2020;1253:141-152.
- ³⁹ Krempski JW, Dant C, Nadeau KC. The Origins of Allergy from a Systems Approach. *Ann Allergy Asthma Immunol*. 2020;S1081-1206
- ⁴⁰ DeKruyff RH, Zhang W, Nadeau KC, Leung DYM, Wills-Karp M. Summary of the Keystone Symposium "Origins of allergic disease: Microbial, epithelial and immune interactions," March 24-27, Tahoe City, California. *J Allergy Clin Immunol*. 2020;145:1072-1081
- ⁴¹ Weström B, Arévalo Sureda E, Pierzynowska K, Pierzynowski SG, Pérez-Cano FJ. The Immature Gut Barrier and Its Importance in Establishing Immunity in Newborn Mammals. *Front Immunol*. 2020;11:1153
- ⁴² Pali-Schöll I, Jensen-Jarolim E. Anti-acid medication as a risk factor for food allergy. *Allergy*. 2011;66:469-477
- ⁴³ Mennini M, Fierro V, Di Nardo G, Pecora V, Fiocchi A. Microbiota in non-IgE-mediated food allergy. *Curr Opin Allergy Clin Immunol*. 2020;20(3):323-328
- ⁴⁴ Diamanti A, Fiocchi AG, Capriati T, et al. Cow's milk allergy and neonatal short bowel syndrome: comorbidity or true association? *Eur J Clin Nutr*. 2015;69(1):102-106
- ⁴⁵ Brough HA, Nadeau KC, Sindher SB, et al. Epicutaneous sensitization in the development of food allergy: What is the evidence and how can this be prevented? *Allergy*. 2020; *published online ahead of print, 2020 Apr 6*
- ⁴⁶ Celebi Sözen Z, Cevhertas L, Nadeau K, Akdis M, Akdis CA. Environmental factors in epithelial barrier dysfunction. *J Allergy Clin Immunol*. 2020;145:1517-1528
- ⁴⁷ Patel NN, Kohanski MA, Maina IW, Workman AD, Herbert DR, Cohen NA. Sentinels at the wall: epithelial-derived cytokines serve as triggers of upper airway type 2 inflammation. *Int Forum Allergy Rhinol*. 2019;9:93-99
- ⁴⁸ Kortekaas Krohn I, Shikhagaie MM, Golebski K, Bernink JH, Breynaert C, Creyngs B, et al. Emerging roles of innate lymphoid cells in inflammatory diseases: Clinical implications. *Allergy* 2018;73:837-850
- ⁴⁹ Forbes EE, Groschwitz K, Abonia JP, et al. IL-9- and mast cell-mediated intestinal permeability predisposes to oral antigen hypersensitivity. *J Exp Med*. 2008;205:897-913
- ⁵⁰ Chu DK, Llop-Guevara A, Walker TD, et al. IL-33, but not thymic stromal lymphopoietin or IL-25, is central to mite and peanut allergic sensitization. *J Allergy Clin Immunol*. 2013;131:187-200

- ⁵¹ Galand C, Leyva-Castillo JM, Yoon J, et al. IL-33 promotes food anaphylaxis in epicutaneously sensitized mice by targeting mast cells. *J Allergy Clin Immunol*. 2016;138:1356-1366
- ⁵² Moretta L, Locatelli F. Innate lymphoid cells in normal and disease: An introductory overview. *Immunol Lett*. 2016;179:1
- ⁵³ Noval Rivas M, Burton OT, Wise P, et al. Regulatory T cell reprogramming toward a Th2-cell-like lineage impairs oral tolerance and promotes food allergy. *Immunity*. 2015;42:512-523.
- ⁵⁴ Johnston LK, Hsu CL, Krier-Burris RA, et al. IL-33 Precedes IL-5 in Regulating Eosinophil Commitment and Is Required for Eosinophil Homeostasis. *J Immunol*. 2016;197(9):3445-3453
- ⁵⁵ Chu DK, Mohammed-Ali Z, Jiménez-Saiz Ret, al. T helper cell IL-4 drives intestinal Th2 priming to oral peanut antigen, under the control of OX40L and independent of innate-like lymphocytes. *Mucosal Immunol*. 2014;7:1395-404
- ⁵⁶ Ford AQ, Dasgupta P, Mikhailenko I, Smith EM, Noben-Trauth N, Keegan AD. Adoptive transfer of IL-4Rα+ macrophages is sufficient to enhance eosinophilic inflammation in a mouse model of allergic lung inflammation. *BMC Immunol*. 2012;13:6
- ⁵⁷ Cianferoni A. Non-IgE Mediated Food Allergy. *Curr Pediatr Rev*. 2020;16:95-105.
- ⁵⁸ Adel-Patient K, Lezmi G, Castelli FA, et al. Deep analysis of immune response and metabolic signature in children with food protein induced enterocolitis to cow's milk. *Clin Transl Allergy*. 2018;8:38
- ⁵⁹ Pecora V, Prencipe G, Valluzzi R, et al. Inflammatory events during food protein-induced enterocolitis syndrome reactions. *Pediatr Allergy Immunol*. 2017;28:464-470. doi:10.1111/pai.12723
- ⁶⁰ Ruffner MA, Wang KY, Dudley JW, et al. Elevated Atopic Comorbidity in Patients with Food Protein-Induced Enterocolitis. *J Allergy Clin Immunol Pract*. 2020;8:1039-1046
- ⁶¹ Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. *Lancet*. 2020;396(10247):345-360
- ⁶² Klonowska J, Gleń J, Nowicki RJ, Trzeciak M. New Cytokines in the Pathogenesis of Atopic Dermatitis-New Therapeutic Targets. *Int J Mol Sci*. 2018;19(10):3086
- ⁶³ He H, Suryawanshi H, Morozov P, et al. Single-cell transcriptome analysis of human skin identifies novel fibroblast subpopulation and enrichment of immune subsets in atopic dermatitis. *J Allergy Clin Immunol*. 2020;145:1615-1628
- ⁶⁴ Salimi M, Barlow J, Saunders S, Xue L, Gutowska-Owsiak D, Wang X, Huang LC, et al. A role for IL-25 and IL-33-driven type-2 innate lymphoid cells in atopic dermatitis. *J. Exp. Med*. 2013, 210, 2939–2950.
- ⁶⁵ Lee EB, Kim KW, Hong JY, Jee HM, Sohn MH, Kim KE. Increased serum thymic stromal lymphopoietin in children with atopic dermatitis. *Pediatr Allergy Immunol*. 2010; 21:e457–e460
- ⁶⁶ Gutowska-Owsiak G, Schaupp A, Salimi M, Selvakumar TA, McPherson T, Taylor S, Ogg GS. IL-17 downregulates filaggrin and affects keratinocyte expression of genes associated with cellular adhesion. *Exp. Dermatol*. 2012, 21, 104–110
- ⁶⁷ Oka T, Sugaya M, Takahashi N, Nakajima R, Otobe S, Kabasawa M, Suga H, Miyagaki T, Asano Y, Sato S. Increased Interleukin-19 Expression in Cutaneous T-cell Lymphoma and Atopic Dermatitis. *Acta Derm Venereol* 2017, 97, 1172–1177
- ⁶⁸ Cianferoni A, Shuker M, Brown-Whitehorn T, Hunter H, Venter C, Spergel JM. Food avoidance strategies in eosinophilic oesophagitis. *Clin Exp Allergy*. 2019;49(3):269-284
- ⁶⁹ Biedermann L, Holbreich M, Atkins D, et al. Food-induced immediate response of the esophagus-A newly identified syndrome in patients with eosinophilic esophagitis [published online ahead of print, 2020 Jul 14]. *Allergy*. 2020;10.1111/all.14495
- ⁷⁰ Kottyan LC, Parameswaran S, Weirauch MT, Rothenberg ME, Martin LJ. The genetic etiology of eosinophilic esophagitis. *J Allergy Clin Immunol*. 2020;145(1):9-15
- ⁷¹ O'Shea KM, Aceves SS, Dellon ES, et al. Pathophysiology of eosinophilic esophagitis. *Gastroenterology*. 2018;154:333e345.
- ⁷² Chandramouleeswaran PM, Shen D, Lee AJ, et al. Preferential secretion of thymic stromal lymphopoietin (TSLP) by terminally differentiated esophageal epithelial cells: relevance to eosinophilic esophagitis (EoE). *PloS One*. 2016; 18(11):e0150968.
- ⁷³ Venkateshaiah SU, Kandikattu HK, Mishra A. Significance of Interleukin (IL)-15 in IgE associated eosinophilic Esophagitis (EoE). *Int J Basic Clin Immunol*. 2019;2:1-12.
- ⁷⁴ Chawla K, Alabbas B, Sheth D, Papademetriou M. As Easy as EoE: A Novel and Effective Multidisciplinary Approach to Care of Patients with Eosinophilic Esophagitis in the Age of Biologics. *Dig Dis Sci*. 2020;65(8):2196-2202
- ⁷⁵ Shukla A, Mishra A, Venkateshaiah SU, Manohar M, Mahadevappa CP, Mishra A. Elements Involved In Promoting Eosinophilic Gastrointestinal Disorders. *J Genet Syndr Gene Ther*. 2015;6(2):265

- ⁷⁶ Youngblood BA, Brock EC, Leung J, et al. Siglec-8 antibody reduces eosinophils and mast cells in a transgenic mouse model of eosinophilic gastroenteritis. *JCI Insight*. 2019;4(19):e126219.
- ⁷⁷ Lyles J, Rothenberg M. Role of genetics, environment, and their interactions in the pathogenesis of eosinophilic esophagitis. *Curr Opin Immunol*. 2019;60:46-53.
- ⁷⁸ Nowak-Wegrzyn A, Szajewska H, Lack G. Food allergy and the gut. *Nat Rev Gastroenterol Hepatol*. 2017;14(4):241-257.
- ⁷⁹ Pesek RD, Gupta SK. Future therapies for eosinophilic gastrointestinal disorders. *Ann Allergy Asthma Immunol*. 2020;124(3):219-226.
- ⁸⁰ Chinthrajah S, Cao S, Liu C, et al. Phase 2a randomized, placebo-controlled study of anti-IL-33 in peanut allergy. *JCI Insight*. 2019;4(22):e131347.
- ⁸¹ Corren J, Parnes JR, Wang L, et al. Tezepelumab in Adults with Uncontrolled Asthma. *N Engl J Med*. 2017;377:936-946.
- ⁸² Uppal SK, Kearns DG, Chat VS, Han G, Wu JJ. Review and analysis of biologic therapies currently in phase II and phase III clinical trials for atopic dermatitis. *J Dermatolog Treat*. 2020:1-11 (Epub ahead of print).
- ⁸³ Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Sher L, Gooderham MJ, et al. Efficacy and Safety of Dupilumab in Adolescents With Uncontrolled Moderate to Severe Atopic Dermatitis: A Phase 3 Randomized Clinical Trial. *JAMA Dermatol*. 2020;156:44-56.
- ⁸⁴ Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, Busse WW, Ford L, Sher L, FitzGerald JM, Katelaris C, Tohda Y, Zhang B, Staudinger H, Pirozzi G, Amin N, Ruddy M, Akinlade B, Khan A, Chao J, Martincova R, Graham NMH, Hamilton JD, Swanson BN, Stahl N, Yancopoulos GD, Teper A. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *N Engl J Med*. 2018 Jun 28;378:2486-2496.
- ⁸⁵ Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet* 2019; 394: 1638-50.
- ⁸⁶ Gandhi NA, Pirozzi G, Graham NMH. Commonality of the IL-4/IL-13 pathway in atopic diseases. *Expert Rev Clin Immunol*. 2017;13:425-437.
- ⁸⁷ Harb H, Chatila TA. Mechanisms of Dupilumab. *Clin Exp Allergy*. 2020;50:5-14.
- ⁸⁸ Rial MJ, Barroso B, Sastre J. Dupilumab for treatment of food allergy. *J Allergy Clin Immunol Pract*. 2019;7:673-4.
- ⁸⁹ <https://clinicaltrials.gov/ct2/show/NCT03682770>, accessed January 2nd, 2021.
- ⁹⁰ <https://clinicaltrials.gov/ct2/show/NCT03793608>, accessed January 2nd, 2021.
- ⁹¹ Chen JB, Wu PC, Hung AF, Chu CY, Tsai TF, Yu HM, et al. Unique epitopes on C epsilon mX in IgE-B cell receptors are potentially applicable for targeting IgE-committed B cells. *J Immunol*. 2010;184:1748-56.
- ⁹² Gauvreau GM, Harris JM, Boulet LP, Scheerens H, Fitzgerald JM, Putnam WS, et al. Targeting membrane-expressed IgE B cell receptor with an antibody to the M1 prime epitope reduces IgE production. *Sci Transl Med*. 2014;6:243-85.
- ⁹³ Chu SY, Horton HM, Pong E, Leung IW, Chen H, Nguyen DH, Bautista C, Muchhal US, Bennett MJ, Moore GL, Szymkowski DE, Desjarlais JR. Reduction of total IgE by targeted coengagement of IgE B-cell receptor and FcγRIIb with Fc-engineered antibody. *J Allergy Clin Immunol*. 2012;129:1102-15.
- ⁹⁴ <https://www.clinicaltrials.gov/ct2/show/NCT02148744>, accessed February 7th, 2021.
- ⁹⁵ Li T, Zhang Q, Liu Y, Chen D, Hu B, Blake DA, Liu F. Production of recombinant ScFv antibodies against methamidophos from a phage-display library of a hyperimmunized mouse. *J Agric Food Chem*. 2006;54:9085-91.
- ⁹⁶ Peng X, Wang J, Li X, Lin L, Xie G, Cui Z, et al. Targeting mast cells and basophils with anti-FcεRIα Fab-conjugated celastrol-loaded micelles suppresses allergic inflammation. *J Biomed Nanotechnol*. 2015;11:2286-99.
- ⁹⁷ Perez-Witzke D, Miranda-Garcia MA, Suarez N, Becerra R, Duque K, Porras V, et al. CTLA4Fcεpsilon, a novel soluble fusion protein that binds B7 molecules and the IgE receptors, and reduces human in vitro soluble CD23 production and lymphocyte proliferation. *Immunology*. 2016;148:40-55.
- ⁹⁸ Leung DY, Sampson HA, Yunginger JW, Burks AW Jr, Schneider LC, Wortel CH, Davis FM, Hyun JD, Shanahan WR Jr; Avon Longitudinal Study of Parents and Children Study Team. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med*. 2003;348:986-93.
- ⁹⁹ Savage JH, Courneya JP, Sterba PM, et al. Kinetics of mast cell, basophil, and oral food challenge responses in omalizumab-treated adults with peanut allergy. *J Allergy Clin Immunol*. 2012;130:1123-1129.
- ¹⁰⁰ Sampson HA, Leung DY, Burks AW, Lack G, Bahna SL, Jones SM, Wong DA. 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

¹⁰¹ <https://clinicaltrials.gov/ct2/show/NCT03881696>, accessed on January 3rd, 2021.

¹⁰³ Dantzer JA, Wood RA. Omalizumab as an adjuvant in food allergen immunotherapy. *Curr Opin Allergy Clin Immunol*. 2021 Feb 16. Epub ahead of print

¹⁰⁴ Nadeau KC, Schneider LC, Hoyte L, et al. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. *J Allergy Clin Immunol*. 2011;127:1622-4

¹⁰⁵ Bedoret D, Singh AK, Shaw V, Hoyte EG, Hamilton R, DeKruyff RH, Schneider LC, Nadeau KC, Umetsu DT. Changes in antigen-specific T-cell number and function during oral desensitization in cow's milk allergy enabled with omalizumab. *Mucosal Immunol*. 2012;5:267-76

¹⁰⁶ Wood RA, Kim JS, Lindblad R, 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.

¹⁰⁷ Takahashi M, Soejima K, Taniuchi S, et al. Oral immunotherapy combined with omalizumab for high-risk cow's milk allergy: a randomized controlled trial. *Sci Rep*. 2017;7:17453.

¹⁰⁸ Martorell-Calatayud C, Michavila-Gómez A, Martorell-Aragón A, et al. Anti-IgE-assisted desensitization to egg and cow's milk in patients refractory to conventional oral immunotherapy. *Pediatr Allergy Immunol*. 2016;27:544-6.

¹⁰⁹ Schneider LC, Rachid R, LeBovidge J, 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.

¹¹⁰ Yee CSK, Albuhairei S, Noh E, et al. Long-Term outcome of Peanut Oral Immunotherapy facilitated initially by Omalizumab. *J Allergy Clin Immunol Pract*. 2019;7:451-61.

¹¹¹ <https://clinicaltrials.gov/ct2/show/NCT02402231>, accessed January 2nd, 2021

¹¹² Brandström J, Vetander M, Lilja G, et al. Individually dosed omalizumab: an effective treatment for severe peanut allergy. *Clin Exp Allergy*. 2017;47:540-550.

¹¹³ Brandström J, Vetander M, Sundqvist AC, et al. Individually dosed omalizumab facilitates peanut oral immunotherapy in peanut allergic adolescents. *Clin Exp Allergy*. 2019;49:1328-41

¹¹⁴ MacGinnitie AJ, Rachid R, Gragg H, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. *J Allergy Clin Immunol*. 2017;139:873-81

¹¹⁵ Bégin P, Dominguez T, Wilson SP, Bacal L, Mehrotra A, Kausch B, Trela A, Tavassoli M, Hoyte E, O'Riordan G, Blakemore A, Seki S, Hamilton RG, Nadeau KC. 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

¹¹⁶ Andorf S, Purington N, Block WM, Long AJ, Tupa D, Brittain E, Rudman Spergel A, Desai M, Galli SJ, Nadeau KC, Chinthrajah RS. Anti-IgE treatment with oral immunotherapy in multifoed allergic participants: a double-blind, randomised, controlled trial. *Lancet Gastroenterol Hepatol*. 2018;3:85-94

¹¹⁷ Andorf S, Purington N, Kumar D, Long A, O'Laughlin KL, Sicherer S, Sampson H, Cianferoni A, Whitehorn TB, Petroni D, Makhija M, Robison RG, Lierl M, Logsdon S, Desai M, Galli SJ, Rael E, Assa'ad A, Chinthrajah S, Pongracic J, Spergel JM, Tam J, Tilles S, Wang J, Nadeau K. A Phase 2 Randomized Controlled Multisite Study Using Omalizumab-facilitated Rapid Desensitization to Test Continued vs Discontinued Dosing in Multifoed Allergic Individuals. *EClinicalMedicine*. 2019;7:27-38

¹¹⁸ Dahdah L, Ceccarelli S, Amendola S, et al. IgE Immunoabsorption Knocks Down the Risk of Food-Related Anaphylaxis. *Pediatrics*. 2015;136(6):e1617-20.

¹¹⁹ <https://clinicaltrials.gov/ct2/show/NCT03964051>, accessed January 2nd, 2021

¹²⁰ Langlois A, Laverne MH, Leroux H, Killer K, Azzano P, Paradis L, Samaan K, Lacombe-Barrios J, Mâsse B, Des Roches A, Bégin P. Protocol for a double-blind, randomized controlled trial on the dose-related efficacy of omalizumab in multi-food oral immunotherapy. *Allergy Asthma Clin Immunol*. 2020;16:25

¹²¹ <https://clinicaltrials.gov/ct2/show/NCT02879006>, accessed January 2nd, 2021

¹²² <https://clinicaltrials.gov/ct2/show/NCT03679676>, accessed January 2nd, 2021

¹²³ Azzano P, Paquin M, Langlois A, et al. Determinants of omalizumab dose-related efficacy in oral immunotherapy: Evidence from a cohort of 181 patients. *J Allergy Clin Immunol*. 2021;147:233-243

¹²⁴ Arasi S, Mennini M, Cafarotti A, Focchi A. Omalizumab as monotherapy for food allergy. *Curr Opin Allergy Clin Immunol*. 2021 Mar 23. Epub ahead of print

¹²⁵ Lafuente I, Mazon A, Nieto M, Uixera S, Pina R, Nieto A. Possible recurrence of symptoms after discontinuation of omalizumab in anti-IgE-assisted desensitization to egg. *Pediatr Allergy Immunol*. 2014; 25:717-9

- ¹²⁶ Fiocchi A, Bouygue GR, Martelli A, Terracciano L, Sarratud T. Dietary treatment of childhood atopic eczema/dermatitis syndrome (AEDS). *Allergy*. 2004;59 Suppl 78:78-85
- ¹²⁷ Lacombe Barrios J, Be'gin P, Paradis L, et al. Anti-IgE therapy and severe atopic dermatitis: a pediatric perspective. *J Am Acad Dermatol* 2013;69:832-4.
- ¹²⁸ Wang HH, Li YC, Huang YC. Efficacy of omalizumab in patients with atopic dermatitis: A systematic review and meta-analysis. *J Allergy Clin Immunol* 2016;138:1719-1722
- ¹²⁹ Chan S, Cornelius V, Cro S, et al. Treatment Effect of Omalizumab on Severe Pediatric Atopic Dermatitis: The ADAPT Randomized Clinical Trial. *JAMA Pediatr* 2019;174:29-37.
- ¹³⁰ Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, Simpson EL, Papp KA, Hong HC, Rubel D, Foley P, Prens E, Griffiths CEM, Etoh T, Pinto PH, Pujol RM, Szepietowski JC, Ettler K, Kemény L, Zhu X, Akinlade B, Hultsch T, Mastey V, Gadkari A, Eckert L, Amin N, Graham NMH, Pirozzi G, Stahl N, Yancopoulos GD, Shumel B. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10086):2287-2303
- ¹³¹ Thomson J, Wernham AGH, Williams HC. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a critical appraisal. *Br J Dermatol*. 2018;178:897-902
- ¹³² Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, Silverberg JI, Deleuran M, Kataoka Y, Lacour JP, Kingo K, Worm M, Poulin Y, Wollenberg A, Soo Y, Graham NM, Pirozzi G, Akinlade B, Staudinger H, Mastey V, Eckert L, Gadkari A, Stahl N, Yancopoulos GD, Ardeleanu M; SOLO 1 and SOLO 2 Investigators. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *N Engl J Med*. 2016 Dec 15;375:2335-2348
- ¹³³ Mennini M, Dahdah L, Fiocchi A. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *N Engl J Med*. 2017;376:1090
- ¹³⁴ Sawangjit R, Dilokthornsakul P, Lloyd-Lavery A et al. Systemic treatments for eczema: a network meta-analysis. *Cochrane Database Syst Rev*. 2020;9:CD013206.
- ¹³⁵ <https://clinicaltrials.gov/ct2/show/NCT03736967>, accessed on January 7th 2021.
- ¹³⁶ Wollenberg A, Howell MD, Guttman-Yassky E, Silverberg JI, Kell C, Ranade K, Moate R, van der Merwe R. Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb. *J Allergy Clin Immunol*. 2019 143(1):135-141.
- ¹³⁷ Boguniewicz M. Biologics for Atopic Dermatitis. *Immunol Allergy Clin North Am*. 2020;40:593-607
- ¹³⁸ Simpson EL, Flohr C, Eichenfield LF, et al. Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: A randomized, placebo-controlled phase II trial (TREBLE). *J Am Acad Dermatol* 2018;78:863-71.
- ¹³⁹ Guttman-Yassky E, Blauvelt A, Eichenfield LF, et al. Efficacy and safety of lebrikizumab, a high-affinity interleukin 13 inhibitor, in adults with moderate to severe atopic dermatitis: A phase 2b randomized clinical trial. *JAMA Dermatol* 2020; 156:411-20.
- ¹⁴⁰ Kabashima K, Furue M, Hanifin JM, et al. Nemolizumab in patients with moderate to-severe atopic dermatitis: randomized, phase II, long-term extension study. *J Allergy Clin Immunol* 2018;142:1121-30.
- ¹⁴¹ Stander S, Yosipovitch G, Legat FJ, et al. Trial of nemolizumab in moderate-to severe prurigo nodularis. *N Engl J Med* 2020;382:706-16.
- ¹⁴² Simpson EL, Parnes JR, She D, et al. Tezepelumab, an anti-thymic stromal lymphopoietin monoclonal antibody, in the treatment of moderate to severe atopic dermatitis: A randomized phase 2a clinical trial. *J Am Acad Dermatol* 2019;80:1013-21.
- ¹⁴³ Hirano I, Chan ES, Rank MA, et al; AGA Institute Clinical Guidelines Committee; Joint Task Force on Allergy-Immunology Practice Parameters. AGA institute and the joint task force on allergy-immunology practice parameters clinical guidelines for the management of eosinophilic esophagitis. *Ann Allergy Asthma Immunol*. 2020;124:416-423
- ¹⁴⁴ Rank MA, Sharaf RN, Furuta GT, et al; Joint Task Force on Allergy-Immunology Practice Parameters collaborators. Technical Review on the Management of Eosinophilic Esophagitis: A Report From the AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters. *Ann Allergy Asthma Immunol*. 2020;124:424-440
- ¹⁴⁵ Metcalfe JR, D'Vaz N, Makrides M, Gold MS, Quinn P, West CE, Loh R, Prescott SL, Palmer DJ. Elevated IL-5 and IL-13 responses to egg proteins predate the introduction of egg in solid foods in infants with eczema. *Clin Exp Allergy*. 2016;46:308-16.
- ¹⁴⁶ Chawla K, Alabbas B, Sheth D, Papademetriou M. As Easy as EoE: A Novel and Effective Multidisciplinary

Approach to Care of Patients with Eosinophilic Esophagitis in the Age of Biologics. *Dig Dis Sci.* 2020;65:2196-2202

¹⁴⁷ Loizou D, Enav B, Komlodi-Pasztor E, et al. A pilot study of omalizumab in eosinophilic esophagitis. *PLoS ONE.* 2015;10:e0113483

¹⁴⁸ Assa'ad AH, Gupta SK, Collins MH, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. *Gastroenterology.* 2011;141:1593–1604.

¹⁴⁹ Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2012;129:456–63

¹⁵⁰ Markowitz JE, Jobe L, Miller M, Frost C, Laney Z, Eke R. Safety and efficacy of reslizumab for children and adolescents with eosinophilic esophagitis treated for 9 years. *J Pediatr Gastroenterol Nutr.* 2018;66:893–897.

¹⁵¹ Roufosse F. Targeting the interleukin-5 pathway for treatment of eosinophilic conditions other than asthma. *Front Med.* 2018;5:49.

¹⁵² Hirano I, Dellon ES, Hamilton JD, et al. Efficacy of Dupilumab in a phase 2 randomized trial of adults with active eosinophilic esophagitis. *Gastroenterology.* 2020;158:111–122.

¹⁵³ Kuang FL, Curtin BF, Alao H, Piligian B, Berry A, Holland-Thomas N, Powers A, Quezado M, Lumbard K, Fay MP, Klion AD, Kumar S, Khoury P, . Single-organ and Multisystem hypereosinophilic syndrome patients with gastrointestinal manifestations share common characteristics. *J Allergy Clin Immunol Pract.* 2020 Apr 25.S2213-2198(20)30376-7

¹⁵⁴ Lucendo AJ, Serrano-Montalbain B, Arias A, et al. Efficacy of dietary treatment for inducing disease remission in eosinophilic gastroenteritis. *J Pediatr Gastroenterol Nutr* 2015;61:56–64

¹⁵⁵ Foroughi S, Foster B, Kim NY, et al. Anti-IgE treatment of eosinophil-associated gastrointestinal disorders. *J Allergy Clin Immunol* 2007;120:594–601

¹⁵⁶ Prussin C, James SP, Huber MM, Klion AD, Metcalfe DD. Pilot study of anti-IL-5 in eosinophilic gastroenteritis. *J Allergy Clin Immunol* 2003;111(2):S275

¹⁵⁷ Lucendo AJ, López-Sánchez P. Targeted Therapies for Eosinophilic Gastrointestinal Disorders. *BioDrugs.* 2020;34:477-493.

TABLE. Specific food-induced allergic conditions, mechanisms and involved foods (modified from ²)

Disorder	Key features	Mechanisms	Involved foods
IgE-mediated (acute onset)			
Acute urticaria/angioedema	Food commonly causes acute (20%) but rarely chronic urticaria	IL-33, TSLP, IL-4, IL-13, IgE	Major food allergens
Anaphylaxis	Rapidly progressive, multiple organ system reaction can include cardiovascular collapse	IL-33, TSLP, IL-4, IL-13, IL-31, IL-33, IgE	Peanut, tree nuts, shellfish, fish, milk, egg (...) .
Food-associated, exercise-induced anaphylaxis	Food triggers anaphylaxis only if ingestion is followed temporally by exercise	IgE	Wheat, shellfish, and celery most often described
Oral allergy syndrome (pollen-associated food allergy syndrome)	Pruritus and mild oedema confined to oral cavity. Uncommonly progress beyond the mouth (about 7%) Rarely progresses to anaphylaxis (1% to 2%). Might increase after pollen season.	IgE	Raw fruit/vegetables; cooked forms tolerated; examples of relationships: birch (apple, peach, pear, carrot), ragweed (melons)
Combined IgE and cell-mediated (delayed onset/chronic)			
Atopic dermatitis (AD)	Associated with food allergy in about 35% of children with moderate-to-severe rash	CCL2, CCL19, TSLP, IL-4, IL-13, IL-17, IL-19, IL-22,	Major allergens, particularly egg, milk

		IL-26, IL-31RA, IL-33	
Eosinophilic esophagitis	Feeding disorders, reflux symptoms, vomiting, dysphagia, and food impaction.	IL-4, IL-5, IL-13, TSLP	Milk, wheat, egg, peanut, soybean, tree nuts, shellfish, fish
Eosinophilic gastroenteritis	Vary on site(s)/degree of eosinophilic inflammation; might include ascites, weight loss, oedema, obstruction	IL-4, IL-5, IL-13, eotaxin-3, CRTH2, SIGLEC-8, TGF- β	Multiple
IgE and cell-mediated (delayed onset/chronic)			
Food Protein-Induced Enterocolitis Syndrome (FPIES)	Emesis, diarrhoea, poor growth, lethargy; re-exposure after restriction: emesis, diarrhoea, hypotension 2 hours after ingestion	IL-8, IL-4, IL-5, TNF- α , IL-6, IL-13	Milk, soy, fish, rice, wheat, beef, apple
Food protein-induced allergic proctocolitis	Mucus-laden, bloody stools in infants	IL-5	Milk (through breastfeeding)
Allergic contact dermatitis	Often occupational because of chemical moieties, oleoresins. Systemic contact dermatitis is a rare variant because of ingestion	Similar to AD?	Spices, fruits, vegetables...

Figure 1 – Hypotheses for the OIT mechanisms²⁸:

- Reduction of the establishment of Treg cells
- Inception of counter regulatory immune responses
- Reduction of excessive effector responses
- Decrease in TH2 cell activity and IL-10 production
- Change in IgE/IgG4 ratio
- Epigenetic modifications at the *Foxp3* locus during Treg cell differentiation mechanisms

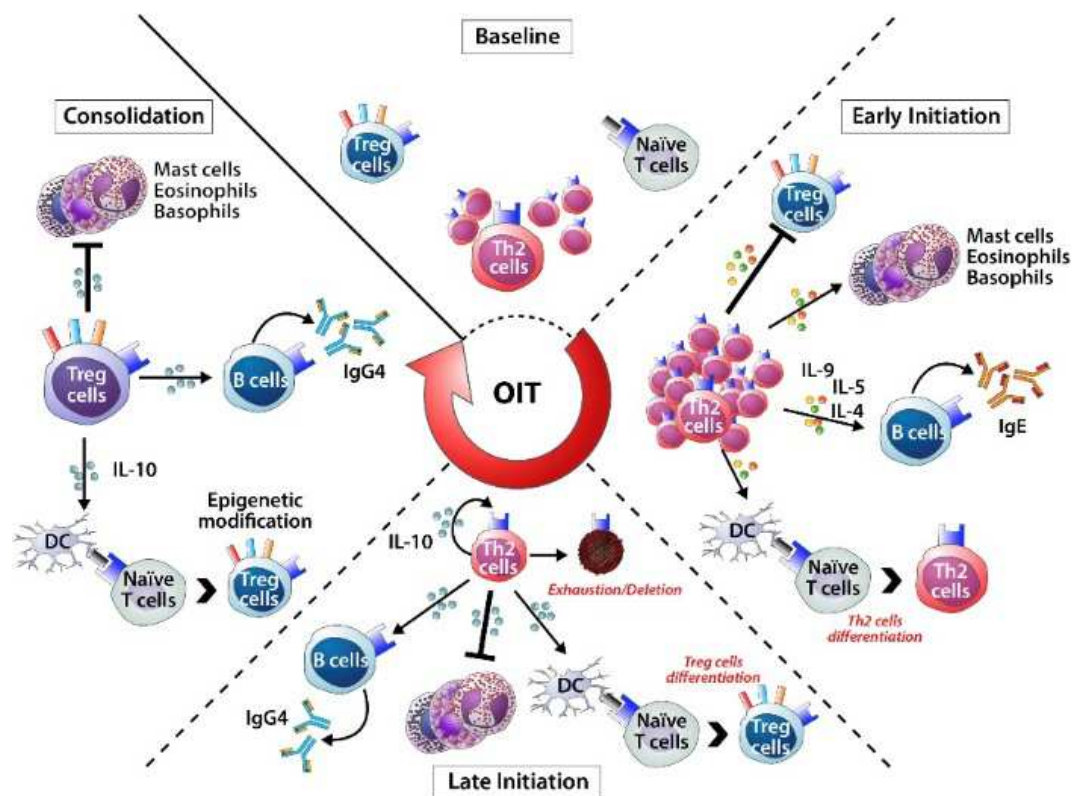


Figure 2. Mechanisms involved in the pathogenesis of food allergy of possible therapeutic significance³⁶.

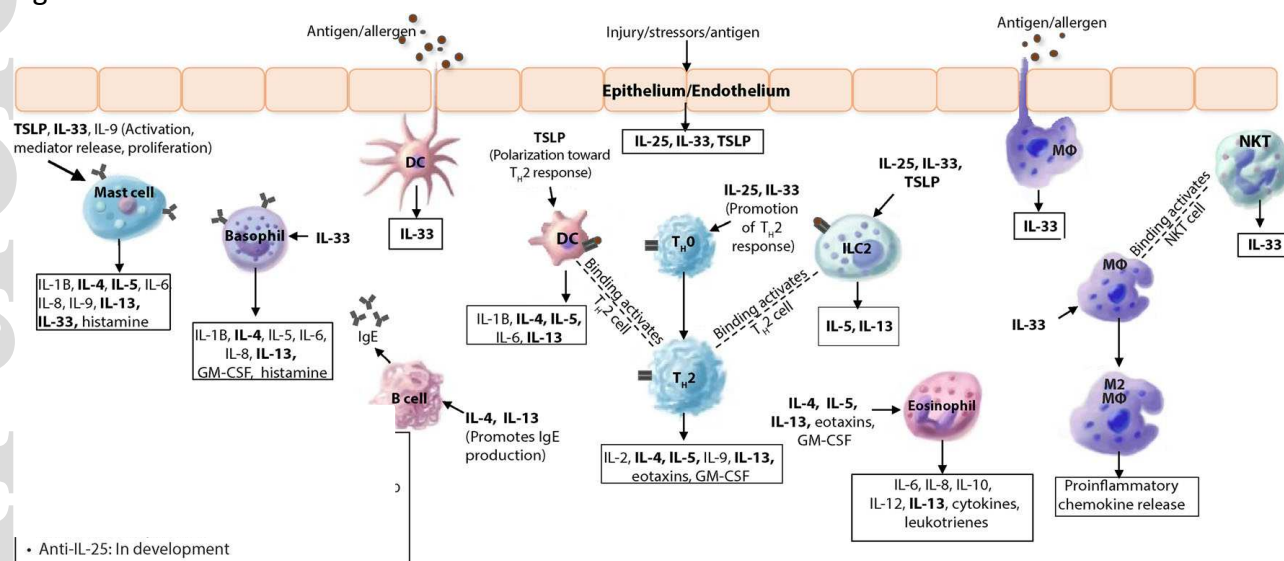


Figure 3. Thresholds for wheat, egg, baked milk and milk before and after four months' treatment with Omalizumab for asthma¹¹.

