



# New Developments in Non-allergen-specific Therapy for the Treatment of Food Allergy

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## Abstract

**Purpose of Review** The prevalence of food allergy is increasing. At the current time, there are no approved treatments for food allergy. Major limitations of immunotherapy are long treatment periods (months or years), frequent clinic visits, high costs, increased risk of adverse events during treatment, and lack of durability of desensitization. Additionally, it is allergen-specific, and in those allergic to multiple allergens, the length and cost of treatment are further increased. In this review, we summarize recent developments in novel non-allergen-specific treatments for food allergy.

**Recent Findings** A number of monoclonal antibodies that block IgE or specific pro-allergenic cytokines or their receptors have shown promise in clinical trials for food allergy.

**Summary** The insight we have gained through the use of one drug for the treatment of an atopic disease is quickly being translated to other atopic diseases, including food allergy. The future for food allergy treatment with biologics looks bright.

**Keywords** Food allergy · Immunotherapy · Biologics · Atopy · Omalizumab · Dupilumab

## Introduction

Food allergy (FA) is a growing public health issue, affecting up to 8% of young children [1] and 10.8% of adults in the USA alone [2]. Among adults, 45% are estimated to have multiple food allergies [2]. It causes significant impairment in quality of life (QoL) and may lead to nutritional deficiencies [3–5]. Foods generally responsible for FA include milk, eggs, peanuts, soybeans, tree nuts, wheat, fish, and crustaceans [6]. Current guidelines recommend dietary avoidance of the implicated food allergen(s) for management of FA, with administration of emergency medications in cases of accidental exposure [7–9]. Despite these recommendations, approximately

50% and 75% of patients with food allergies have reported accidental ingestion to their allergen within 5 and 10 years, respectively. Among those with peanut allergy, nearly 50% report accidental ingestion within the last 2 years [10]. Increases in food-induced emergency department visits have seen an increase of 214% between 2005 and 2014 [11]. Symptoms of exposure range from mild to severe and may include anaphylaxis, a severe and potentially life-threatening allergic reaction that requires immediate treatment.

The first published and successful treatment for FA was in 1908 for egg allergy using oral immunotherapy (OIT) [12]; however, it was not until a century later that there was renewed interest in using immunotherapy for FA. Today, immunotherapy is still an experimental therapy with no standardized protocols and mainly conducted in research centers or in a few specialized allergy centers. Major limitations of immunotherapy are long treatment periods (months or years), frequent clinic visits, high cost, increased risk of adverse events during treatment, and lack of durability of desensitization. Additionally, it is allergen-specific and in those allergic to multiple allergens, the length and cost of treatment are further increased [13]. Non-allergen-specific treatments for FA, particularly for those with multiple food allergies, are desirable.

In this review, we discuss the fundamentals of immunotherapy, basic mechanisms involved in FA, and the non-allergen-

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specific therapies that currently show promise as potential treatments for FA.

## Immunotherapy

To date, there are still no approved drugs or standardized immunotherapy protocols for the treatment of FA, and published studies on immunotherapy vary with respect to allergen type, dose, length, population studied, mode of administration, drugs used for pre-treatment or as adjunctive treatment, and clinical endpoints studied. The ultimate goal of FA immunotherapy is to establish *tolerance*, which indicates a cure, whereby patients can consume the foods they were previously allergic to at any time and in amounts similar to normal dietary intakes; however, at this time, evidence suggests that although immunotherapy can increase reaction thresholds to allergens, continued ingestion of the allergen is necessary to maintain increased reaction threshold levels. While these patients are said to be *desensitized*, the allergy often returns and the protective effect is lost if allergen dosing is interrupted or discontinued [13]. The criteria for desensitization vary between studies with reaction thresholds set to either amounts that prevent reaction on accidental ingestion [14] or to near normal dietary levels [15]. Data on tolerance is limited as long-term studies (years) to measure tolerance are difficult to conduct. As a surrogate for tolerance, studies measure *sustained unresponsiveness* (SU), which indicates the persistence of increased allergen threshold after successful immunotherapy and after discontinuation of allergen consumption for a predefined period (varying with studies).

Routes of immunotherapy for FA include subcutaneous, epicutaneous, oral, and sublingual immunotherapy (SCIT, EPIT, OIT, and SLIT, respectively) [16]. SCIT, commonly used for aeroallergens, has previously been abandoned as a therapeutic approach due to unacceptably high rates of adverse systemic reactions [17]. While EPIT, OIT, and SLIT are relatively safer with promising rates of efficacy, each method carries the risk of treatment-related adverse events. OIT is the most commonly used method of immunotherapy, followed by SLIT and EPIT. Both OIT and EPIT are in phase 3 trials.

Systematic reviews and meta-analyses have evaluated the collective evidence regarding efficacy and safety of OIT, with OIT generally demonstrating clinically relevant benefits [13, 18–20]. The data suggest that desensitization is successfully achieved in the majority of treated individuals who remain compliant, with 28–75% of patients maintaining SU depending on the criteria used to define desensitization and SU [15, 18, 21–26, 27••]. While the evidence supporting the efficacy of OIT in allergen-specific desensitization [16] to peanut, cow's milk, and egg [28] is strong, more information is needed regarding long-term efficacy, QoL assessments, and cost-

effectiveness. Despite the general success of OIT, it is not without risk. The majority of treatment-related adverse events are mild-to-moderate in nature depending on dosing methodology, typically involving oropharyngeal pruritus and transient abdominal pain [21, 24, 28, 29]; however, more severe adverse reactions are also occasionally observed, including, but not limited to, wheezing, vomiting, urticaria, and angioedema [18]. Additional data suggest that the occurrence of intolerable symptoms or severe allergic reactions may increase rates of withdrawal from studies of OIT between 10 and 20% [29]. Severe cases of anaphylaxis have been documented to occur unpredictably, including to doses of allergen previously tolerated, usually triggered by cofactors such as infection, exercise, anxiety, or allergen co-exposure [20]. Additionally, while more work is needed to understand the underlying mechanism, eosinophilic infiltration of the gastrointestinal tract (such as in eosinophilic esophagitis) has been reported as a complicating disorder in 2.7% of OIT-treated patients [13, 30, 31]. As expected, a recently published systematic review found significantly higher rates of overall allergic reactions among patients receiving OIT as compared with avoidance management [32].

## Mechanisms

We have gained much insight into the mechanism of FA and atopic diseases in the last decade, which has assisted with the development of novel drugs [33, 34]. IgE-mediated food allergies stem from an abnormal response to dietary antigens, mainly proteins. It is estimated that approximately 2% of consumed dietary proteins reach the gut [35, 36] and interact with the intestinal immune system. Whether the interaction results in a tolerogenic or pro-allergic response is dictated by a delicate balance [37]. Sensitization, one of the first steps in the development of FA, can occur not only through oral food exposure but also via the skin. While decreases in gastrointestinal tight junction integrity, alterations of stomach pH, and variation in the gut microbiome have all been associated with increased risk of FA, epidemiological studies and experimental mouse models have demonstrated that sensitization can also start from defects in skin integrity, especially in cases of eczema and atopic dermatitis (AD) [38, 39]. In addition to epithelial exposure to stressors and damage, potential food allergens passing through damaged epithelia and avoiding normal mechanisms of transport have been shown to induce the release of alarmins, a group of cytokines implicated in the promotion of T helper 2 (Th2)-dominant immune responses toward such allergens [40]. This group includes the alarmins interleukin-25 (IL-25), IL-33, and thymic stromal lymphopoietin (TSLP) (Fig. 1). IL-25 stimulates type 2 innate lymphoid cells (ILC2s) to release both IL-13 and IL-5 and, together with TSLP, induces T helper 9 cells which produce

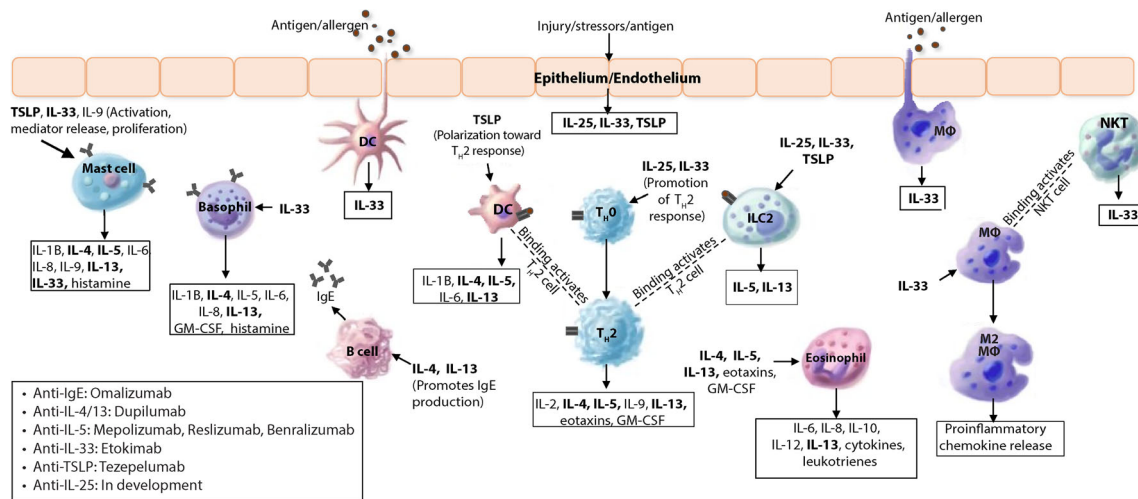


**Fig. 1** Mediators of food sensitization and allergy. Alarmins, including IL-25, IL-33, and TSLP, are released in response to cell injury or stress, including exposure to viruses, bacteria, or alloantigens. These alarmins broadly promote a downstream shift away from a tolerogenic, Th1-dominant state and toward a pro-allergic, Th2-characterized response. The inhibition of IL-33 via etokimab is currently under investigation for the treatment of food allergy, with additional anti-alarmin agents under similar consideration. Interleukins 4, 5, and 13 play critical roles in the downstream mediation and maintenance of the pro-allergic response. Agents directed against these mediators are hypothesized to provide

significant benefit in the treatment of food allergy, with studies evaluating dupilumab for the treatment of peanut allergy currently underway. The production of allergen-specific IgE is a net result of the upstream, pro-inflammatory mediators. Free IgE ultimately binds to FcεRI receptors on the surface of basophils and MCs, priming the cells for activation upon subsequent allergen exposure. Omalizumab has shown considerable efficacy in its ability to inhibit the binding of IgE to its receptor, leading to significant reductions in surface-bound IgE and allergic responses following food allergen exposure

IL-9 [41]. IL-9 is a mast cell (MC) growth factor correlated with intestinal mastocytosis and food-induced anaphylaxis [35]. In addition to acting directly on MCs and promoting their IgE-mediated activation, IL-33 has been shown to activate ILC2s, in turn inducing the production of IL-13 and IL-4. Both of these cytokines can enhance the release of IL-25, which establishes a positive feedback loop with ILC2 in the production of IL-13 and IL-4 [42, 43]. ILC2-released IL-4 suppresses allergen-specific induced-Treg cell differentiation during FA [44, 45]. Similar to IL-25 and IL-33, TSLP is capable of inducing ILC2 expansion and IL-4 production. IL-4 is associated with B cell class-switching and synthesis of antigen-specific immunoglobulin E (IgE), the suppression of Treg induction in favor of Th2 differentiation, and the activation of MCs [35, 44, 46, 47]. Additionally, TSLP itself has been shown to shift the differentiation of naïve CD4<sup>+</sup> T cells away from Tregs and toward Th2 cells while enhancing the production of IgE from memory B cells via an IL-4- and/or IL-13-dependent mechanism [48]. Murine models of induced FA have provided evidence for the role of TSLP in the onset of FA, demonstrating that the absence of TSLP receptor in knock-out mice results in a reduced Th2-type profile in favor of a predominantly dendritic cell (DC)-induced Th1 profile [49]. Additional murine models have demonstrated that all three alarmins are needed to induce FA; however, the presence of any of them was sufficient to maintain allergic inflammation [50]. The sum effects of the alarmins lead to an increased

production of IL-4, IL-5, and IL-13, in turn promoting and maintaining a Th2-dominant phenotype typical of type-I hypersensitivity reactions. In addition to the functions previously described, IL-4 drives intestinal MC expansion and activation, IL-5 promotes eosinophil accumulation, and IL-13 prompts CD103<sup>+</sup> DC homing to the draining lymph nodes wherein the DC promotes the differentiation of naïve CD4<sup>+</sup> T cells into Th2 [19, 42, 51].

While OIT has remained the most studied method of desensitization for FA, the underlying mechanisms are still not completely understood. It has been observed that IgE serum levels increase during initial phase of therapy followed by a gradual decrease [13, 18, 26, 52, 53]. Levels of food-specific IgG4, on the other hand, steadily increase throughout [29, 53]. Allergen-specific and type 1 regulatory T (Tr1) [54] cells induced via repeated allergen exposure secrete IL-10, reducing IgE production and promoting IgG4 production [53]. Moreover, allergen-induced Tregs are capable of inhibiting DC-mediated induction of both pro-allergic Th2 cells and MCs [19, 55, 56]. During OIT, basophils and MCs gradually present with a reduced reactivity that can be observed in skin prick and basophil activation tests. This can be explained by the reduced levels of IgE and its receptor, as well as the presence of IgG4 antibodies with blocking properties [13, 19, 57]. During prolonged OIT, additional changes can be observed on the epigenetic level. Gradual decreases in the methylation of the FOXP3 gene within Treg cells result in a progressive

increase in the Treg-mediated suppression of the pro-allergic immune response and shifts in the Th2/Th1 balance toward a Th1-characterized profile [18, 22].

A number of biologics that target key cytokines and antibodies have been developed and approved for the treatment of atopic diseases, such as asthma and AD (Table 1). These therapies are non-allergen-specific. As indicated earlier, around 45% of adults with FA are allergic to multiple foods [2] with over two-thirds having comorbid atopic conditions. Based on our understanding of the key cells and cytokines in FA, these non-allergen-specific treatments can potentially be used to simultaneously desensitize multi-food allergic patients to their multiple allergens.

As we have gained a deeper understanding of the mechanisms involved in FA and the common mechanisms it shares with other atopic diseases, such as AD, allergic rhinitis, and allergic asthma, there has been increased development of vaccines, biologics, and other therapies for the treatment of these diseases. Among these novel treatments, biologics stand out as non-allergen treatments. In 2003, omalizumab was the first biologic that was approved for an atopic disease (asthma). At the current time, five biologics have been approved, primarily for asthma but also for chronic idiopathic urticaria and AD (Table 1). The insight that we have gained from the use of one drug in the treatment of an atopic disease is quickly being translated for other atopic diseases. For example, dupilumab was first approved for AD and was then later approved for asthma. Clinical trials evaluating dupilumab for the treatment of FA are now underway. At the current time, there are no

approved biologics for the treatment of FA, but many are being evaluated in clinical trials (Table 2).

## Biologics

### IgE-Targeted Therapies

Given the potential risks associated with immunotherapy for FA, recent studies have begun to evaluate the use of biologic agents as both monotherapies and adjuncts to allergen-specific immunotherapy in an attempt to increase safety. The majority of these biologics are characterized by their ability to inhibit and suppress the pro-inflammatory pathways specific to food allergies, potentially increasing the dose of allergen required for an allergic reaction and decreasing the likelihood of allergic reaction upon accidental allergen exposure. While the agents themselves are typically unable to induce desensitization when used alone given the lack of necessary allergen exposure, it is hypothesized they may provide continuous protection against accidental allergen exposure when used as a monotherapy, in addition to providing a safer environment in which allergens can be introduced and escalated during allergen-specific immunotherapy with a lower risk of reaction. As desensitization is achieved through repeated allergen exposure, the biologic may likely be discontinued as the immune system shifts toward a desensitized state.

Omalizumab is one of the most widely researched biologics in the treatment of IgE-mediated FA. Omalizumab is

**Table 1** Biologics currently approved for atopic diseases

| Drug                    | Target              | Approval date | Disease                      | Indications                                                                                                                                                                                                                                                                                                 |
|-------------------------|---------------------|---------------|------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Omalizumab (Xolair®)    | Anti-IgE            | 2003          | Asthma                       | Moderate-to-severe persistent allergic asthma in patients 6 years of age or older not controlled by inhaled corticosteroids. Persistent asthma; chronic idiopathic urticaria (CIU, chronic hives without a known cause) in patients 12 years of age and older not controlled by H1 antihistamine treatment. |
| Omalizumab (Xolair®)    | Anti-IgE            | 2014          | Chronic idiopathic urticaria | Chronic idiopathic urticaria (CIU, chronic hives without a known cause) in patients 12 years of age and older not controlled by H1 antihistamine treatment.                                                                                                                                                 |
| Mepolizumab (Nucala®)   | Anti-IL-5           | 2015          | Asthma                       | Add-on maintenance treatment for patients 12 years and older with severe eosinophilic asthma.                                                                                                                                                                                                               |
| Reslizumab (Cinqair®)   | Anti-IL-5           | 2016          | Asthma                       | Add-on maintenance treatment of severe asthma in patients aged 18 years and older.                                                                                                                                                                                                                          |
| Benralizumab (Fasenra®) | Anti-IL-5R          | 2017          | Asthma                       | Add-on maintenance treatment of patients 12 years and older with severe eosinophilic asthma.                                                                                                                                                                                                                |
| Dupilumab (Dupixent®)   | Anti-IL-4R $\alpha$ | 2017          | Atopic dermatitis (AD)       | Dupixent is indicated for the treatment of patients 12 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.                                                                                 |
| Dupilumab (Dupixent®)   | Anti-IL-4R $\alpha$ | 2018          | Asthma                       | Patients aged 12 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.                                                                                                                       |

**Table 2** Select studies for treatment of food allergy

| Intervention                                                                                                                                           | Target                           | Disease characteristics | Phase                       | Clinical trial (title, number)                 | Status                               |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|-------------------------|-----------------------------|------------------------------------------------|--------------------------------------|
| Omalizumab as monotherapy and as adjunct therapy to multi-allergen OIT in food allergic participants (OUMATCH)                                         | Anti-IgE                         | Multi-food allergy      | Phase 3                     | <a href="#">Clinicaltrials.gov NCT03881696</a> | Recruiting                           |
| Study using Xolair in rush multi-oral immunotherapy in multi-food allergic patients (MAP-X)                                                            | Anti-IgE                         | Multi-food allergy      | Phase 2                     | <a href="#">Clinicaltrials.gov NCT02643862</a> | Completed. Results published [58].   |
| Omalizumab (monotherapy)                                                                                                                               | Anti-IgE                         | Multi-food allergy      | Observational study         | N/A                                            | Completed. Results published [59].   |
| Multi-immunotherapy to test tolerance and Xolair (M-TAX)                                                                                               | Anti-IgE                         | Multi-food allergy      | Phase 2                     | <a href="#">Clinicaltrials.gov NCT02626611</a> | Completed. Results published [60••]. |
| E-B-FAHF-2, multi-OIT and Xolair (omalizumab) for food allergy                                                                                         | Anti-IgE                         | Multi-food allergy      | Phase 2                     | <a href="#">Clinicaltrials.gov NCT02879006</a> | Recruiting                           |
| Peanut Reactivity Reduced by Oral Tolerance in an Anti-IgE Clinical Trial (PRROTECT)                                                                   | Anti-IgE                         | peanut allergy          | Randomized controlled study | <a href="#">Clinicaltrials.gov NCT01781637</a> | Completed. Results published [61].   |
| Efficacy and safety of omalizumab (anti-IgE monoclonal antibody) on oral immunotherapy for patients with cow's milk allergy (randomized control study) | Anti-IgE                         | Milk allergy            | Randomized controlled study | UMIN Clinical Trials (Japan); UMIN000015545    | Completed. Results published [62].   |
| Study to evaluate the efficacy and safety of dupilumab monotherapy in pediatric patients with peanut allergy                                           | Anti-IL-4R $\alpha$              | Peanut allergy          | Phase 2                     | <a href="#">Clinicaltrials.gov NCT03793608</a> | Ongoing                              |
| Study in pediatric subjects with peanut allergy to evaluate efficacy and safety of dupilumab as adjunct to AR101 (peanut oral immunotherapy)           | Anti-IL-4R $\alpha$              | Peanut allergy          | Phase 2                     | <a href="#">Clinicaltrials.gov NCT03682770</a> | Ongoing                              |
| Clinical study using biologics to improve multi-OIT outcomes                                                                                           | Anti-IgE and Anti-IL-4R $\alpha$ | Multi-allergy           | Phase 2                     | <a href="#">Clinicaltrials.gov NCT03679676</a> | Ongoing                              |
| Placebo-controlled study to investigate ANB020 activity in adult patients with peanut allergy                                                          | Anti-IL-33                       | Peanut allergy          | Randomized controlled study | <a href="#">Clinicaltrials.gov NCT02920021</a> | Completed                            |

a humanized anti-IgE monoclonal IgG1 antibody approved for therapeutic use in severe allergic asthma and chronic idiopathic urticaria [63]. The primary mechanism of action involves the binding of free serum IgE, decreasing its availability to bind the high-affinity IgE receptor, FcεRI, expressed on MCs and basophils, in turn reducing their potential for activation in the presence of allergen. The binding of omalizumab additionally inhibits the binding of IgE to CD23 on both B cells and antigen-presenting cells [64]. As such, omalizumab has been evaluated as an adjunct to immunotherapy across various allergic conditions, particularly in its ability to reduce immunotherapy-associated adverse reactions and/or enhance the effectiveness of immunotherapy, independent of the specific allergies being treated. In allergen immunotherapy for inhaled allergens, the use of omalizumab as a pre-treatment or adjunct to immunotherapy was associated with a significant reduction in allergic rhinitis symptoms scores and adverse events, including local injection site redness and swelling, compared with immunotherapy alone [65, 66]. Benefits specific to the treatment of food allergies were initially demonstrated in a study of talizumab (TNX-901), an anti-IgE antibody similar to omalizumab, wherein its use was associated with significant increases in the threshold of peanut protein required to provoke allergic symptoms in peanut-allergic individuals [67]. Omalizumab has since been studied in FA both as a monotherapy [68] and as an adjunct to OIT, demonstrating increased safety and efficacy compared with placebo [58, 61, 69•, 70–72]. Within milk-OIT, these studies demonstrate significant reductions in OIT-related adverse events while facilitating significantly faster allergen dose escalation; however, its use did not improve overall rates of desensitization or SU, potentially due to the study duration allowing those on the placebo enough time to escalate to the maximum OIT dose [63, 69•, 72]. Studies of peanut-OIT have demonstrated similar benefits of adjunct omalizumab therapy, allowing for a tenfold higher tolerated protein dose on the first day of peanut exposure as well as a significant increase in the tolerability of rapid peanut-OIT dose escalation [61]. Given the non-allergen-specific nature of omalizumab's IgE binding, it has also been studied in a number of multi-allergen OIT trials [60•, 73•]. Similar to findings for single-allergen therapy, adjunct omalizumab use following short-term pre-treatment with omalizumab alone in multi-OIT has been associated with significantly faster allergen dose escalations, significantly greater rates of desensitization after 36 weeks of therapy, and significantly lower median per-participant percentages of OIT doses associated with any adverse event when compared with the placebo [70]. Despite promising reductions in adverse events, a median 27% of OIT doses per-participant was still associated with an adverse event, the most common

events being those affecting the gastrointestinal system [60•, 73•].

Omalizumab is also being used adjunctive with enhanced butanol-purified Food Allergy Herbal Formula-2 (E-B-FAHF-2), a Chinese herbal formula ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02879006), NCT02879006). E-B-FAHF-2 is a 9-herb formula. FAHF-2 has been shown to block peanut-induced anaphylaxis in a murine model [74]. In a phase I study, FAHF-2 was found to be safe and well tolerated [75]. In vitro studies have shown favorable immunomodulatory effects [76]. While OIT has been shown to lead to desensitization, it is unclear whether it can lead to lasting protection, and the study aims to determine whether the combination of multi-allergen OIT, omalizumab, and E-B-FAHF-2 can establish SU.

Studies investigating the immunological changes present in patients treated with omalizumab and milk-OIT found that those treated with omalizumab demonstrated lower basophil CD63 expression after both omalizumab administration alone and during omalizumab plus OIT when compared with controls [30, 77•]. Following the cessation of treatment, basophil responsiveness returned to baseline, suggesting that the effects on basophil reactivity are dependent on active therapy and are transient in nature. Additionally, there were no significant differences in Treg levels between those receiving OIT plus omalizumab compared with OIT alone; however, a subgroup of patients was identified in which those with CD63 expression greater than 40% were more likely to benefit from the administration of omalizumab and experience significant reductions in rates of allergic adverse events compared with those subjects with expression under 40% that experienced similar rates of allergic adverse events regardless of whether they received omalizumab or not. While additional studies are needed to better identify those individuals most likely to benefit from omalizumab in terms of both safety and efficacy [77•, 78], the evidence supporting the general benefits of omalizumab in FA is robust. Omalizumab has shown significant promise in the ability to accelerate desensitization with OIT, independent of the specific allergen(s) being treated, by allowing patients to initiate allergen up dosing at higher initial doses than conventional OIT while shortening the escalation phase by reducing the number of doses and time required to reach the targeted OIT maintenance dose. In addition to contributing toward the observed reductions in time-to-desensitization, reductions in the rate of OIT-related adverse events may potentially serve to reduce rates of premature OIT discontinuation due to allergen intolerance and anaphylaxis.

#### IL-4- and IL-13-Targeted Therapies

With the observed benefits of omalizumab, a number of new biologics have recently been investigated or proposed for the treatment of FA, both as monotherapies and adjuncts to OIT, typically targeting mechanisms further upstream in the pro-

allergic pathway driving food allergies. Dupilumab is a recombinant human IgG4 monoclonal antibody directed against the  $\alpha$ -chain of the IL-4 receptor (IL-4R $\alpha$ ) [79], a receptor common to both IL-4 and IL-13. The binding of IL-4 or 13 to IL-4R $\alpha$  typically results in the activation of a signaling pathway that promotes the differential expression of genes involved in IgE class switching, Th2 cell differentiation, and macrophage polarization into the pro-inflammatory (M2) phenotype [80]. By preventing this interaction, dupilumab is thus able to target a large number of cells involved in the pathophysiology of Th2 allergic responses, such as B lymphocytes, eosinophils, DCs, monocytes/macrophages, basophils, keratinocytes, bronchial epithelial cells, endothelial cells, fibroblasts, and airway smooth muscle cells [81]. Dupilumab is currently approved by both the Food and Drug Administration (FDA) and European Medicines Agency for use as a biologic treatment in moderate-to-severe AD [82]. It was recently approved by the FDA also for asthma [83]. The first report of its efficacy in the field of FA was a case report in which a patient with severe AD receiving dupilumab became desensitized and passed a confirmatory oral food challenge to two foods previously responsible for allergic reactions [84••]. In order to better understand the potential safety and efficacy of dupilumab in FA, three placebo-controlled studies are currently underway. Two of the trials are for peanut allergy (either as monotherapy or adjunctive therapy) and the third is for those with multiple allergies (Table 2).

### IL-5-Targeted Therapies

Similar to IL-4 and IL-13, IL-5 is another key mediator driving the Th2 state, playing a key role in eosinophil maturation, proliferation, migration to site, and effector functions. It is synthesized and secreted by various cells, such as eosinophils, Th2 cells, MCs, natural killer T cells, and ILC2s [85]. This latter population is involved in the pathogenesis of asthma but may also act in the onset of FA via their ability to activate in response to alarmins and produce IL-5 and IL-13 in response to IL-25 [41, 86]. Moreover, a recent mouse model of FA demonstrated that interactions between IgE-activated MCs may be capable of inducing intestinal ILC2s that can, in turn, enhance responsiveness to the mediators of anaphylaxis produced by MCs [87]. Mepolizumab and reslizumab are both humanized monoclonal antibodies that bind to IL-5, preventing its interaction with its receptor. Both agents are FDA-approved as add-on therapy for patients with asthma of an eosinophilic phenotype, with mepolizumab additionally approved for the treatment of eosinophilic granulomatosis with polyangiitis [88]. Mepolizumab has also been investigated for the treatment of eosinophilic esophagitis; however, pilot study results were uncertain with a decrease in peripheral and tissue eosinophilia in the absence of convincing clinical improvement [89, 90]. Benralizumab, a monoclonal antibody

that binds to the  $\alpha$ -chain of IL-5 receptor on eosinophils and basophils, is similarly approved as add-on maintenance therapy for patients with severe asthma of an eosinophilic phenotype. Receptor blockade on eosinophils leads to cell apoptosis and nearly complete depletion of eosinophils. Data suggest promising efficacy both in reducing annual exacerbation rates and increasing the glucocorticoid-sparing effect [88, 91, 92]. While the focus of anti-IL-5 agents has centered on the treatment of eosinophil-related disease states, their potential applications as adjuncts to FA immunotherapy, particularly in the prevention or treatment of concurrent eosinophilia, are likely to be investigated in the future.

### Alarmin-Targeted Therapies

As previously described, IL-33, IL-25, and TSLP play a broad and critical role in the early development and maintenance of FA. Recent efforts have begun to focus on these alarmins as potential targets for the treatment of FA given their broad influence. The inhibition of these upstream targets during OIT could theoretically provide advantages over other agents, such as anti-IgE and anti-IL-4R $\alpha$  antibodies, that only block downstream mediators of the allergic response. In addition, the use of anti-alarmin agents could be leveraged to prevent initial allergen sensitization, especially in high-risk patients presenting with atopic conditions such as eczema or AD.

In a murine model of allergic rhinitis sensitized to ovalbumin, anti-IL-33 treatment was effective in improving allergic symptoms and reducing both total and allergen-specific IgE in the serum. This reduction is thought to result from the inhibition of Th2-type cytokine release and B cell activation, with the resulting decrease in IgE reducing the likelihood of MC degranulation and allergic reaction [93]. In an additional murine model of asthma, treatment with anti-IL-33 significantly reduced serum IgE secretion; eosinophil and lymphocyte count; and concentrations of IL-4, IL-5, and IL-13 in bronchoalveolar lavage fluid compared with controls [94]. The treatment was also associated with reductions in allergen-induced lung eosinophilic inflammation and mucus hypersecretion in lung biopsy. Etokimab, a humanized IgG1/kappa monoclonal antibody, has been specifically developed to bind to and neutralize the biological effects of human IL-33. It is currently under investigation for a number of atopic conditions, including a phase II study for adults with peanut allergy. The study involves a single administration of etokimab, with double-blind, placebo-controlled food challenges to peanut at baseline and 14 days post-etokimab administration to evaluate changes in tolerance and the occurrence of adverse events during challenge (Clinical trials NCT02920021) [95]. Etokimab is also being evaluated in clinical trials for chronic rhinosinusitis with nasal polyps (phase 2, NCT03614923), severe eosinophilic asthma (proof of concept study, NCT03469934), and AD (phase 2, NCT03533751).

Similar to IL-33, an anti-TSLP antibody has also been developed for human use. Tezepelumab is the first human monoclonal antibody that binds to TSLP and inhibits its interaction with the TSLP receptor complex [96]. Studies investigating the use of tezepelumab have demonstrated its significant benefit not only in the reduction of asthma exacerbations in those with moderate-to-severe asthma but also in the attenuation of allergen-induced early and late asthmatic responses after bronchial allergen challenge in those with mild allergic asthma and a sensitization to pollens [97, 98]. A study in healthy individuals and in patients with AD found that the antibody is safe and well tolerated. Additional clinical trials of tezepelumab for treatment of asthma and AD are underway.

While studies investigating the blockade of IL-25 in humans with FA are not yet underway, anti-IL-25 treatment in a murine model of nasal polyposis (commonly associated with those with chronic rhinosinusitis) reduced polyp formation, mucosal thickness, collagen deposition, and infiltration of inflammatory cells, including eosinophils and neutrophils [99]. Ovalbumin-sensitized IL-25 knockout mice had alleviated ovalbumin-induced eosinophil infiltration in the airway and newly formed eosinophils were reduced in the lung, suggesting a potential role for IL-25 in allergen-induced trafficking of eosinophil-lineage committed progenitor cells to the airways and local differentiation promoting tissue eosinophilia in asthmatic responses [100].

The role of alarmins in induction and maintenance of FA was evaluated in a mouse model. Researchers found that injection of monoclonal antibodies to all 3 alarmins strongly inhibited FA development, although no single monoclonal antibody could suppress established FA, and optimal FA suppression required treatment with a mixture of monoclonal antibodies to all 3 alarmins [50]. Antibodies toward alarmins are showing promise as treatments for atopic diseases. Their safety and efficacy for the treatment of FA is yet to be determined.

## Conclusion

As efforts to optimize the safety and efficacy of immunotherapy continue, an increasing number of biologic agents are under investigation for their potential applications in the treatment and prevention of FA. Traditional forms of immunotherapy, such as OIT, are often plagued by extensive treatment durations while treating a single allergen at a time. Additionally, the process is not without risk, with a portion of patients prematurely discontinuing therapy due to treatment-related adverse events. The use of biologics that function through the inhibition of pathways specific to atopy may hold the answer to these challenges, providing a safer environment in which multiple allergens, regardless of allergen type, may be administered simultaneously with a decreased risk of reaction as the immune system shifts toward

a tolerogenic state. While additional studies are certainly needed to further understand how these biologics are best administered and how they impact long-term SU, preliminary data thus far holds promise.

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## Compliance with Ethical Standards

**Conflict of Interest** Dr. Sharon Chinthrajah receives grant support from CoFAR NIAID, Aimmune, DBV Technologies, Astellas, AnaptysBio, Novartis, and Regeneron and is a scientific advisory board member for Alladapt Immunotherapeutics. All other authors declare no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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