Biologics for the Treatment of Food Allergies

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KEYWORDS

• Food allergy • Biologic • Omalizumab • Monoclonal antibody • Peanut • Cow's milk

KEY POINTS

- Food allergies are increasing and are a global health problem.
- Omalizumab may be combined with oral immunotherapy for enhanced safety and tolerability of foods.
- Other biologic therapies and small molecule inhibitors may target the type II allergic pathway and play a role in food allergy treatment.

INTRODUCTION

Food allergies affect 2.5% to 8% of children and 5% to 10.8% of adults in the United States.[1–4] One-third of children are allergic to multiple foods.[2] Food allergies may be more severe and undertreated in low-income and minority children.[1,5–7] Food allergy prevalence seems to be increasing, at an estimated rate of 1.2% per decade.[8] This is particularly true for peanut allergy, which had a prevalence of 2% among children in a 2011 US survey, compared with 0.4% of children in a 1997 survey.[2,9] The health care costs associated with food allergies are also increasing, with increased hospitalizations and emergency department visits being reported globally, but not an increase in anaphylaxis-related fatalities.[10–12]

Risk factors for the development of food allergy include the presence of other atopic diseases, particularly atopic dermatitis (AD) or eczema, which can lead to the development of the atopic march through mechanisms of cutaneous sensitization. Allergen introduction through barrier-impaired skin, as is seen in AD, can result in the activation

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of cytokines, such as thymic stromal lymphopoietin (TSLP), interleukin (IL)-33, and IL-25. This can activate type II inflammation, leading to the downstream production of cytokines including IL-4, IL-5, and IL-13, resulting in allergen-specific IgE, and thus sensitization.[13–15] Allergen introduction that begins in the gastrointestinal (GI) epithelium induces regulatory T cells, suppressing allergen-specific responses, resulting in the establishment of mucosal tolerance, which is most often durable and long-lasting.[16] Targeting of these pathways may help in the treatment of food allergies, and if administered early in life, could theoretically prevent development of allergy.

Other factors in the development of food allergy include delayed introduction of food allergens to the infant diet, changes to the modern diet, and antacid exposure, which can all affect the development of mucosal tolerance.[13,14] Delayed mucosal exposure to foods may potentiate risk factors for cutaneous sensitization because of increased environmental food protein exposure, particularly in patients with AD.[13] Other factors that affect the microbiota, such as delivery by caesarean section and early exposure to antibiotics, may also play a role.[13,14] Current strategies for food allergy prevention are focused on early introduction of foods in high-risk infants, such as those with eczema and established egg allergy, with the goal of building mucosal tolerance from an early age before cutaneous sensitization can occur.[15,17] There is growing evidence that early introduction of peanut and possibly also egg and milk can prevent food allergy among the general population.[15,18] However, this strategy is not effective for all children. Some children develop allergy despite successful early introduction with regular consumption, whereas others develop significant sensitization early in life, and are unable to attempt early introduction. In these circumstances, immune dysregulation seems to override the early exposures, and treatments aimed at the targets of immune dysregulation, such as TSLP, which polarizes T-helper (Th) cells to Th2, and the cytokine signaling pathways, such as Janus kinase (JAK) signaling pathways, may alter a type II-skewed immune system. Current biologics available for the treatment of food allergy, such as anti-IgE, are aimed at minimizing clinical reactivity; however, in the future, potential interventions may focus more on prevention of food allergy.

BIOLOGICS IN ATOPIC CONDITIONS

Biologics used in atopic conditions, such as asthma, target immune pathways that are also relevant in the development of food allergy and anaphylaxis. The number of approved biologic therapies for use in allergy and asthma have drastically increased over the last few years, and there are now five approved biologics for use in asthma. The first approved biologic therapy was omalizumab for moderate-to-severe persistent asthma in 2003. Omalizumab is a humanized, monoclonal anti-IgE antibody, and is currently available as a prefilled syringe or reconstituted solution for subcutaneous use. It is a Food and Drug Administration (FDA)-approved treatment of asthma down to 6 years of age, and chronic idiopathic urticaria (CIU) down to 12 years of age. Dosing is individualized according to weight and IgE level when used for asthma, whereas it is fixed at 150 mg or 300 mg every 4 weeks for CIU. Common side effects include headache and injection site reaction. Omalizumab carries a black box warning for a risk of anaphylaxis, including delayed-onset anaphylaxis, and all patients prescribed omalizumab should receive an epinephrine autoinjector. Anti-IgE treatment downregulates expression of Fcε receptors (FcεR) in addition to inhibiting binding of IgE to mast cells and basophils.[19] Basophil FcεRI expression is markedly decreased after 1 week of treatment with omalizumab, whereas mast cell expression of FcεRI is suppressed after 10 weeks.[20] It may also inhibit allergen-specific activation of T cells.[19]

Subsequently, additional drugs have been approved targeting other pathways and molecules in the type II pathway, including mepolizumab, benralizumab, and reslizumab, each of which target IL-5 and its receptor to treat eosinophilic asthma; and dupilumab targeting IL-4 and IL-13 to treat a range of atopic conditions including asthma, AD, and chronic rhinosinusitis with nasal polyps.

BIOLOGICS IN FOOD ALLERGY

There is no currently FDA-approved biologic therapy for use in food allergy. Omalizumab has been studied as monotherapy and as an adjuvant therapy in the treatment of food allergies, in conjunction with oral immunotherapy (OIT). Omalizumab was initially studied in conjunction with OIT for peanut, cow's milk, and hen's egg, but is now also being studied with multiple food allergen OIT. Combining omalizumab with OIT can result in more rapid desensitization, or a reduction in the inflammatory response during up-dosing by increasing the threshold dose of food protein required to elicit a reaction. This increase in threshold is often temporary, and likely does not represent a "cure" for food allergy in most patients undergoing OIT even with the use of a biologic. However, the increased threshold may help eliminate daily anxiety associated with food allergies given a likely decreased risk of reaction from accidental ingestion or cross-contamination. In the future, therapeutics targeting type II inflammatory pathways, and broader signaling pathways may also have a role in the treatment of food allergies, and aid in the development of durable, long-term tolerance.[21,22] Some are currently undergoing clinical trials.

ANTI-IgE MONOTHERAPY FOR FOOD ALLERGY

The first study to investigate food allergy therapy with a biologic medicine was performed in adolescents and adults with peanut allergy by Leung and colleagues,[19] published in 2003. In this randomized, double-blind, placebo-controlled (DBPC) trial, TNX-901, a humanized IgG1 monoclonal antibody against IgE, increased the threshold of sensitivity to peanut on oral food challenge (OFC) when administered every 4 weeks for a 16-week period, without OIT or any other specific immunotherapy. Subjects 12 to 60 years old given the highest dose of TNX-901 (450 mg) had an increase in mean eliciting threshold dose of 2627 mg of peanut protein at exit OFC (approximately equivalent to nine peanut kernels), from a baseline eliciting dose of 178 mg at entry OFC (approximately equivalent to one-half of one peanut kernel). The study drug was never approved; however, results were positive and indicated that monotherapy with an anti-IgE biologic can increase the reaction threshold among peanut-allergic adolescents and adults, although long-term, durable desensitization was not directly studied.

These promising results led to a trial of omalizumab in peanut-allergic individuals by Sampson and colleagues[23] in 2011. The study became a small phase II trial, because it was stopped early from severe anaphylactic reactions during the qualifying OFC phase of the study. Only 14 subjects completed the trial, including a post-treatment OFC. A small subset of patients (n = 4) treated with omalizumab monotherapy demonstrated a threshold of tolerance greater than or equal to 1000 mg of peanut flour compared with placebo (n = 1). Yet, a similar number of subjects experienced reactions with less than or equal to 1000 mg of peanut flour in both groups. Although there was an increase in reaction threshold between the omalizumab and placebo groups, this was not statistically significant. In a larger study of omalizumab, in which basophil allergen threshold sensitivity was used as a biomarker for clinical peanut allergy,

treatment with omalizumab for 8 to 24 weeks resulted in absence of or only mild allergic symptoms during open peanut OFC.[24]

In a 6-month, open-label study of omalizumab in peanut-allergic individuals, the mechanism by which omalizumab may be exerting its effect on increased reaction threshold was further elucidated.[25] By performing OFCs early and late in the treatment period, and following associated diagnostic tests, it was determined that basophil histamine release is suppressed early in treatment, whereas mast cell release as determined by skin prick test (SPT) titration is suppressed later during treatment. Clinically, this was seen as a significant increase in threshold dose of peanut-causing allergic reaction (80–6500 mg; $P<.01$) between the early and late OFCs. This suggests that the basophil has a role in acute food allergic reactions and may explain why omalizumab, which interacts with the FcεR on basophils, nonspecifically aids in rapid desensitization to food allergens.[26,27] In one study, this desensitization was sustained 12 weeks after stopping omalizumab when combined with daily peanut consumption.[26]

Based on this body of evidence, including clinical and mechanistic end points, omalizumab was granted breakthrough status by the FDA in 2018 to expedite its future approval as a treatment of severe food allergic reactions. Since being granted breakthrough status in the United States, Fiocchi and colleagues[28] in Italy have published their experience treating patients with severe asthma, while observing its effects on a subset of 15 patients with food allergy. Subjects ranged in age from 8 to 23 years, and either had multiple food allergies (clinical reactivity to at least two different foods) or a single food allergy, but failed OIT. They underwent periodic open OFCs as part of clinical care, including before initiating treatment with omalizumab (unless there was a recent history of anaphylaxis) and after 4 to 6 months of therapy. Of the 23 different foods evaluated collectively, nine patients were able to tolerate full servings of 16 different foods and subsequently consume these foods in their diet *ad libitum* without undergoing induction, and without experiencing any reactions after introduction. They also noted a decrease in accidental reactions experienced while receiving omalizumab therapy by 95.7%. This real-world, observational study has several significant limitations, including a small sample size without sufficient statistical power, and none of these patients discontinued omalizumab because it was being used for long-term asthma management. However, this Italian clinical experience mirrors other published trials and the data are encouraging.[27,29]

OMALIZUMAB AS AN ADJUNCT TO PEANUT ORAL IMMUNOTHERAPY

In addition to omalizumab being studied as monotherapy, which has a nonspecific effect on food allergy, it has also been studied in combination with specific food allergen OIT. The goal of using omalizumab as an adjunct to OIT is to improve the tolerability by reducing side effects of OIT dosing. It can also facilitate more rapid up-dosing and/or the achievement of higher maintenance doses. Most current food OIT studies aim to increase the reaction threshold in subjects with food allergy so they are less likely to experience reactions on accidental exposure.[30] To accomplish this, some OIT protocols begin with an initial escalation day that is similar to an OFC to determine the starting reaction threshold, and then begin OIT dosing with the last tolerated dose or the protocol-defined maximum starting dose.[31] Other studies have used a fixed dosing schedule, including an initial dose escalation day, after which all subjects begin at a low dose (eg, 3 mg of peanut protein) of OIT, which is taken daily at home.[32] All protocols then continue with a build-up period over several months. Up-dosing is performed under observation in clinic, with continued daily home dosing between

visits. This is followed by a long-term maintenance phase with continued, regular home-dosing.[30] Side effects observed in a large, DBPC, randomized controlled trial (RCT) phase III peanut OIT study are typical of type I allergic reactions, including oral pruritis, urticaria, and a risk for systemic reactions including anaphylaxis.[32] GI symptoms, including nausea, abdominal pain, and vomiting, are also common, and can occur shortly after dosing or delayed several hours after dosing, suggesting that there may be IgE- and non-IgE-mediated mechanisms leading to GI symptoms.[33] There is also a slight risk for developing eosinophilic esophagitis (EoE) among patients undergoing OIT; however, this has never been systematically studied.[34] Concurrent or pretreatment with omalizumab can improve the safety profile of OIT by reducing the frequency and severity of allergic reactions.[27,29] However, GI symptoms are not significantly improved by the addition of omalizumab, and GI adverse events are the most common reason for subjects to withdraw from OIT studies.[32,35,36]

In a pilot study of six patients with peanut allergy 12 years of age and older, omalizumab was administered for 4 months before initiation of peanut OIT.[37] This resulted in a higher median initial peanut OIT dose, and fewer reactions on dose escalation days, compared with a comparison group that did not receive omalizumab. These promising results led to further studies, including a larger, DBPC trial.[27] Omalizumab was administered before initiation of peanut OIT to facilitate rapid desensitization. This allowed for faster up-dosing, resulting in a larger dose of peanut protein tolerated on the initial escalation day (250 mg) compared with placebo (22.5 mg). These subjects were also able to achieve a higher maintenance dose of OIT, compared with subjects in other studies, which may provide additional immunologic benefits, including the deletion of allergen-specific T cells.[38] Additionally, this higher dose benefit remains even after omalizumab is discontinued, possibly as long as 72 months in a small cohort of seven patients.[27,39]

OMALIZUMAB AS AN ADJUNCT TO MILK AND EGG ORAL IMMUNOTHERAPY

Cow's milk and hen's egg allergies are the most common IgE-mediated food allergies among younger children.[1] Avoidance of milk and egg is difficult because they are ubiquitous in most diets, and they are important sources of nutrition for children, putting these children at risk for nutritional deficiencies and poor growth.[40,41] Given these considerations, although 70% to 80% of children outgrow these allergies,[42,43] there is interest in offering patients a safe and effective method for desensitization to milk and egg.

The most robust study for omalizumab and cow's milk allergy was a DBPC trial including 57 subjects ages 7 to 35 years with confirmed cow's milk allergy.[29] They received omalizumab or placebo injections for 16 months, and milk OIT was started on Month 4 of injections. The study was unblinded at Month 12 when placebo injections were discontinued, whereas omalizumab injections continued for 12 additional months. Subjects were required to reach a minimum dose of 520 mg of milk protein with a goal of 3800 mg. The active treatment group required a shorter escalation period (median, 25.9 vs 30.0 weeks), had a more successful desensitization (88.9% of omalizumab vs 71.4% of placebo group passed OFC), and experienced significantly fewer symptoms during the escalation phase (91.5% omalizumab vs 73.9% of placebo were symptom free). Immunologic changes showed initial increases in the sIgE to milk and casein in the omalizumab group with eventual decreases lower than baseline, consistent with other OIT studies.[44] However, the sIgE levels in the placebo group trended downward from the beginning.[29] There were no statistically significant differences in efficacy, including rates of desensitization and sustained

unresponsiveness (after 8 weeks off milk OIT), between groups, despite the improved safety outcomes in the omalizumab group.

An open-label, prospective study in Spain evaluated the efficacy and safety of omalizumab-assisted OIT to milk and egg in 14 children ages 3 to 13 years who had failed conventional OIT.[45] Omalizumab was administered for 9 weeks before OIT was started simultaneously to both cow's milk protein (goal of 6600 mg) and pasteurized liquid raw egg white (goal of 1800 g egg protein, which is equivalent to one-half of an egg). OIT was started with a 2-day rush procedure followed by continued up-dosing over 18 weeks. One week after the goal maintenance dose was achieved, open OFCs were performed, and after 2 months, omalizumab was discontinued. At the OFC while on omalizumab, all patients had achieved complete desensitization. Side effects were all mild, and only experienced in a minority of patients during up-dosing. However, nearly half experienced anaphylaxis with OIT 2 to 4 months after discontinuing omalizumab. A case series from another Spanish group reported three patients who underwent omalizumab-assisted egg OIT, but developed reactions to OIT doses 2 to 4 months after stopping omalizumab.[46] These experiences suggest that longer dosing of omalizumab may be required to maintain the safety benefits observed during up-dosing.

OMALIZUMAB AS AN ADJUNCT TO MULTIFOOD ORAL IMMUNOTHERAPY

Given the growing body of evidence for the efficacy and safety of omalizumab as monotherapy for food allergy, and combined with OIT to some foods, several studies have been undertaken to examine the potential use of omalizumab with OIT to multiple different foods concurrently. An open-label, phase I study demonstrated early success using a rush desensitization protocol.[47] Twenty-five children between the ages of 4 and 15 years were enrolled, and underwent baseline DBPC OFCs before starting omalizumab for 9 weeks, at which point a rush, initial escalation day was performed. Peanut was the most common allergen included in OIT, in addition to milk, egg, tree nuts, grains, and sesame seed. All foods included in OIT were mixed in equal amounts, including two to five foods, starting with 5 mg of total food protein, regardless of the number of foods included, increasing over six doses to a maximum total dose of 1250 mg of food protein. The maximum dose was achieved by 76% of subjects despite 52% experiencing reactions that were all graded as mild. Subjects started OIT dosing with the highest tolerated dose and then returned for up-dosing visits every 2 weeks, up to a maximum of 4000 mg per allergen (cumulative protein dose of 20,000 mg for 5 allergens), which was achieved by all subjects within 9 months. Home doses resulted in reactions in 5.3% of doses, mostly mild, and typically occurring within the first months of dosing, but there was one serious reaction requiring epinephrine. Omalizumab was stopped 8 weeks after the initial escalation day, and no increase in reactions was seen. This study showed that rush desensitization to multiple food allergens could be done safely with omalizumab and has led to two published phase II studies. The first used a similar protocol as the phase I study, including open-label omalizumab for 16 weeks, but investigated the efficacy of two different maintenance doses (300 mg vs 1000 mg of food protein, per food) compared with stopping OIT dosing.[48] Among 70 subjects, ages 5 to 22 years of age, they found a similar safety profile, but 10 subjects were not able to be randomized to one of the three long-term treatment groups, including five who were not able to achieve a maintenance OIT dose of 1000 mg of each food. The combined long-term treatment groups were more effective at maintaining desensitization to multiple foods after stopping omalizumab, compared with a placebo maintenance OIT for

6 weeks. However, 55% of those on the placebo dose could tolerate 2000 mg of at least two different food proteins at the exit OFC, compared with 85% of the combined treatment groups. There was no difference between the two maintenance doses. A phase II, DBPC, RCT has been performed in 48 subjects between the ages of 4 and 15 years comparing omalizumab with placebo for 16 weeks, in conjunction with multifood (2–5 foods) OIT started after 8 weeks of omalizumab.[49] The same end point as the other phase II study was achieved in 83% of the omalizumab group compared with 33% in the placebo group. The placebo group also achieved a lower dose on the initial dose escalation day and took longer to achieve the maintenance OIT dose than the omalizumab group. Safety results were similar to the prior studies.[47,48]

These promising results have led to a large, multicenter, phase III, DBPC RCT of omalizumab and multifood OIT undertaken by the National Institutes of Health/National Institute of Allergy and Infectious Diseases–sponsored Consortium of Food Allergy Research (NCT03881696). This trial is currently underway and seeks to enroll 225 subjects with peanut allergy between the ages of 2 and 55 years, with a food allergy to at least two additional foods (including milk, egg, wheat, walnut, cashew, and hazelnut).

ADDITIONAL BIOLOGIC THERAPIES

In addition to omalizumab, there are numerous other biologic therapies in development, with the potential to treat food-allergic individuals (**Table 1**). Most of these agents are monoclonal antibodies, which have been approved for other atopic conditions and typically target cytokines or other mediators of the type II inflammatory pathway.

Ligelizumab, an anti-IgE monoclonal antibody similar to omalizumab, may provide additional benefits in combination with OIT. Ligelizumab binds to IgE with greater affinity than omalizumab and has been shown to have faster onset and more sustained control of symptoms in patients with CIU. Additionally, unlike omalizumab there have been no reports of anaphylaxis to ligelizumab to date. It has not yet been studied in food allergy, but could be a potential future indication.[50]

In mouse models, a monoclonal antibody directed against FcεRIα (anti-FcεRIα mAb), the high-affinity mast cell/basophil IgE receptor, has been used to achieve rapid desensitization against egg white, although it has not yet been studied in humans.[51,52] In mice, rapid desensitization with anti-FcεRIα mAb was safer and longer-lasting than rapid desensitization with egg white antigen alone.[52] anti-FcεRIa mAb also suppressed anaphylaxis more rapidly than the anti-IgE biologics omalizumab and ligelizumab.[51]

Dupilumab is a fully human monoclonal antibody against the alpha subunit of the IL-4 receptor, which inhibits binding of IL-4 and IL-13. It is FDA-approved for uncontrolled moderate-to-severe eosinophilic or oral steroid–dependent asthma and uncontrolled moderate-to-severe AD in patients ages 12 years and older, and chronic rhinosinusitis with nasal polyposis in adults. It is available in 200-mg or 300-mg prefilled syringes for subcutaneous administration every 2 weeks with a loading dose at onset of treatment when used in AD and asthma. Phase II trials are underway investigating dupilumab for the treatment of EoE.[53] There is a single case report from 2019 of a 30-year-old woman who had resolution of clinical food allergy symptoms while on dupilumab for severe AD. She was diagnosed with corn and pistachio allergy and following six injections of dupilumab, she inadvertently ate pistachios in a salad. She previously experienced an urticarial rash following ingestion of two pistachios

Table 1
Other biologics of interest/therapeutic pipeline

Name	Mechanism of Action	Clinical Trial Phase/Details	Study Results/Immunologic Changes	Side Effects/Comments	PMID
Etokimab (ANB 020)	Anti-IL-33	Phase IIa: 20 adults with peanut allergy and a history of anaphylaxis 6-wk placebo-controlled study Single dose Phase IIb: 300 adults with atopic dermatitis	73% and 57% increases in tolerated threshold allergen dose of active treatment group (Days 15 and 45, respectively) IL-4, IL-5, IL-9, IL-13, and ST2 levels in $CD4^+$ T cells reduced in the active vs placebo arm on peanut-induced T-cell activation Peanut-specific IgE reduced in active vs placebo	Headache in 4 participants OFC did not test for amounts >375 mg of peanut protein Primary end points not met for atopic dermatitis	31723064 31645451
Ibrutinib	Irreversible BTK inhibitor	6 healthy subjects with a history of IgE-mediated allergy to peanut and/or tree nuts 7-d course FDA approved: B-cell malignancies	Effectively reduced mast cell and basophil activation 77% reduction in wheal size of skin prick tests Nonsustained response, participants were back to baseline skin test reactivity within a week of medication discontinuation	In cancer studies, bleeding events in 39% of patients, more severe in 4%, fatal in 0.4% of 2838 patients Fenebrutinib (GDC-0853) is potent, nonselective, covalent BTK inhibitor in trials for refractory chronic spontaneous urticaria	29360526 29484638 29457982
Dupilumab	Anti-IL-4R (inhibits IL-4 and IL-13)	Phase II: peanut allergy Phase II: peanut-allergic patients on AR101 Phase II: EoE FDA approved: atopic dermatitis, chronic rhinosinusitis with nasal polyps, eosinophilic and/or steroid-dependent asthma	Ongoing, no results EoE: dupilumab reduced the peak esophageal intraepithelial eosinophil count by a mean 86.8 eosinophils per high-power field Dupilumab increased esophageal distensibility by 18% vs placebo	Hypersensitivity reactions, injection site erythema, conjunctivitis, and keratitis	31761117 31593702 31505066

Mepolizumab Reslizumab	Anti-IL-5	No trials in food allergy FDA approved: severe eosinophilic asthma	EoE: significant reduction in tissue eosinophilia but limited clinical improvement compared with placebo		25199059
Benralizumab	Anti-IL-5 receptor-α	No trials in food allergy FDA approved: severe eosinophilic asthma Orphan drug: EoE	Blocks IL-5 receptor, inducing target-cell depletion through natural killer cell–mediated antibody-dependent cellular cytotoxicity		31919743 28530840
Tezepelumab (AMG 157/ MEDI-9929)	Anti-TSLP	No trials in food allergy Phase Ia: 113 adults with atopic dermatitis Phase III: 396 adults with severe uncontrolled asthma	$\geq$50% reduction in the EASI at Week 12, although not statistically significant Less asthma exacerbations Decreased blood eosinophil count, total IgE, and FENO		28877011 31549891 30550828
Enokizumab (MEDI-528)	Anti-IL-9	No trials in food allergy Phase IIb: 329 adults with uncontrolled asthma	No improvement in ACQ-6 score, asthma exacerbation rate, FEV_1, or health-related quality of life	Primary end points not met for asthma	24050312
Lebrikizumab	Anti-IL-13	No trials in food allergy Phase IIb: 280 adults with atopic dermatitis Phase III: 2149 adults with uncontrolled asthma	At Week 16, treatment group achieved dose-dependent, significant improvement in EASI scores from baseline Absence of consistent efficacy in asthma trial	Adverse events include URI, nasopharyngitis, headache, injection site pain Lower rates of ocular complications compared with dupilumab Serious adverse events for asthma trial: aplastic anemia and eosinophilia	32101256 27616196
Tralokinumab	Anti-IL-13	No trials in food allergy Phase III: 380 adults with atopic dermatitis Phase III: 2051 adolescents and adults with uncontrolled asthma	At Week 16, treatment group IGA score of clear (0) or almost clear (1) and significant improvement in EASI scores from baseline	Primary end points not met for asthma Serious adverse events for asthma trial: eosinophilia (>1500 cells per μL) and 1 death from urosepsis	29906525 29792288

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Table 1
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Name	Mechanism of Action	Clinical Trial Phase/Details	Study Results/Immunologic Changes	Side Effects/Comments	PMID
Ligelizumab (QGE031)	IgG1κ anti-IgE	No trials in food allergy Phase IIb: 382 adults with chronic spontaneous urticaria Phase II: 37 adults with mild allergic asthma	Binds free serum IgE with much higher affinity than omalizumab Higher percentage of patients had complete control of symptoms of chronic spontaneous urticaria in comparison with omalizumab Greater efficacy than omalizumab for inhaled allergen challenges and skin prick test suppression	Similar side effect profile to omalizumab: injection site reactions and erythema No anaphylaxis reported	31577874 25200415 27185571
Toll-like receptor agonists	TLR9 agonist	Murine model	Decrease in gastrointestinal inflammation, reduction in peanut-specific IgE, and increase in IgG2 values Protection from peanut anaphylaxis	No human studies	29968170
Ruxolitinib	JAK inhibitor	Murine model for food allergy FDA approved: intermediate- or high-risk myelofibrosis and polycythemia vera	Decreased the occurrence rates and severity scores of anaphylactic reaction Decreased IL-4 production Inhibited degranulation of mast cells	No human studies for food allergy	24332884

Abbreviations: ACQ-6, Asthma Control Questionnaire-6; BTK, Bruton's tyrosine kinase; EASI, Eczema Area and Severity Index; FENO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; IGA, Investigators Global Assessment; TLR, toll-like receptor; URI, Upper Respiratory infections.
Data from Refs.[50,53,56–58,60–78]

during an observed OFC and had positive SPT to pistachio. A subsequent OFC confirmed her higher level of tolerance while on dupilumab, at nearly 100 pistachios (50 g unshelled). She also underwent an OFC to corn, to which she had a prior history of anaphylaxis and positive testing. While on dupilumab she tolerated 100 g of corn during OFC without any adverse reactions.[54] Dupilumab is currently being studied in peanut allergy. Concurrent phase II studies are comparing the efficacy and safety of dupilumab versus placebo as monotherapy (NCT03793608) and as an adjunct to peanut OIT (NCT03682770).

Mepolizumab, reslizumab, and benralizumab are IL-5-targeted treatments that are FDA-approved for eosinophilic asthma and may have a potential role in treating food allergy. Mepolizumab and reslizumab bind with high affinity and specificity to IL-5, preventing it from binding to its receptor and reducing the production and survival of eosinophils. Benralizumab binds to the IL-5Rα expressed on eosinophils and basophils, hindering access of IL-5 to its receptor and inducing target-cell depletion through natural killer cell–mediated, antibody-dependent cellular cytotoxicity. These anti-IL-5 therapies have been investigated in EoE, and there seems to be improvement in laboratory and histologic parameters.[55] However, symptoms persist in some subjects despite histologic improvement. The anti-IL-5 treatments have not yet been studied in IgE-mediated food allergy.

Newer anti-IL-13 treatments, lebrikizumab and tralokinumab, have been studied in phase II trials of allergic asthma, AD, and EoE. There are currently no trials investigating anti-IL-13 therapies in food allergy.

POTENTIAL FUTURE TARGETS

Additional biologics in development include those targeting IL-33 and TSLP. Both are epithelial cell cytokines, which play a role in T-cell polarization to Th2 cells.

Etokimab, an anti-IL-33 monoclonal antibody, was used in a small, phase IIa, multicenter, randomized, DBPC trial including 20 adults with peanut allergy. Compared with the placebo group, a single dose of etokimab resulted in a significant increase in the threshold dose of peanut protein eliciting a reaction (73% vs 0%).[56] Additionally, etokimab-treated subjects had reduced levels of IL-4, IL-5, IL-9, and IL-13 in $CD4^+$ T cells on peanut stimulation in vitro, and significantly lower peanut sIgE levels compared with baseline. Although the results seem promising, the sample size was small and the maximum dose of peanut protein during entry and exit OFCs was 375 mg (just greater than one peanut kernel).

Another biologic of interest is tezepelumab, an anti-TSLP monoclonal antibody. In a phase II trial, tezepelumab led to a significant decrease in the rate of asthma exacerbations compared with placebo in adults with uncontrolled asthma.[57] It has also been studied in a phase II trial in adults with moderate-to-severe AD; however, it failed to demonstrate statistically significant improvement in measurable eczema area and severity index scores when compared with placebo.[58] Currently, there are no trials investigating tezepelumab in food allergy.

Bruton's tyrosine kinase, small molecule inhibitors, such as ibrutinib and fenebrutinib, have shown the potential to suppress SPT reactivity, although it is unclear if this could also result in suppression of clinical allergy. Bruton's tyrosine kinase is a downstream enzyme that is required for mast cell and basophil signaling. Ibrutinib is FDA-approved for B-cell malignancies. In a study of two patients with chronic lymphocytic leukemia on ibrutinib with a diagnosis of allergic rhinitis and sensitization to cat and/or ragweed, allergen reactivity was reduced while on treatment. One week after initiation of ibrutinib, SPT wheal size was reduced to 0 mm from greater than 5 mm and there

was near complete inhibition of basophil activation. However, the response was not sustained, and subjects' SPT reactivity returned to baseline within a week of medication discontinuation. There was no assessment of their clinical allergic symptoms. This same group studied the short-term use of ibrutinib in six adults with peanut and/or tree nut allergy. After 2 days of treatment with ibrutinib, SPT wheal and flare area decreased significantly (76.6% and 86.0%, respectively), but OFCs were not performed. A phase II open label study of Ibrutinib in adults with food allergy is currently recruiting (NCT03149315).

JAK inhibitors have been widely used in rheumatologic, hematologic, and oncologic conditions with FDA approval for rheumatoid arthritis, psoriasis, myelofibrosis, and polycythemia vera. JAK inhibitors target key cytokine signaling pathways, such as IL-4 and IL-13, and their interaction with the IL-4αR. There is emerging evidence of their efficacy from phase II clinical trials in the treatment of AD. Oral upadacitinib and topical ruxolitinib have been studied with significant improvement in eczema area and severity index scores along with itch scores.[59] In food allergy, JAK inhibitors have thus far only been studied in murine models. Ruxolitinib selectively inhibits JAK1 and JAK2, and has been shown to blunt anaphylactic symptoms and decrease Th2 cytokines in mice. Daily dosing of ruxolitinib in ova-allergic mice significantly decreased rates and severity of anaphylaxis. The mechanism was identified as multifactorial through suppression of mast cell activation, inhibition of intestinal mast cell hyperplasia, and antigen-specific immunosuppression. An advantage of the JAK inhibitors is that as small molecules, they can be administered orally with once daily dosing.[60] However, JAK inhibitors have several associated toxicities, including immune suppression, increased risk of cancers, and pulmonary embolism.

There are limited data on the use of toll-like receptor agonists in a murine model of food allergy. This approach targets the antigen presentation to the innate immune system. Toll-like receptor-4 and -9 agonists are currently in preclinical trials for peanut allergy and have been shown to decrease the severity of anaphylaxis, while also increasing interferon-γ and peanut-specific IgG1 (the murine equivalent to human IgG4). This favors a Th1 and regulatory T-cell response, although this raises concern for the development of autoimmunity if unregulated activation occurs.[61]

SUMMARY

Current biologic treatment of food allergies aims at protecting against accidental ingestion and increasing food allergen tolerability. Anti-IgE treatment has been used with good success for management of food allergies, and is especially effective when combined with OIT, but is not yet FDA-approved for food allergy. Use of anti-IgE treatment, such as omalizumab, allows for modification of not just a single allergen, but multiple allergens at once, because they share a common pathway via basophils, acutely, and mast cells, long term in the manifestation of clinical reactions. This is important because nearly one-third of all individuals with food allergy have multiple food allergies. Future treatments, including dupilumab, an anti-IL-4 and IL-13 antibody, show promise in reducing type II signaling, and clinical trials using dupilumab for peanut allergy are ongoing. Other potential future treatments, such as oral JAK inhibitors, may offer broader immune suppression of key signaling pathways in type II skewed individuals with atopy, but may also carry an increased risk for significant side effects.

In the future, biologics targeting key players in the type II immune pathways essential in the development of atopic disorders may play a role in the sustained treatment and prevention of food allergies.

CLINIC CARE POINTS

- Omalizumab improves safety of food oral immunotherapy,
- Omalizumab monotherapy may also be an option for select patients.
- Real-world long-term efficacy and safety of these novel biologic therapies for food allergy remain to be determined.
- Costs of the novel therapies may limit real-world application.

DISCLOSURE

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