Biologic therapy for food allergy

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ABSTRACT

With the rising prevalence, food allergies have become a significant health burden that affects 6% to 13% of the global population. Although oral immunotherapy (OIT) has been promising for food allergies, this therapy has limitations, including high rates of adverse reactions and long treatment periods. Biologics may address these limitations by increasing the safety and tolerability of OIT and decreasing treatment periods. The use of biologics and vaccines are actively being explored as monotherapy as well as adjunctive therapy in combination with allergen specific OIT. A number of biologics that target key molecules known to be involved in food allergy are under investigation, including anti–immunoglobulin E therapy (omalizumab), anti–interleukin (IL) 4 receptor α (dupilumab), anti–IL-5 (mepolizumab and reslizumab), and anti–IL-5R (benralizumab), anti–IL-33 (etokimab), and peanut DNA plasmid vaccines. In the era of precision medicine, the future of food allergy looks promising, and biologics will provide treatment as well as further insights into the molecular mechanisms associated with food allergy.

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With the rising prevalence, food allergies (FA) have become a significant health burden, which affects 6% to 13% of the global population.[1,2] The U.S. Food and Drug Administration (FDA) and the European Medicines Agency have approved five biologics for a variety of atopic disorders; however, none are currently approved for FA treatment (Table 1). There is ongoing interest in evaluating these biologics and in developing new biologics for treating FA. Several biologics are currently being evaluated for FA in clinical trials, both as monotherapy and as adjunctive therapy in combination with oral immunotherapy (OIT). Biologics are advantageous because they act as non–allergen-specific therapy, which potentially addresses multiple FAs with one treatment. Biologics can also mitigate upstream and early signaling immunologic pathways of FA. In addition, as adjunctive therapy, biologics may increase the safety and tolerability of OIT, which is often limited by adverse reactions.[3] There is also increasing interest in developing vaccine strategies for the treatment of FA. In this article, we discuss the biologics and vaccines currently under investigation for the treatment of FA. M. Chen, W. Zhang, L. Lee, J. Saxena, and S. Sindher performed the literature search, drafted, and critically revised the work. R.S. Chinthrajah, C. Dant, and K. Nadeau critically reviewed the work.

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IMMUNOGLOBULIN E TARGETED THERAPY

Omalizumab a recombinant humanized anti–immunoglobulin E (IgE) monoclonal antibody, demonstrated its potential to treat a range of allergic disorders. Omalizumab acts by binding free serum IgE, which decreases high-affinity IgE receptor expression on mast cells and basophils, and, in turn, reduces histamine release. Omalizumab also inhibits IgE binding to CD23 on B cells and antigen-presenting cells. The efficacy of omalizumab has been validated in clinical trials for treating allergic asthma and chronic idiopathic urticaria, and is approved for the treatment of these indications.

The use of omalizumab in treating IgE-mediated FA has been evaluated both as a monotherapy and as an adjunct to OIT in an attempt to increase treatment safety. A phase II randomized, double-blind, parallel-group, placebo controlled study evaluated omalizumab monotherapy in subjects with peanut allergy.[4] The participants were treated with omalizumab or placebo for 20–22 weeks.[4] At the 24-week oral food challenge, there was a trend in tolerating a greater amount of peanut protein compared with the baseline oral food challenge in subjects who received omalizumab compared with placebo.[4] Unfortunately, this trial was stopped early due to two severe anaphylactic reactions during the baseline oral food challenges.

Table 1 **Biologics and targets for atopic disorders**

Biologic	Target	Indication(s)
Omalizumab (Xolair)	Anti-IgE	Moderate-to-severe persistent atopic asthma in patients ages ≥ 6 y inadequately controlled by inhaled corticosteroids; chronic idiopathic urticaria in patients ages ≥ 12 y inadequately controlled by H_1 antihistamine treatment; currently in phase III clinical trial evaluating omalizumab as monotherapy and as adjunct therapy to OIT in subjects with multiple food allergies (NCT03881696)
Mepolizumab (Nucala)	Anti-IL-5	Severe eosinophilic asthma in patients ages ≥ 12 y as add-on maintenance treatment
Reslizumab (Cinqair)	Anti-IL-5	Severe eosinophilic asthma in patients ages ≥ 18 y as add-on maintenance treatment
Benralizumab (Fasenra)	Anti-IL-5R	Severe eosinophilic asthma in patients ages ≥ 12 y as add-on maintenance treatment
Dupilumab (Dupixent)	Anti-IL-4Rα	Currently in four clinical trials for food allergy: (a) dupilumab monotherapy for treating peanut allergy (NCT03793608), (b) dupilumab as adjunctive therapy with OIT for peanut allergy (NCT03682770), (c) dupilumab as adjunctive therapy with OIT for multiple food allergies (NCT03679676), and (d) dupilumab as an adjunctive therapy with OIT for cow's milk allergy (NCT04148352)
Etokimab	Anti-IL-33	Completed phase IIa clinical trial for adults with peanut allergy (NCT02920021)

IgE = Immunoglobulin E; IL = interleukin; IL-4Rα = IL-4 receptor α.

The majority of clinical trials focused on the use of omalizumab as an adjunct to OIT. In a randomized, double-bind, placebo controlled study that evaluated omalizumab combined with cow's milk OIT, the combination therapy significantly improved safety outcomes in the subjects who received omalizumab.[5] The subjects treated with omalizumab experienced fewer reactions during OIT dose escalation versus the subjects who received placebo (2.1% versus 16.1%, $p = 0.0005$).[5] However, this trial found no significant differences between those treated with omalizumab and OIT compared with OIT alone in terms of efficacy as measured by desensitization or sustained unresponsiveness.[5]

In a placebo controlled, single-allergen peanut-OIT trial, adjunct omalizumab allowed the participants with peanut allergy to be rapidly desensitized over as little as 8 weeks of OIT, which was sustained after omalizumab was discontinued.[6] The subjects were continued on a dose of 2000 mg of peanut after omalizumab discontinuation, and some subjects were subsequently able to tolerate a 4000 mg oral food challenge and continue on a daily maintenance dose of 4000 mg of peanut protein.[6]

In a phase I multi-allergen (≤5) OIT trial, omalizumab was given alone as pretreatment for 8 weeks, followed by omalizumab concurrent with multi-allergen OIT dose escalation for an additional 8 weeks, followed by OIT alone.[7] All the participants were able to reach a daily maintenance dose of 4000 mg of each allergen by 9 months.[8] This treatment approach significantly improved allergen desensitization after 36 weeks of therapy and significantly decreased adverse events, which allowed faster allergen dose escalation compared with placebo.[7] Thus, anti-IgE adjunctive treatment may decrease premature termination from OIT trials due to intolerance and anaphylaxis. In a phase II multi-OIT placebo controlled trial, despite the decrease in adverse events in the active group, a median 27% of OIT doses per participant was nonetheless related to an adverse event, with gastrointestinal events the most common in both groups.[8]

Although additional studies are still needed to identify and profile individuals who are expected to benefit the most from adjunctive omalizumab in OIT, the trial evidence to date has shown significant advantages of adjunctive anti-IgE therapy in treating FA. There is currently a phase III trial aimed at evaluating omalizumab as monotherapy and as adjunct therapy to OIT in subjects with multiple FAs (NCT03881696).

Il-4 AND IL-13 TARGETED THERAPY

Dupilumab is a recombinant human IgG4 monoclonal antibody directed against the α-chain of the IL-4 receptor α (IL-4Rα).[9] Both IL-4 and IL-13 bind to IL-4Rα, which

results in a signaling cascade that promotes allergic inflammation. Dupilumab prevents the initiation of this inflammatory cascade and potentially may mitigate the upstream pathophysiologic events that lead to FA.

Dupilumab is currently approved by the FDA and the European Medicines Agency for treating moderate-to-severe atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyposis.[10] The first reported use of dupilumab in FA was in a case report from a patient who received dupilumab for severe atopic dermatitis.[11] The patient was incidentally found to tolerate foods to which she was previously allergic; she was originally diagnosed with corn allergy (anaphylactic shock and positive testing) and pistachio allergy (positive testing and positive oral food challenge).[11] After starting dupilumab, she subsequently passed two oral challenges to corn and pistachio.[11]

There currently are four ongoing clinical trials that are evaluating the safety and potential efficacy of dupilumab in FA: (1) NCT03793608 dupilumab monotherapy for treating peanut allergy, (2) NCT03682770 dupilumab as adjunctive therapy with OIT for peanut allergy, (3) NCT03679676 dupilumab as adjunctive therapy with OIT for multiple FAs, and (4) NCT04148352 dupilumab as an adjunctive therapy with OIT for cow's milk allergy. In addition, dupilumab is also being evaluated in the treatment of eosinophilic esophagitis (EOE) in adults and adolescents (NCT03633617).

IL-5 TARGETED THERAPY

As part of the pathogenic mechanism of FA, the release of IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) induces IL-5 production. Specifically, type 2 innate lymphoid cells may be activated by IL-25, which, in turn, produces increased levels of IL-5, an interleukin that promotes eosinophil production, maturation, proliferation, and migration.[12] Currently, three anti–IL-5 products have been approved by the FDA for treatment of eosinophilic asthma: mepolizumab, reslizumab, and benralizumab. Mepolizumab and reslizumab bind to IL-5, which blocks receptor interaction, and benralizumab binds to the α-chain of IL-5 receptor on eosinophils and basophils. This blockade depletes the production and activity of eosinophils.[12] Mepolizumab and reslizumab have demonstrated efficacy in reducing eosinophil counts in patients with EOE,[13] and benralizumab is currently being evaluated for treating eosinophilic gastrointestinal disease (NCT03473977).

Certain foods have been identified as EOE triggers, which has been a concern related to FA in the context of OIT. A meta-analysis of studies shows that EOE occurs in ~2.7% of patients who are undergoing OIT.[14] Anti–IL-5 agents may potentially be useful adjuncts to facilitate IgE-mediated FA immunotherapy, especially in preventing or treating concomitant eosinophil-related disease. Future clinical investigation is likely.

ALARMIN TARGETED THERAPY

Alarmins, including IL-25, IL-33, and TSLP, play a critical role in developing and maintaining FA. The release of alarmins can be induced in response to exposure of food allergens and promote a shift away from a T-helper (Th) type 1 tolerogenic state to a Th2-dominant proallergic state by inducing the activation and expansion of type 2 innate lymphoid cells and production of cytokines IL-4, IL-5, and IL-13. TSLP has been shown to enhance the production of IgE from memory B cells *via* an IL-4– and/or IL-13–dependent mechanism.[15,16]

Anti-alarmin agents have been evaluated for treating several atopic conditions. The inhibition of IL-33 by using the humanized IgG1/kappa monoclonal antibody etokimab has been investigated for treating FA. A phase II, double-blind, placebo controlled study determined that 73% of patients who received a single dose of etokimab were able to tolerate a cumulative dose of 275 mg of peanut protein compared with 0% of patients who received placebo; in this trial, etokimab was well tolerated and safe.[17]

Additional anti-alarmin agents are under similar evaluation in clinical trials. Tezepelumab, a human monoclonal antibody that binds to TSLP, has been evaluated for treating asthma and atopic dermatitis but not yet for FA. Although trials to investigate the blockade of IL-25 and TSLP in humans with FA are not yet underway, a murine model study showed that injecting a monoclonal antibody against IL-25, IL-33 receptor, and/or TSLP strongly inhibited FA development.[18] Overall, antibodies toward alarmins are showing promise as treatments for atopic diseases. The safety and efficacy of anti-alarmin agents for treating patients with FA has yet to be determined.

VACCINES

Vaccines have long been used to target and train immune processes as a method to combat pathogens. Researchers hope to use this same platform to ameliorate the immune response in allergic reactions, including FA and anaphylaxis. Mechanistically, a vaccine-based strategy offers a novel approach compared with traditional protein immunotherapy and potentially a more favorable safety profile. Traditional immunotherapy with ongoing exposure to the intact food protein allergen carries the risk of inducing IgE-mediated allergic reactions. Vaccine-based strategies have focused on the delivery of different forms of these culprit allergens (such as recombinant proteins and plasmid DNA) that redirect the underlying immune response away from the Th2 pathway and IgE production while avoiding directly challenging patients with intact food proteins. There are known risks associated with vaccine

immunotherapy, and the evidence for sustained protection is lacking. Current efforts are aimed at positioning vaccines as a long-term therapeutic option.

The complex immune system provides multiple avenues through which an FA vaccine might modulate the immune response. An initial phase I trial of rectally administered vaccine that contains recombinant peanut allergens (Ara h 1, Ara h 2, and Ara h 3) decreased basophil activation and peanut skin titration but did not significantly change levels of peanut IgE or peanut IgG4; in this trial, severe allergic reactions occurred in 20% of the patients who received the vaccine.[19] The route of vaccine immunization is also being considered. In a preclinical mouse study, an intranasal peanut vaccine suppressed Th2 cytokines, thereby reducing allergic inflammation and protecting against anaphylaxis, with some evidence of sustained unresponsiveness; specifically, this vaccine engaged the Th1 and Th17 immune responses, which directed the immune response away from the Th2 pathway.[20]

Researchers are now exploring novel ways to evaluate vaccines to treat FA. For example, viruses are being tested as vectors for manipulating the immune response. In one study, Ara h 1 and Ara h 2 peanut allergens were coupled with engineered virus-like particles and administered to peanut-sensitized mice.[21] With subsequent peanut challenges, the mice were protected against anaphylaxis and had reduced local skin-prick test reactions and eosinophilic infiltration in the gut.[21] DNA vaccines have shown promise as a therapeutic option for allergic diseases and, although not new, their effectiveness has been limited by their relatively poor immunogenicity.[22] Efforts are now focused on optimizing immunogenicity *via* adjuvants and other alterations.

A recent mouse study introduced an intradermal plasmid DNA vaccine encoding Ara h 2 and pretreated with a synthetic amino acid to improve DNA delivery.[23] In this study, mice injected intradermally with the pretreated Ara h 2 vaccine displayed increased uptake of the modified DNA and a reduced allergic response, including fewer anaphylaxis symptoms.[23] Currently, there are no FDA-approved vaccines for FA, but results from the current research are promising. Clinical trials are actively evaluating the safety of a multivalent peanut lysosomal-associated membrane protein DNA plasmid vaccine for treating peanut allergy [NCT03755713 and NCT02851277]. These efforts to evaluate vaccines are part of a promising future of groundbreaking therapies for treating FA.

CONCLUSION

Several biologic agents and vaccines are being investigated in clinical trials for FA. Although additional studies will be needed to better understand their potential efficacy, including sustained unresponsiveness and safety, preliminary preclinical and clinical data have been promising, and show that biologics create a safer treatment environment for patients undergoing OIT, skewing the immunologic balance toward tolerance.

CLINICAL PEARLS

- Several biologics are approved for use in a range of atopic disorders.
- Biologics are being evaluated both as monotherapy and as adjunctive therapy in combination with OIT for treating FA.
- The advantage of biologics include the ability to act as non–allergen-specific therapy, thus potentially addressing multiple FAs with one treatment.
- As adjunctive therapy, biologics may increase the safety and tolerability of OIT, which is often limited by allergic adverse effects.
- Vaccines are also actively being studied as a novel therapy for FA.

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