

Biologics and Novel Therapies for Food Allergy



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KEYWORDS

- Food allergy • Biologics • Microbiome • Fecal microbiota transplantation
- Omalizumab • Dupilumab

KEY POINTS

- New therapeutic modalities in food allergy are needed to minimize the risk of anaphylaxis and improve associated anxiety, nutritional deficiencies, and patient's quality of life.
- Biologics are promising modalities, as they may potentially target multiple food allergies instead of one, in addition to possibly treating other concomitant atopic diseases.
- Although omalizumab has been evaluated extensively in allergic diseases, most biologics are more novel and have broader immunologic impact. Hence, careful evaluation of their safety and their modulation of the immune system should be conducted.

INTRODUCTION

Food allergy is a significant public health burden with a significant increase in its prevalence over the last decades globally. In the United States, food allergy affects around 10% of adults and 8% of children.^{1–3} The potential risk of severe or fatal anaphylaxis, the associated anxiety and nutritional issues of the affected patients, and the significantly negative impact on quality of life all underscore the need for developing effective therapeutic options for food allergy.^{4,5}

Although the current standard of care for most food allergy consists of avoiding the culprit allergens and keeping rescue medicine available for emergency use, AR101, the first treatment of peanut oral immunotherapy (OIT), received Food and Drug

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Administration (FDA) approval in January 2020.^{6,7} OIT is the most evaluated therapeutic approach in food allergy. Desensitization is achieved in most of the patients.⁷⁻¹⁰ However, OIT has many limitations, including the risk of allergic reactions from the food itself, taste aversion to the food as well as variable rates of sustained unresponsiveness (SU) after stopping it.¹¹⁻¹³ Compliance with therapy over time can be a significant barrier, as the food needs to be taken regularly in order to maintain desensitization. SU was demonstrated in 50% of patients who stopped OIT for 4 weeks after up to 5 years of therapy,¹² whereas it was achieved in only 15% of subjects 6 months after discontinuation.^{12,13} Other immunotherapy approaches using the sublingual, epicutaneous, and subcutaneous routes are under evaluation.¹⁴⁻¹⁶ None of these are known to lead to a cure.

There is therefore an unmet need for evaluating other therapeutic approaches in food allergy. Biologics are particularly attractive, as by modifying the allergic response, they can potentially target multiple food allergies instead of one, in addition to possibly treating other concomitant atopic diseases. In addition, as they are administered often intermittently as opposed to the daily or regular dosing of food immunotherapies, they are likely to be associated with better compliance and possibly patient satisfaction with the therapy.

In this article, the authors review the biological therapies that are currently under evaluation for food allergy treatment, as well as some of the potential candidates that could be used for further investigation (**Table 1**).

ANTI-IMMUNOGLOBULIN E ANTIBODY

The hallmark of the allergic reaction is the release of inflammatory mediators including histamine, leukotriene, cytokines, and prostaglandins that are activated after cross-linking of antigen-specific immunoglobulin E (IgE) complex on the surface of the mast cells and basophils on exposure to the antigen.^{17,18} Omalizumab is antihuman IgE monoclonal antibody that binds to the 2 constant domains of free IgE, thus forming an IgE/anti-IgE immune complex that impedes the IgE linkage to its receptors on mast cells and basophils, hence inhibiting antigen-triggered degranulation.¹⁹

Omalizumab has been evaluated as monotherapy in small trials that demonstrated significant increase in threshold of reactivity to peanut after 3 to 24 weeks of therapy.^{20,21} Asthmatic children given omalizumab for asthma therapy for 4 months showed an increased threshold of reactivity for multiple food allergens including cow's milk, egg, wheat, and hazelnut.²²

As an adjunct therapy to OIT, omalizumab had been successfully used to facilitate rapid up dosing.²³⁻²⁹ The authors have shown that omalizumab can rapidly desensitize patients who were reactive to less than 50 mg peanut protein at study entry to 2000 mg 20 weeks later. In that study, participants received omalizumab first for 12 weeks, followed by an additional 8 weeks of therapy combined with peanut OIT.²⁷ In a double-blinded placebo-controlled milk OIT trial, participants received omalizumab or placebo for 4 months before initiation of milk OIT and continued on the assigned therapy for 24 months. Although there was no differences in efficacy, the omalizumab-treated group had significantly less allergic reactions to OIT.²⁶ Omalizumab also has been used successfully to facilitate rapid desensitization in multiallergen food OIT.^{28,29} Androf and colleagues²⁸ found that 83% of patients who received omalizumab combined with multifood OIT passed a food challenge to 2 or more food up to 2000 mg of protein compared with 33% patients who received placebo with OIT.

A multicenter double-blinded placebo-controlled phase III trial is currently evaluating the use of omalizumab as monotherapy and as adjunct to multiallergen food

Table 1
List of biologics that are either currently evaluated or are potential investigational therapies in food allergy

Therapeutic Agents	Clinical Use in Food Allergy or Other Atopic Diseases
Anti-IgE	
Omaliuzumab (anti-IgE mAb)	Currently investigated in phase III trials as monotherapy or as adjunct therapy to food OIT.
Ligelizumab (anti-IgE mAb)	Evaluated in chronic spontaneous urticaria and asthma. Not evaluated yet in food allergy.
Anti-TH2 cytokines antibodies	
Anti-IL-4R	Dupilumab is currently investigated as monotherapy or as adjunct therapy to food OIT in phase II trials.
Anti-IL-5 and anti-IL-5R	Mepolizumab (anti-IL-5 mAb), reslizumab (anti-IL-5 mAb), and benralizumab (Anti IL-5-R mAb) are FDA approved for treatment of eosinophilic asthma. They have not been evaluated yet in food allergy.
Anti-IL-13	Lebrikizumab and tralokinumab are currently being evaluated in phase III for asthma and atopic dermatitis. They have not been evaluated yet in for food allergy.
Acalabrutinib (Bruton's tyrosine kinase inhibitor) Ruxolitinib (JAK 1/2 inhibitor) Syk inhibitor	All effective in preventing anaphylaxis reaction in food-allergic mouse model.
Epithelial cytokines	
Anti-IL-33	Etokimab (anti-IL-33 Ab) was evaluated in a phase IIa trial for peanut allergy.
Anti-TSLP	Tezepelumab (anti-TSLP mAb) currently investigated for asthma and atopic dermatitis. It has not been evaluated yet in food allergy.
TH1 adjuvants	
Glucopyranosyl lipid A (GLA)	GLA is being investigated as an adjunct therapy to peanut sublingal immunotherapy in a phase I trial.
Monophosphoryl lipid A (MPL) and CpG oligodeoxynucleotides	Both were investigated in treatment of allergic rhinitis but not in food allergy yet.
DNA vaccines	ASP0892 (ARA-LAMP-vax) is being investigated in phase I peanut allergy trial.
Modified food allergen proteins	Encapsulated, Recombinant Modified Peanut Proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) was investigated in peanut allergy. HAL-MPE1 is currently being evaluated for peanut allergy in a phase I trial.

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Table 1 (continued)	
Therapeutic Agents	Clinical Use in Food Allergy or Other Atopic Diseases
Anti-sialic acid-binding immunoglobulin-like lectin 8 (Siglec-8) antibody (AK002)	Currently evaluated in eosinophilic esophagitis, eosinophilic gastritis, and eosinophilic duodenitis. Not evaluated yet in IgE-mediated food allergy.
Microbiome interventions	
Probiotics	Lactobacillus GG (LGG), bifidobacterium, and lactobacillus lactis supplemented with extensively hydrolyzed milk formula were evaluated in cow's milk allergy. Lactobacillus rhamnosus was evaluated in combination with peanut OIT. VE416 is currently being evaluated with and without peanut OIT in phase I/II trial.
Fecal microbiota transplantation (FMT)	FMT is being currently investigated in a phase I clinical trial in peanut allergy.

OIT (including milk, egg, wheat, cashew, hazelnut, or walnut (<https://clinicaltrials.gov/show/NCT03881696>)).

Ligelizumab (QGE031) is an anti-IgE antibody that binds with higher affinity to serum IgE than omalizumab.³⁰ QGE031 was found to have greater efficacy than omalizumab on inhaled and skin allergen responses in patients with mild allergic asthma.³¹ A phase II study comparing QGE031 with omalizumab and placebo in severe asthma has been conducted but the results have not been published yet (<https://clinicaltrials.gov/show/NCT01716754>). Ligelizumab was found to be more effective in complete control of chronic urticaria symptoms compared with omalizumab and placebo.³² Another phase II trial assessed QGE031 for the treatment of atopic dermatitis but the results have not published yet (<https://clinicaltrials.gov/show/NCT01552629>). Ligelizumab has not been evaluated yet in food allergy. Given its higher affinity to IgE, it potentially may have better efficacy allowing for higher levels of desensitization or quicker up dosing and/or a higher safety profile as a monotherapy or as an adjunct therapy to OIT compared with omalizumab.

ANTI-T HELPER CELLS TYPE 2 CYTOKINES ANTIBODIES

The interleukin-4 (IL-4) receptor and its ligands IL-4 and IL-13 play a central role in allergic inflammation and the promotion of T helper cells type 2 (TH2) differentiation. Dupilumab is a humanized IgG4 monoclonal antibody that targets the IL-4 receptor alpha chain (IL-4R α), which is common to both IL-4R complexes: type 1 (IL-4R α / γ C; IL-4 specific) and type 2 (IL-4R α /IL-13R α 1; IL-4 and IL-13 specific). There is little published in vitro or in vivo data on the precise mechanism of action of Dupilumab. However, proposed mechanisms of action of Dupilumab have been described by Harb and Chatila.³³ Dupilumab is FDA approved for the treatment of moderate-to-severe asthma, chronic rhinosinusitis with nasal polyposis, and atopic dermatitis.^{34–37}

The authors have shown in patients who received omalizumab as an adjunct therapy to OIT that peanut-specific regulatory T cells (Treg cells), which at baseline exhibited a TH2 cell-like phenotype, characterized by increased IL-4 expression, progressively reversed on OIT administration. Peanut-specific Treg cell suppressor

activity was initially absent at the start of omalizumab/OIT therapy; however, it became robust with OIT. Furthermore, the absent peanut-specific Treg cell function was recovered by the acute blockade of IL-4/IL-4R receptor signaling in Treg cells, which inhibited their IL-4 production.³⁸ These findings highlight the potential therapeutic effect of IL-4 signaling inhibition in food allergy. Interestingly, a 30-year-old patient with a history of pistachio allergy and corn anaphylaxis was treated with dupilumab for severe atopic dermatitis. Three months after treatment with Dupilumab, pistachio and corn were tolerated during an open food challenge.³⁹ Currently, there are 3 ongoing phase II clinical trials evaluating dupilumab in peanut allergy, one as a monotherapy (<https://clinicaltrials.gov/show/NCT03793608>) and another one as an adjunct therapy to peanut OIT (<https://clinicaltrials.gov/show/NCT03682770>). The third trial evaluates omalizumab alone, dupilumab alone, or omalizumab followed by dupilumab therapy, in patients on multi-food OIT (<https://clinicaltrials.gov/show/NCT03679676>).

Lebrikizumab and QAX576 are both anti-IL-13 monoclonal antibodies that have been evaluated in asthma and eosinophilic esophagitis, respectively.^{40–42} In a meta-analysis of 5 trials, lebrikizumab was shown to be effective in decreasing the asthma exacerbations and improving the lung function and had a greater efficacy in asthmatics with high periostin level.⁴¹ In adults with eosinophilic esophagitis, esophageal eosinophil counts were decreased by 60% in patients who received QAX576 compared with an increase of 23% in patients who received placebo.⁴² Monoclonal antibodies mepolizumab and reslizumab that bind to IL-5 and benralizumab that binds to IL-5Ra are FDA approved for treatment of eosinophilic asthma.^{43,44} These antibodies have not been evaluated yet in food allergy.

SPLEEN TYROSINE KINASE

Spleen tyrosine kinase (Syk) plays a key role in the allergic response early in the signaling cascade following binding of allergen to receptor-bound IgE on the mast cell.

In an adjuvant-free mouse model of peanut allergy, mast cell–targeted genetic deletion of Syk or Syk blockade prevented peanut sensitization. In mice with established peanut allergy, Syk blockade facilitated desensitization and induction of Treg cells. In addition, when Syk inhibitor was administered with peanut immunotherapy, it completely protected from anaphylaxis to peanut after interruption of therapy.⁴⁵

BRUTON'S TYROSINE KINASE

Bruton's tyrosine kinase (BTK) has been identified as a key downstream component of FcεRI signaling in human mast cells and basophils.⁴⁶ IgE-receptor crosslinking in basophils is followed by phosphorylation of Syk, which, once activated, phosphorylates BTK.⁴⁷ Ibrutinib and acalabrutinib are both oral FDA-approved irreversible BTK inhibitors for the treatment of B cell malignancies.⁴⁸ In a small pilot study, 2 standard doses of ibrutinib reduced or eliminated skin prick test reactivity to peanut and tree nuts in food-allergic adults. In a humanized mouse model, pretreatment with 2 oral doses of acalabrutinib completely prevented moderate IgE-mediated anaphylaxis and also significantly protected against death during severe anaphylaxis.⁴⁹

JANUS KINASE INHIBITORS

The Janus kinase–signal transducer and activator of transcription pathway is used by different cytokines such as interleukins and interferons to transmit signals intracellularly from the cell membrane to the nucleus.⁵⁰ They are FDA approved for conditions such as rheumatoid arthritis, polycythemia vera, and myelofibrosis.⁵⁰ Several JAK

inhibitors are in phase II and III clinical trials as oral therapies for moderate-to-severe atopic dermatitis or as topical treatments for mild-to-moderate atopic dermatitis.⁵¹ Recently, in large international phase III trial, a once daily dose of abrocitinib, a selective JAK 1 inhibitor, for 12 weeks demonstrated significant efficacy and tolerability in adolescent and adults with moderate-to-severe atopic dermatitis.⁵² JAK inhibitors have not been investigated in food allergy clinical trials. However, in murine studies, administration of ruxolitinib, a JAK 1/2 inhibitor, reduced anaphylaxis to ovalbumin and inhibited proliferation and degranulation of mast cells.⁵³

ANTI-SIALIC ACID-BINDING IMMUNOGLOBULIN-LIKE LECTIN 8 ANTIBODY

Sialic acid-binding immunoglobulin-like lectin (Siglec)-8 is an inhibitory receptor of the CD33-related subfamily of Siglecs expressed on mature mast cells, eosinophils, and to a lesser extent basophils. When bound to anti-Siglec-8 antibody, it induces apoptosis in eosinophils and inhibits mast cell activity.⁵⁴ Lirentelimab or AK002, a humanized anti-Siglec-8 antibody, induced apoptosis of IL-5 ex vivo. Its murine precursor mA002 prevented passive systemic anaphylaxis through mast cell inhibition in humanized mice.⁵⁵ Lirentelimab is currently being investigated as a therapy in eosinophilic esophagitis (NCT04322708) and eosinophilic duodenitis and gastritis (NCT04322604).

EPITHELIAL CYTOKINES: INTERLEUKIN-33 AND THYMIC STROMAL LYMPHOPOIETIN

On allergen exposure, the gut epithelium actively produces cytokines and chemokines, including thymic stromal lymphopoietin (TSLP) and IL-33, which promote dendritic cell activation and TH2 upregulation.¹⁷ IL-33 was shown to be necessary for sensitization to peanut allergens and allergic responses in murine studies.⁵⁶ Eto kimab (ANB020), an anti-IL-33 monoclonal antibody, was evaluated in a small phase IIa multisite double-blind placebo-controlled trial. Fifteen days after a single dose of eto kimab administered to peanut-allergic adults, 73% of those on active therapy tolerated a cumulative dose of 275 mg peanut protein compared with 0% of placebo group.⁵⁷

In a phase II clinical trial, patients receiving Tezepelumab, an anti-TLSP antibody, experienced lower rates of asthma exacerbation compared with those on placebo.⁵⁸ A large multicenter double-blind placebo-controlled phase III clinical trial evaluating tezepelumab in adults and adolescents with severe uncontrolled asthma is ongoing (NCT03347279). Adult patients with moderate-to-severe atopic dermatitis actively treated with tezepelumab had improvement in the eczema area and severity index compared with those who received placebo, although the difference between the 2 treatment groups did not reach statistical significance.⁵⁹ Tezepelumab has not been investigated yet in treatment of food allergy.

TH1 ADJUVANTS

TH1 adjuvants combined with an allergen may be used to skew the immunologic response toward Th1 polarization. Toll-like receptor (TLR) agonists combined with an allergen such as CpG oligodeoxynucleotides may be another potential therapeutic approach for allergic diseases.⁶⁰ Anaphylaxis was reduced when CpG oligodeoxynucleotides were coadministered with ovalbumin and peanut allergen in murine studies.^{61–64} In humans, the administration of CpG combined with ragweed allergen has shown efficacy in allergic rhinitis.^{65,66}

TLR4 agonist monophosphoryl lipid A (MPL) is another Th1 adjuvant that has shown to improve the clinical symptoms of allergic rhinitis.^{67–69} A synthetic form of MPL, glucopyranosyl lipid A, is currently being investigated in a phase I double-blind, placebo-controlled study as adjunctive therapy to peanut SLIT (<https://clinicaltrials.gov/show/NCT03463135>).

DNA VACCINES

DNA vaccines consist of a bacterial plasmid vectors expressing a target protein gene for *in vivo* administration and transfection. Inclusion of a lysosomal associated membrane protein 1 (LAMP-1) to the DNA plasmid directs the antigen from a proteasomal class I pathway toward a lysosomal class II pathway, hence enhancing their immunogenicity.^{70,71} Phase I trials in peanut-allergic adults and teenagers are evaluating the safety, tolerability, and immune response of intradermal and intramuscular ASP0892 (ARA-LAMP-vax), which is a single multivalent peanut (Ara h1, h2, h3) LAMP-DNA plasmid vaccine (<https://clinicaltrials.gov/ct2/show/NCT02851277> and <https://clinicaltrials.gov/show/NCT03755713>).

MODIFIED FOOD ALLERGEN PROTEINS

Modifying an allergen protein may potentially lead to a decreased risk of allergic reaction during desensitization compared with natural protein. Modified food allergen protein was investigated in a phase I trial as a potential therapy for peanut-allergic patients using rectal administered, Heat/Phenol Killed, *E. coli* Encapsulated, Recombinant Modified Peanut Proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123). This study demonstrated frequent adverse events including anaphylaxis in 20% of peanut-allergic patients compared with none in healthy control subjects.⁷²

A randomized, double-blind, placebo-controlled phase I trial evaluated the safety, tolerability, and immunologic effects of subcutaneous HAL-MPE1, a chemically modified adsorbed aluminum hydroxide to peanut extract, in adult and pediatric subjects with peanut allergy (<https://clinicaltrials.gov/show/NCT02991885>).

TARGETING THE MICROBIOME FOR THE TREATMENT OF FOOD ALLERGY

There is now substantial evidence that the gut microbiota play a significant role in the pathogenesis of food allergy.⁷³ The natural immune tolerance promoted by healthy commensal gut bacteria targets both innate and adaptive immune response and protects the intestinal mucosa barrier. Several environmental factors such as diet, antibiotics, cesarean section, and western lifestyle may affect the gut microbiome compositions that subsequently could alter immune tolerance, hence increasing susceptibility to atopic diseases.⁷⁴ Conversely, other factors may protect from atopic diseases, such as increased family size and early childhood exposure to pets due to more commensal microbiota diversity.^{74,75} Although several studies have evaluated dysbiosis in food allergy, comparison between studies is difficult however, given the significant variability in study design, methods of microbiome analysis, geographic location, and inclusion/exclusion criteria to name a few.⁷⁴ The authors recently showed in a prospective study that there is evolving dysbiosis in food-allergic infants that affects 77 different bacterial taxa.⁷⁶ Administration of bacteriotherapy including 6 Clostridiales strains and separately 5 Bacteroidales strains, which were affected by the dysbiosis in infants, to a highly allergic food allergy mouse model (*Il4ra*^{F709} mice) prevented food allergy and completely suppressed anaphylaxis.⁷⁶ The authors' studies have demonstrated that the mechanism by which bacteriotherapy regulates food tolerance is complex and

depends on $\text{TGF}\beta$ -1, as well as upregulation of $\text{RoR}\gamma$ +t Treg cells via a TLR/MyD88-dependent mechanism, as well as downregulation of the allergic phenotype of Treg cells, such as GATA3 transcription factor or IL-4 expression.⁷⁶ Hence these studies suggest that targeted bacteriotherapy is a promising approach in food allergy treatment. However, the role of the clinically available probiotics in food allergy remains unclear. Infants with cow's milk allergy who received extensively hydrolyzed milk formula (EHMF) supplemented with *Lactobacillus* GG demonstrated quicker acquisition of tolerance compared with those who received EHMF without probiotic.⁷⁷ Patients with cow's milk anaphylaxis or other food allergies were however excluded from the trial. Conversely, a randomized, double-blind placebo-controlled trial among cow's milk allergic infants showed no difference in acquisition of tolerance between infants who received EHMF supplemented with *Lactobacillus casei* and *Bifidobacterium lactis* versus those who received EHMF alone.⁷⁸ Moreover, the potential role in reducing the risk of atopic diseases and food hypersensitivity was examined in a systematic review that included 2947 infants from 17 studies. Although the study suggested the probiotics could reduce the risk of atopy and food sensitivity when administered prenatally to pregnant women and postnatally to the child, a similar outcome was not observed when the probiotics were given either only prenatally or postnatally.⁷⁹

Lactobacillus rhamnosus CGMCC combined with peanut OIT was evaluated in a randomized double-blind placebo-controlled trial in 62 children aged from 1 to 10 years. Sustained unresponsiveness, evaluated after discontinuation of therapy for 2 to 5 weeks, was noted in 82% of children who received probiotic and peanut OIT compared with 3.6% in the placebo group.⁸⁰ However, no solid conclusion could be drawn, given the lack of a comparative treatment arm (peanut OIT with placebo). VE416 is bacterial consortium currently being evaluated as a monotherapy or in combination with peanut OIT in adults and teenagers in a phase I/II trial (NCT03936998).

Fecal microbiota transplantation (FMT) is the transfer of a healthy donor's feces to the gastrointestinal of the diseased recipient with the aim of reestablishing the normal microbiome. FMT can be administered via enema, nasogastric route, orally, or by colonoscopy. It has been evaluated very successfully in the treatment of recurrent *Clostridium difficile* colitis.^{81,82} The authors have shown that administering FMT from healthy human babies into *Il4ra*^{F709} mice rescued the mice from severe anaphylaxis, unlike when FMT from FA babies was administered into these mice.⁷⁶ Similar results were observed in a different mouse model sensitized to milk. FMT from healthy babies into mice that were subsequently sensitized to cow's milk allergen β -lactoglobulin protected from anaphylaxis, unlike FMT taken from milk allergic infants.⁸³ Given these promising results, the authors are currently evaluating in a phase I open-label trial the safety and efficacy of oral, frozen encapsulated FMT in peanut allergic adults aged 18 to 40 years with and without pretreatment with antibiotics (NCT02960074).

SUMMARY

Earlier this year, the first oral immunotherapy for food allergy was FDA approved. New therapeutic approaches are however urgently needed to improve treatment outcome. Biologics are attractive options either as monotherapy or as adjunct to food immunotherapy, as they may improve compliance, target multiple food allergies, and treat other concomitant atopic diseases. Although omalizumab has been evaluated extensively in allergic diseases, most biologics are more novel and have broader immunologic impact. Hence, although many of these biologics have very promising preliminary data on suppressing the allergic response, careful evaluation of their safety and their modulation of the immune system should be conducted.

CLINICS CARE POINTS

- AR101 (Palforzia) is the first FDA-approved oral immunotherapy for peanut allergy. There is an unmet need for investigating other therapies.
- There are currently no biologics approved for food allergy treatment, but studies are on the way for some.
- Careful evaluation of the safety of these biologics and their effect on immunomodulation in vivo should be conducted.

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