



Perspective

The emerging biologic therapies on food allergy

Sultan Albuhairei, MD^{*}; Rima Rachid, MD[†]^{*} Department of Pediatrics, College of Medicine, Majmaah University, Al-Majmaah, Saudi Arabia[†] Division of Immunology, Boston Children's Hospital, Division of Immunology and Department of Pediatrics Harvard Medical School, Boston, Massachusetts

ARTICLE INFO

Article history:

Received for publication January 1, 2019.

Received in revised form March 21, 2019.

Accepted for publication March 21, 2019.

Introduction

Food allergy affects approximately 8% of children and up to 5% of adults. Standard-of-care consists of food avoidance and keeping rescue epinephrine and antihistamines available.¹ Although oral immunotherapy (OIT) or epicutaneous immunotherapy products may receive Food and Drug Administration (FDA) approval within the next 1 to 2 years, these require long-term compliance, are not known to lead to a cure, and may cause recurrent allergic reactions. A number of biologics have been used to treat atopic diseases and asthma, but only few have been evaluated in food allergy (Table 1).

Mechanism of Food Allergy

Food allergy is the result of immunological sensitization to food allergens. The exact mechanism that leads to the development of food allergy and the interruption of normal tolerance remains to be elucidated. The process involves increased epithelial cell permeability, skewing of dendritic cell response, down-regulation of regulatory T cells, promotion of Th2 inflammatory response, and production of cytokines interleukin (IL)-4, IL-5, and IL-13, recruitment of mast cells, eosinophils, and basophils, and induction of food antigen-specific immunoglobulin (Ig) E. On reexposure to food, specific IgE bound to the high-affinity receptor FcεR1 on the surface of mast cells and basophils recognizes the antigen, which in turn induces crosslinking of bound IgE. This activates the downstream signaling, resulting in release of inflammatory mediators responsible for the symptoms of allergic reactions and anaphylaxis.²

Reprints: Rima Rachid, MD, Division of Immunology, Boston Children's Hospital, Department of Pediatrics, Harvard Medical School, 300 Longwood Ave, Boston, MA 02115; E-mail: rima.rachid@childrens.harvard.edu.

Disclosures: Rima Rachid holds a patent on therapeutic microbiota for the treatment and prevention of food allergy; is a consultant for Consortia Therapeutics; received research support from Aimmune Therapeutics; received research support from End Allergy Together (EAT). Sultan Albuhairei reports no financial disclosure.

Funding Sources: none.

Anti-IgE Antibody

Omalizumab binds to free IgE and decreases its concentration within a few days of treatment, ultimately down-regulating FcεR1 surface expression, and hence suppressing or decreasing the allergic response on exposure.³ Omalizumab is the most studied biologic for the treatment of food allergy.

As a monotherapy, it was shown in a small study to increase significantly the threshold of reactivity to peanut during food challenges after 3 to 11 weeks of administration.⁴ However, after 6 months of therapy, further changes in the threshold dose were not observed. This suggests that long-term omalizumab monotherapy over several years without the additional risk of OIT may be valuable in some patients, but the potential immunomodulatory effects of such an approach remain unclear.

Patients with very high peanut-IgE (>100 kU/L) are more prone to failing OIT.⁵

We have shown that combining omalizumab as an adjunct therapy to OIT for 20 weeks leads to a decrease in frequency and severity of allergic reactions from OIT, even in patients with very high peanut IgE.⁶ The long-term outcome of this approach has been variable. In 1 study, patients consuming either high or low doses of multiple food OIT, whether initially facilitated or not by omalizumab, had no anaphylactic reactions requiring epinephrine for up to 62 to 72 months of maintenance therapy.^{7,8} In our experience, after up to 67 months of peanut OIT maintenance, only 7 of the 13 initially enrolled patients (54%) continued on OIT.⁹ Hence, although omalizumab allowed for faster and effective desensitization in these very sensitive patients, 46% discontinued therapy. Subjects experienced allergic reactions to peanut during long-term follow-up (1–6 years after OIT initiation and ~½ to 5.5 years after omalizumab discontinuation) despite some patients' very significant drops in peanut IgE. A milk OIT study showed that the concomitant use of omalizumab for 28 months was associated with significant improvement in safety measurement but had no effect on sustained unresponsiveness at 32 months.¹⁰ These results suggest that although omalizumab may successfully decrease the rate of

Table 1
Use of Biologics in Atopic Disease and IgE-Mediated Food Allergy

Biologics	Use in IgE-mediated food allergy	Use in other atopic diseases
Anti- IgE		
Omalizumab (anti-IgE mAb)	Monotherapy or adjunct to oral immunotherapy	FDA-approved for treatment of treatment of Asthma (≥ 6 years), chronic idiopathic urticaria (≥ 12 years)
Ligelizumab (anti-IgE mAb)	N/A	Phase IIIb for chronic spontaneous urticaria Phase II for asthma
Anti-IL-4R		
Dupilumab (Anti-IL-4-R mAb)	Phase II	FDA-approved for treatment of atopic dermatitis (adults) and asthma (≥ 12 years)
Anti-IL-5 and Anti-IL-5R		
Mepolizumab (Anti-IL-5 mAb)	N/A	FDA-approved for asthma treatment (≥ 12 years)
Reslizumab (Anti-IL-5 mAb)	N/A	FDA-approved for asthma treatment (adults)
Benralizumab (Anti-IL-5-R mAb)	N/A	FDA-approved for asthma treatment (≥ 12 years)
Anti-IL-13		
Lebrikizumab (Anti-IL-13 mAb)	N/A	Phase III for atopic dermatitis, asthma
Tralokinumab (anti-IL-13 mAb)	N/A	Phase III for atopic dermatitis, asthma
Anti-epithelial cell cytokines		
ANB020 (Anti-IL-33 mAb)	Phase II (results not published)	N/A
Tezepelumab (Anti-TSLP)	N/A	Phase III for asthma therapy, phase II for atopic dermatitis, allergic rhinitis
Th1 adjuvants		
CpG oligodeoxynucleotides	N/A	Phase II for allergic rhinitis
Glucopyranosyl lipid A (GLA)	Phase I trial combined with sublingual immunotherapy	N/A
Monophosphoryl lipid A (MPL)	N/A	Phase II for allergic rhinitis

reactions from OIT, it appears to lack potential for significant disease modification, at least after 28 months of therapy.

Ligelizumab (QGE031) is another promising anti-IgE antibody that binds free serum IgE with much higher affinity than Omalizumab.¹¹ Phase II trials are ongoing to assess the safety and efficacy of ligelizumab in asthma (NCT01716754), atopic dermatitis (NCT01552629), and chronic spontaneous urticaria (NCT03580369). Ligelizumab has not been evaluated yet in food allergy.

Anti-TH2 Cytokines Antibodies

Dupilumab is a monoclonal antibody directed against the alpha subunit of the IL-4 receptor (IL4R α), blocking the IL-4 and IL-13 signaling pathway. It was recently approved by the FDA for the treatment of adults with moderate to severe atopic dermatitis and of patients ≥ 12 years of age with moderate to severe asthma. We found that treatment of lymphocytes of peanut-allergic patients with anti-IL-4R α monoclonal antibodies (mAb) augmented the suppressive function of peanut-reactive regulatory T cells, highlighting the potential disease-modifying effect of anti-IL-4 therapy.¹² Thus, considering the side effects of oral immunotherapy including allergic reactions and eosinophilic esophagitis, we think that the use of dupilumab as a monotherapy for food allergy warrants further investigation.

One randomized placebo-controlled phase II trial is ongoing in children that aims at evaluating the safety and efficacy of dupilumab as an adjunct therapy to peanut OIT (NCT03682770). Another anticipated study will aim at comparing dupilumab, omalizumab, and a combination of these with placebo in multi-food OIT (NCT03679676). A second anticipated trial will evaluate the role of dupilumab as a monotherapy in peanut allergy (NCT03793608). A phase III trial is currently evaluating the efficacy and safety of dupilumab in eosinophilic esophagitis (NCT03633617).

Other anti-TH2 cytokines used in atopic diseases but not in IgE-mediated food allergy per se include anti-IL-5, anti-IL-5 receptor, and anti-IL-13 antibodies. Anti-IL-5 (mepolizumab and reslizumab) as well as anti-IL-5R α (benralizumab) antibodies are FDA approved for the treatment of eosinophilic asthma. Their potential role in IgE-mediated food allergy is unclear, because the role of eosinophils in this disease is not known to be critical. Treatment with anti-IL-13 antibody (lebrikizumab) did not consistently show

significant reduction in asthma exacerbation,¹³ suggesting that it is not as efficacious as dupilumab for asthma therapy.

Epithelial-Cell–Derived Cytokines (IL-33 and Thymic Stromal Lymphopoietin) Antibodies

Targeting epithelial cells cytokines, which promotes TH2 response, is another potential approach in treating food allergy. A phase 2a trial evaluating the safety of ANB020, a humanized IgG1 anti-IL-33 antibody in peanut-allergic adults, was completed but the results are not published yet (NCT02920021).

A recently published phase 2 study in adults with uncontrolled asthma found that Tezepelumab (AMG 157/MEDI9929), a human-derived mAb against thymic stromal lymphopoietin (TSLP), lead to a significant decrease in the rate of asthma exacerbations compared with placebo,¹⁴ although no significant improvement was found in atopic dermatitis.¹⁵ Although TSLP has not yet been evaluated in food allergy, it is being studied as a combined therapy to cat immunotherapy in allergic rhinitis (NCT02237196).

TH1 Adjuvants

Altering the TH1/TH2 balance and promoting the TH1 response by using TH1 adjuvants is another approach to treat allergic diseases. The TH1 adjuvants include toll-like receptor (TLR) agonists. Treatment with CpG oligodeoxynucleotides (TLR 9 agonists), coupled to ragweed allergen, lead to clinical improvement in allergic rhinitis patients.¹⁶ Similar effects were noted with monophosphoryl lipid A (MPL), a TLR-4 agonist.¹⁷ Glucopyranosyl lipid A, a synthetic form of MPL, is being investigated as an adjunct therapy to peanut sublingual immunotherapy in a phase I trial (NCT03463135).

Safety, Patient Selection, and Economical Considerations

As detailed, several biologics can be or are currently evaluated for the treatment of food allergy. However, the selection of the appropriate candidates who would qualify for such therapy is more perplexing, considering that little is known about the long-term side effects of some of these immunomodulatory agents, and about the efficacy of these agents when given as monotherapy or as adjuncts to food immunotherapy. The duration of optimal therapy also requires investigation. Possibly patients for whom food immunotherapy failed, because of either side effects or compliance issues, may be better candidates for biologic therapy, specifically

those with very high food-specific IgE level. The steep price of these agents remains a significant factor limiting their extended applicability even if safety and efficacy are proven.

In conclusion, there is an urgent need for the evaluation of new therapeutic modalities, including biologics for the treatment of food allergy. At least 4 biologics are being evaluated, either as monotherapy or combined with some form of food immunotherapy. This brings hope that multiple treatment options may be available for patients in the future. However, given the immunomodulatory effects of these biologics, evaluation of long-term safety and efficacy will be critical. In addition, the significant cost of these biologics may prevent the generalization of their applicability in food allergy. Further studies are needed to evaluate the effect of these biologics on disease modification and to help in careful selection of the subset of patients who would best benefit from such interventions.

References

1. Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. *J Allergy Clin Immunol*. 2014;133:291–307. quiz 308.
2. Bauer RN, Manohar M, Singh AM, Jay DC, Nadeau KC. The future of biologics: applications for food allergy. *J Allergy Clin Immunol*. 2015;135:312–323.
3. Liu J, Lester P, Builder S, Shire SJ. Characterization of complex formation by humanized anti-IgE monoclonal antibody and monoclonal human IgE. *Biochemistry*. 1995;34:10474–10482.
4. Savage JH, Courneya JP, Sterba PM, Macglashan DW, Saini SS, Wood RA. Kinetics of mast cell, basophil, and oral food challenge responses in omalizumab-treated adults with peanut allergy. *J Allergy Clin Immunol*. 2012;130:1123–1129.
5. Bird JA, Spergel JM, Jones SM, et al. Efficacy and safety of AR101 in oral immunotherapy for peanut allergy: results of ARC001, a randomized, double-blind, placebo-controlled phase 2 clinical trial. *J Allergy Clin Immunol Pract*. 2018;6:476–485.
6. Schneider LC, Rachid R, LeBovidge J, Blood E, Mittal M, Umetsu DT. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. *J Allergy Clin Immunol*. 2013;132:1368–1374.
7. Andorf S, Manohar M, Dominguez T, et al. Observational long-term follow-up study of rapid food oral immunotherapy with omalizumab. *Allergy Asthma Clin Immunol*. 2017;13:51.
8. Andorf S, Manohar M, Dominguez T, et al. Feasibility of sustained response through long-term dosing in food allergy immunotherapy. *Allergy Asthma Clin Immunol*. 2017;13:52.
9. Yee CSK, Albuhairei S, Noh E, et al. Long-term outcome of peanut oral immunotherapy facilitated initially by omalizumab. *J Allergy Clin Immunol Pract*. 2019;7(2):451–461.e7.
10. Wood RA, Kim JS, Lindblad R, et al. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. *J Allergy Clin Immunol*. 2016;137:1103–1110.
11. Kocaturk E, Zuberbier T. New biologics in the treatment of urticaria. *Curr Opin Allergy Clin Immunol*. 2018;18:425–431.
12. Abdel-Gadir A, Schneider L, Casini A, et al. Oral immunotherapy with omalizumab reverses the Th2 cell-like programme of regulatory T cells and restores their function. *Clin Exp Allergy*. 2018;48:825–836.
13. Hanania NA, Korenblat P, Chapman KR, et al. Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials. *Lancet*. 2016;4:781–796.
14. Corren J, Parnes JR, Wang L, et al. Tezepelumab in Adults with Uncontrolled Asthma. *N Engl J Med*. 2017;377:936–946.
15. Simpson EL, Parnes JR, She D, et al. Tezepelumab, an anti-thymic stromal lymphopoietin monoclonal antibody, in the treatment of moderate to severe atopic dermatitis: a randomized phase 2a clinical trial. *J Am Acad Dermatol*. 2019;80(4):1013–1021.
16. Creticos PS, Schroeder JT, Hamilton RG, et al. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. *N Engl J Med*. 2006;355:1445–1455.
17. Patel P, Holdich T, Fischer von Weikersthal-Drachenberg KJ, Huber B. Efficacy of a short course of specific immunotherapy in patients with allergic rhinoconjunctivitis to ragweed pollen. *J Allergy Clin Immunol*. 2014;133:121–129.