

CME Review

Anti-immunoglobulin E for food allergy



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Key Messages

- Anti-immunoglobulin E therapies are an emerging and promising treatment option for food allergies, particularly in patients with multiple food allergies.
- Omalizumab has exhibited promising results when used as monotherapy or in conjunction with oral immunotherapy (OIT) for food allergies.
- Omalizumab seems to increase the reaction dose threshold, decrease the time to reach maintenance OIT and decrease OIT dosing-related reactions.
- Many unanswered questions remain, including the ideal patient, optimal dosing strategies, and duration of treatment.
- Two phase 3 trials are currently underway studying anti-immunoglobulin E for the treatment of peanut and multfood allergies.

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ABSTRACT

Objective: To review the safety and efficacy of anti-immunoglobulin E (IgE) monotherapy or as an adjunct to oral immunotherapy (OIT) in the treatment of IgE-mediated food allergy.

Data Sources: Literature searches were performed using the Excerpta Medica dataBASE, Medline, Scopus, and PubMed Central to identify articles in English related to food allergy and anti-IgE therapies, including omalizumab and ligelizemab.

Study Selections: Original research articles reviewed include interventional studies, retrospective and prospective observational studies, peer-reviewed reviews, and systematic reviews. Data were reviewed and summarized.

Results: Here, we discuss the current anti-IgE therapies being studied as a potential treatment option for food allergy. We also review trial design, safety, and efficacy data on the use of anti-IgE therapies as monotherapy or in combination with OIT for food allergies. Finally, we discuss clinical trials in progress using omalizumab and ligelizumab and highlight important clinical considerations.

Conclusion: Over the past 20 years, substantial progress has been made in understanding the potential role of anti-IgE therapies for food allergy. Anti-IgE therapies seem to be a promising option that may increase reaction dose thresholds and decrease time to reach OIT maintenance and OIT dosing-related reactions. Two phase 3 trials are currently in progress studying anti-IgE potential monotherapy for the treatment of peanut and multfood allergies. It is important for clinicians to be aware of these emerging treatment options.

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Introduction

Food allergy is a worldwide public health problem in children and adults.¹ This long-term condition impacts individuals from infancy

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through adulthood and has been increasing in prevalence over the past 2 to 3 decades, with many food allergies persisting into adolescence or adulthood.¹ In addition to the risk of potentially severe reactions, food allergies can also affect the quality of life (QOL), nutrition, and cost of living.²⁻⁴ For all these reasons, safe and effective treatment is needed.

Current management primarily includes allergen avoidance and prompt use of emergency medications in the event of an allergic reaction.¹ Successful allergen avoidance can be complex and involves the education of multiple stakeholders, including the patient, caregivers,

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Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Describe the mechanism of anti-IgE therapies for food allergy.
- Evaluate the safety and efficacy of anti-IgE therapies that are being investigated for the treatment of food allergy, either as monotherapy or in combination with oral immunotherapy.

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Physicians involved in providing patient care in the field of allergy/asthma/immunology.

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schools, and childcare providers.⁵ Several studies have reported that there are many misconceptions around allergen labeling and avoidance^{6–9} and that unclear or erroneous labeling, restaurant meals, and risky behaviors can lead to unexpected reactions.¹ Furthermore, epinephrine has been found to be a safe and effective life-saving medication, but numerous barriers exist to prompt use.^{10–12}

It has been approximately 2.5 decades since the first randomized control trial reported on the potential efficacy of food immunotherapy.¹³ Since that time, various forms of food immunotherapy (oral immunotherapy [OIT], sublingual, subcutaneous, and epicutaneous) have been studied as a potential treatment option.¹⁴ Oral immunotherapy has been known to induce desensitization for numerous foods,¹⁵ and in 2020, the US Food and Drug Administration (FDA) approved Palforzia (Nestlé, Vevey, Switzerland) peanut OIT (POIT).¹⁶ Whereas these studies are promising, there are high rates of allergic reactions to the treatment itself, ranging from mild oral pruritus to severe anaphylaxis.¹⁷ A 2019 meta-analysis of POIT found that the risk of anaphylaxis while on POIT is 3.1 times higher compared with peanut avoidance (risk ratio, 3.12, 95% confidence interval, 1.76–5.55).¹⁸ Hence, there is a need to identify alternative or adjunct treatment options that improve safety and, potentially, efficacy.^{19,20} More recently, the landscape has shifted to the evaluation of biological drugs, primarily anti-immunoglobulin E (anti-IgE) treatments, for the treatment of food allergies. Here, we review the use of anti-IgE therapies for the treatment of food allergies.

Anti-immunoglobulin E Therapies: What They Are and How They Work

Immediate-type food allergies are mediated by IgE and result in a specific immune response on exposure to a given food.^{21,22} For that reason, anti-IgE therapy is a logical approach for the treatment of single or multiple IgE-mediated food allergies (Fig 1). Almost 20 years ago, in the first study of an anti-IgE antibody for the treatment of food allergy, tazilumab (TNX-901) was found to increase the peanut threshold dose.²³ That drug was not further developed, but omalizumab was found in multiple studies as monotherapy or as an adjunct to OIT to have potentially dramatic effects for the treatment of peanut and other food allergies.^{23–38} It is fortunate now that both omalizumab and another anti-IgE antibody, ligelizumab, are in phase 3 trials for the treatment of food allergy.

Omalizumab

Omalizumab (Xolair) (Novartis, Basel, Switzerland) is the only licensed anti-IgE therapy for clinical use, with a wealth of clinical experience since its approval for asthma 20 years ago.³⁹ This humanized monoclonal anti-IgE antibody binds to the Cε3 domain located in the heavy chain constant region of the free IgE molecule and prevents IgE from binding to FcεRI and CD23 on effector cells and hence interferes with degranulation and release of proinflammatory

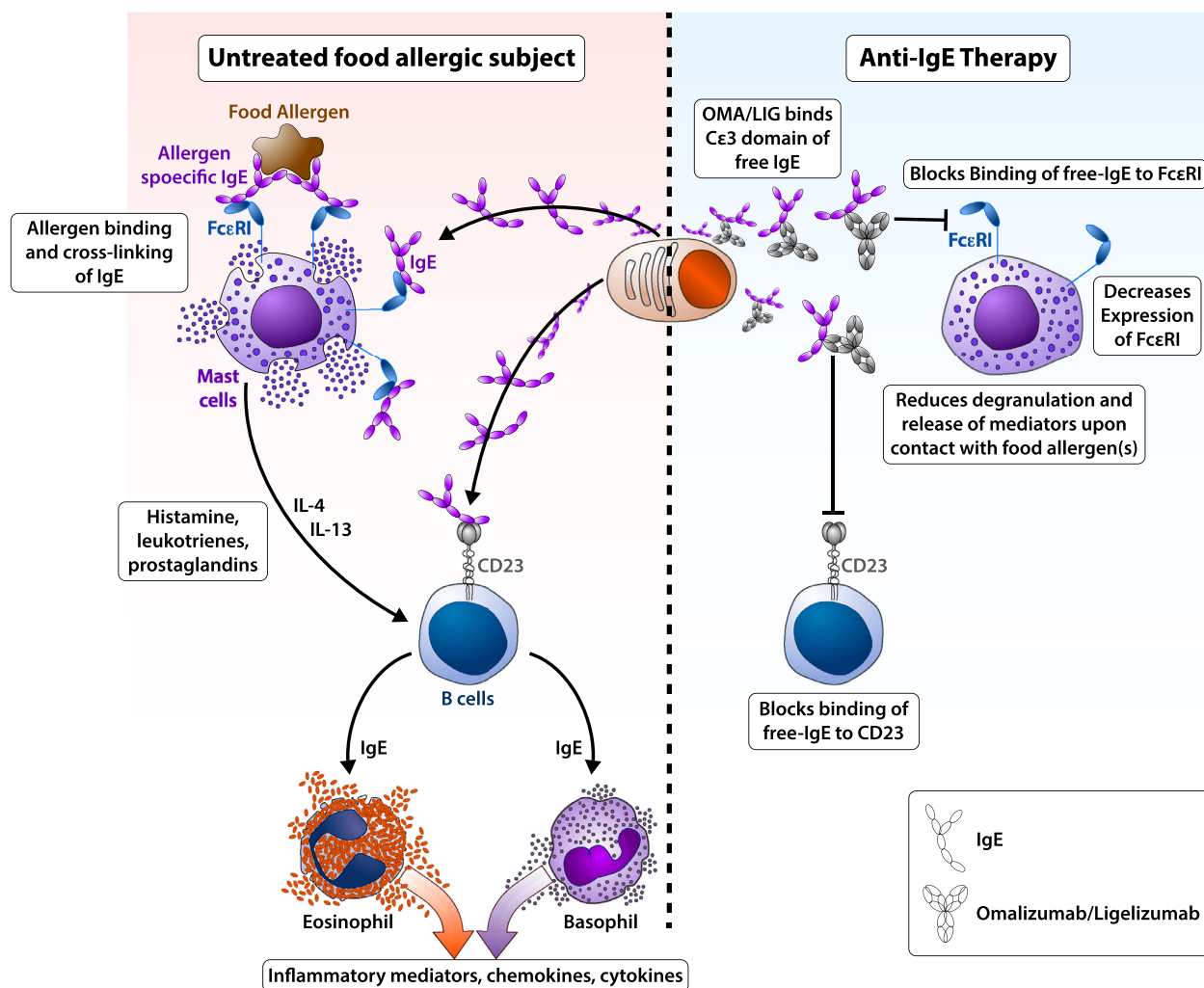


Figure 1. The role of IgE in food allergy. In food allergy, the allergen is recognized by allergen-specific IgE bound to FcεRI, which leads to the degranulation of mast cells. Omalizumab and ligelizumab bind to free IgE, preventing binding to effector cells and limiting the release of inflammatory mediators. IgE, immunoglobulin E.

mediators.^{40–43} In addition, the binding of omalizumab to free IgE leads to a marked decrease in free IgE and down-regulation of FcεRI on basophils and mast cells.^{40,41} Since its approval for the treatment of asthma in 2003, omalizumab has been approved for chronic urticaria and chronic rhinosinusitis with nasal polyps, with expanded labeling in asthma for children down to the age of 6 years.³⁹ Omalizumab has also been studied for numerous other conditions in which IgE may play a role, including food allergy.^{44–46}

Ligelizumab

Ligelizumab (QGE031) (Novartis, Basel, Switzerland) is a next-generation, high-affinity anti-IgE monoclonal antibody.^{47,48} This therapy binds to a distinct epitope in the Cε3 domain of free IgE and has been found to bind to IgE with a 20-fold higher potency than omalizumab.⁴⁹ Compared with omalizumab, *in vitro* data suggest that ligelizumab has enhanced inhibition of IgE binding to FcεRI, effector cell activation, and IgE production by B cells, but is inferior in blocking IgE:CD23 interactions.^{49,50} Though there are no preliminary data on its effect on food allergy, its potential promise for this indication led to the recent initiation of a phase III trial for the treatment of peanut allergy (NCT04984876).

Food Allergy Clinical Trials with Anti-immunoglobulin E

Anti-immunoglobulin E as Monotherapy

In 2003, Leung et al²³ published the first study on the potential clinical benefit of anti-IgE therapy (TNX-901, talizumab) in patients with peanut allergy (Table 1). This was a double-blind, placebo-controlled (DBPC) trial of 84 patients (age 12–64 years) with peanut allergy who were randomized to receive 150 mg, 300 mg, or 450 mg of TNX-901 or placebo every 4 weeks for 4 doses and then undergo a peanut oral food challenge (OFC) 2–4 weeks after the final dose. This study found that the mean dose of peanut eliciting symptoms increased in a dose-responsive manner with the 450 mg TNX-901 group increasing from 178 mg at baseline to 2805 mg peanut flour at the final OFC ($P < .001$).

Rafi et al²⁴ reported the effects of omalizumab on IgE-mediated food allergy symptoms in patients on omalizumab for asthma. There were 82 patients in this real-world study who were on omalizumab and of those, 46 had a food allergy history and positive skin prick test. A total of 22 out of 46 had an accidental ingestion of their allergenic food while on omalizumab and all reported a decrease or absence of clinical symptoms. This study was limited by patient self-report of food allergy, symptoms of allergic reactions, and allergen ingestion, and a lack of information on the exact amount of allergen ingested.

In 2011, Sampson et al²⁵ published a phase 2, randomized, DBPC, parallel-group OFC trial of omalizumab in peanut allergy (Fig 2). The study intended to randomize 150 patients but was stopped early because of anaphylactic reactions that occurred during the screening OFCs (before receiving the study drug), with only 14 patients reaching the final end point. Eligible patients underwent a screening OFC and then a final OFC at week 24. There seemed to be a greater increase in peanut tolerability in the omalizumab group (80.9-fold improvement in tolerated dose compared with only 4.1-fold improvement in the placebo group), but this did not reach statistical significance ($P = .054$).

In 2012, an open-label study evaluated the OFC responses in adults with peanut allergy who were treated with omalizumab for 6 months.²⁶ Patients ($n = 14$) had a DBPC food challenge (DBPCFC) at baseline and then after the basophil histamine release to peanut decreased to less than 20% of baseline values (or at week 8 if no decrease) and again at 6 months. The median dose of peanut required to induce allergic symptoms increased from 80 mg of peanut protein

to 6500 mg at the second OFC. At the 6-month OFC, there did not seem to be added benefit compared with the initial posttreatment OFC.

Brandström et al²⁷ used a novel approach in a 1-armed, two-part, phase 2 trial of individually dosed omalizumab monotherapy, followed by omalizumab-facilitated peanut OIT. In the first part of the study, 23 adolescents with peanut allergy (age 12–19 years) were treated with omalizumab for 8 weeks.²⁷ They then underwent a peanut challenge or received 8 additional weeks with an increased dose of omalizumab on the basis of basophil allergen threshold sensitivity (CD-sens) and symptoms, followed by a peanut challenge or a final 8 weeks of omalizumab. After 8 to 24 weeks of individualized dosed omalizumab, patients completed an open peanut challenge to a maximum of 2800 mg peanut protein with no (18/23) or mild (5/23) symptoms. Part 2 of the study is discussed in the next section.

In 2019, Fiocchi et al²⁸ performed a real-life, retrospective, observational study on the impact of omalizumab on food allergy in patients being treated with asthma. Patients ($n = 15$) underwent diagnostic paired food challenges at baseline and 4 months into omalizumab treatment with dosing on the basis of asthma guidelines. Patients exhibited significantly increased food tolerance thresholds for egg ($P = .04$), baked milk ($P = .04$), milk ($P = .001$), and wheat ($P = .01$).

Anti-Immunoglobulin E Combined With Oral Immunotherapy

Over the past few decades, numerous studies have evaluated the safety and efficacy of food allergen OIT.⁵¹ Whereas OIT is able to increase the threshold of reactivity, most will regain clinical reactivity when OIT is stopped.^{15,51} In addition, reactions can appear at any phase of treatment and range from localized pruritus to severe anaphylaxis.^{15,52–58} Omalizumab has been evaluated as a potential pre- or adjunct treatment to OIT with hopes of reducing adverse reactions, decreasing the time to desensitization, and improving efficacy (Table 2).⁵⁹ These clinical trials have focused on peanut, milk, and multiallergen OIT and have varied in OIT dosing, omalizumab dosing and duration, and study design (open-label vs DBPC) (Fig 2).^{59,60}

Peanut

In a pilot study, omalizumab was used to assist rapid oral desensitization in 13 children with peanut allergy, with peanut IgE of at least 20 kU/L and reactivity to 100 mg or less peanut flour (186 mg cumulative) at baseline.²⁹ Patients received omalizumab as pretreatment for 12 weeks, followed by a 1-day rush initial dose escalation (IDE) and then build-up OIT over weeks 12 to 20.²⁹ Omalizumab was stopped at week 20 and the peanut OIT was continued until final OFC 12 weeks later. All patients reached the goal dose on IDE (500 mg peanut flour) and 12/13 (92%) tolerated a challenge to 8 g of peanut flour (equivalent to approximately 20 peanuts) 12 weeks after stopping omalizumab. Reactions did occur, with 6/13 (46%) experiencing a mild or no reaction, 6/13 (46%) had grade 2 reactions, and 2/13 (15%) had grade 3 reactions. During the up-dosing phase, the most common reactions were nausea and salivation or abdominal pain. One patient received epinephrine at home during the build-up phase (nausea, lightheadedness, and hypersalivation) and 2 patients received epinephrine at home during maintenance and after stopping omalizumab, with 1 participant receiving epinephrine on 3 occasions for grade 2 reactions associated with exercise. A total of 7 out of 13 (54%) were consuming dietary peanuts at month 72, with 6 (46%) stopping because of adverse reactions.³⁰

In the second part of the Brandström study noted above, participants ($n = 23$) were started on peanut OIT combined with individually dosed omalizumab.³¹ Peanut OIT was started at 280 mg of peanut protein and increased to a goal dose of 2800 mg. Omalizumab

Table 1
Use of Anti-IgE as Monotherapy for Food Allergy

Author, y	Individuals	Design	Product and regimen	Allergen	Key inclusion criteria	Main findings
Leung et al, ²³ 2003	N = 84 12-64 y	Multicenter, DBPC dose-ranging trial of TNX-901 vs placebo for 16 wk	Talizumab (TNX-901) 150 mg, 300 mg, or 450 mg or placebo every 4 weeks	Peanut	- Total IgE 30-1000 IU/mL - Body weight within 20% of ideal - Reaction to a single dose of $\leq$ 2000 mg peanut flour at screening	450 mg of TNX-901 significantly increased the dose-reaction threshold from 178 mg to 2805 mg. TNX-901 was well tolerated
Rafi et al, ²⁴ 2010	N = 22 14-66 y	A prospective cohort of patients on omalizumab for asthma, questioned on food reactions while on OMA	Omalizumab Dosing ranged from 150 mg every 4 wk to 300 mg every 2 wk on the basis of weight and IgE	Fish, shellfish, peanuts, tree nuts, egg, soybean, wheat	- Being treated with OMA for moderate to severe asthma - History of an allergic food reaction - Positive SPT to foods - Unintended consumption of allergen while on OMA	All patients reported a decrease or absence of food-induced allergic reaction symptoms
Sampson et al, ²⁵ 2011	N = 14 OMA: mean age 16.3 y Placebo: mean age 26.6 y	Phase 2, RCT Randomized 2:1 to OMA or placebo for 20-22 wk OFC at baseline and 24 wk.	Omalizumab or placebo every 2-4 wk	Peanut	- Total IgE $\geq$ 30 to $\leq$ 1300 IU/mL - Body weight $\geq$ 20 to $\leq$ 150 kg - React to $\leq$ 250 mg peanut flour at baseline	After 24 wk - OMA group had an 80.9-fold improvement in tolerated dose compared with 4.1-fold improvement in the placebo group ($P = .054$) - 5/9 (56%) on OMA and 4/5 (80%) on placebo reacted to $\leq$ 1000 mg peanut flour
Savage et al, ²⁶ 2012	N = 14 18-44 y	Open-label prospective study OFC2 timing on the basis of peanut-BHR OFC3- after 6 mo of OMA	Omalizumab Dosing per package insert	Peanut	- Total IgE of 30 to 700 IU/mL - Body weight within dosing guidelines for OMA - React to a cumulative dose of $\leq$ 1000 mg peanut protein - Peanut allergen-induced BHR of $> 20\%$	- Median threshold dose of peanut increased from 80 mg at baseline to 6500 mg of peanut protein at OFC2 with no additional changes in the threshold at OFC3. - Fold increase in threshold dose ranged from 3.2-1000 mg peanut protein
Brandström et al, ²⁷ 2017	N = 23 12-19 y	Open-label, Phase 2 study (Part 1 of the study- open-label OMA)	Omalizumab Duration of 8-24 wk before OFC2 and the start of OIT Duration and dose on the basis of CD-sens ranged from 100% to 400% of the recommended dose for asthma	Peanut	- Total IgE 30-1500 kU/L - Anaphylaxis to peanut within the past 5 y or at screening OFC	All completed the open peanut OFC after 8-24 wk of OMA: - Mean dose given was 2352 mg of peanut protein - 15/23 (65%) tolerated the 2800 mg peanut protein final OFC2 dose (cumulative of 3083 mg)
Fiocchi et al, ²⁸ 2019	N = 15 8-23 y	Single-center, real-life retrospective observational study in patients being treated for asthma	Omalizumab Dosing per asthma guidelines	23 foods	- Severe asthma - History of immediate food reaction to ≥ 2 foods - Total IgE between 30 and 1500 IU/mL	After 4 mo of OMA, the food allergen reaction threshold increased to $8.6 \times$ baseline

Abbreviations: AE, adverse event; BHR, basophil histamine release; CD-sens, basophil allergen threshold sensitivity tests; DBPC, double-blind placebo-controlled; IgE, immunoglobulin E; IU, international units; OFC, oral food challenge; OMA, omalizumab; SPT, skin prick test.

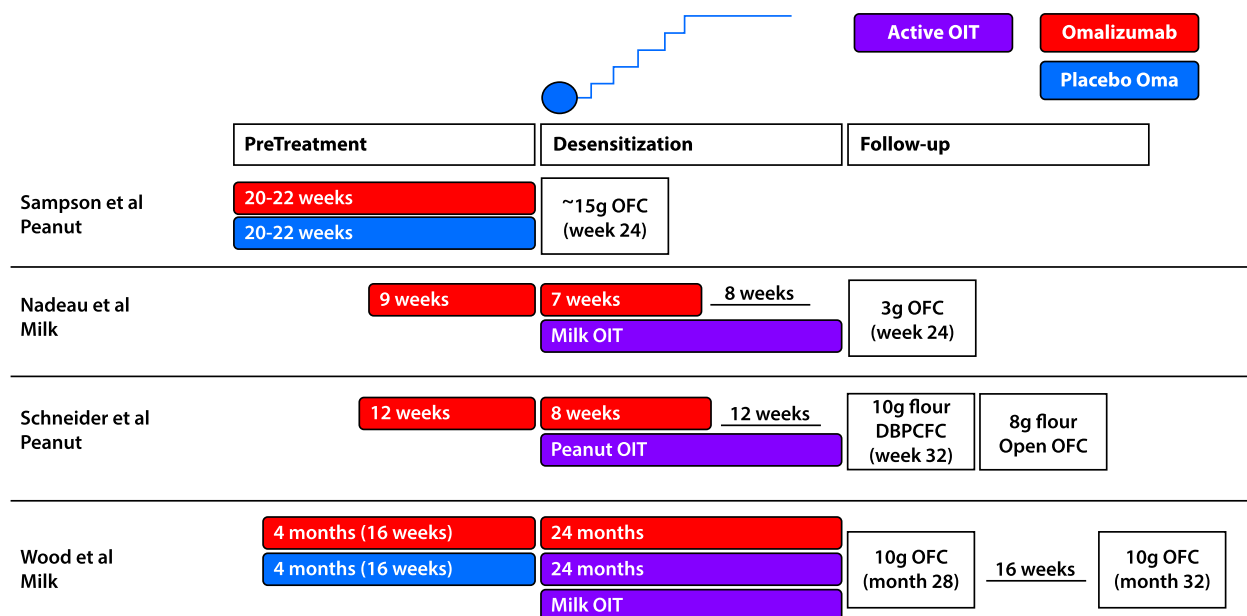


Figure 2. Examples of different trial designs. Studies have reported considerable heterogeneity in the duration of omalizumab pretreatment, the timing of overlap in omalizumab and OIT, the timing of final food challenge in relationship to omalizumab and OIT, and OIT dosing and food challenge protein amounts. OIT, oral immunotherapy.

was withdrawn on the basis of symptoms and CD-sens and then participants continued POIT for 12 weeks without omalizumab ($n = 11$). They then underwent an open single-dose peanut OFC with their current OIT dose. A total of 9 out of 23 patients (39%) met the primary end point of a POIT daily dose of 2800 mg of peanut protein for 12 weeks after stopping omalizumab, followed by a negative open challenge with 2800 mg. Two patients completed the study with a reduced POIT dose (1120 and 700 mg peanut protein) because of taste aversion (not reactions) and, hence, authors considered 11/23 (48%) to have treatment success. After omalizumab was stopped, symptoms returned in 50% of patients with 6 individuals unable to stop omalizumab and 6 dropping out. The authors concluded that omalizumab can be an effective monotherapy or combination therapy with POIT; however, adverse reactions were more frequent with decreased omalizumab dosing and omalizumab doses higher than recommended for asthma might be needed for the treatment of food allergy.^{27,31}

MacGinnitie et al³² performed the first randomized, DBPC multicenter study of the efficacy of peanut OIT combined with omalizumab. A total of 37 patients (age 7–19 years) were randomized to omalizumab ($n = 29$) or placebo ($n = 8$) for 12 weeks, followed by an IDE up to 250 mg of peanut protein (cumulative 490.5 mg), followed by increases up to a goal of 2000 mg peanut protein. The omalizumab group tolerated more than 10 times the peanut protein dose during IDE compared with the placebo group (median 250 vs 22.5 mg, $P < .01$). In addition, in the intention-to-treat analysis, those receiving omalizumab were more likely to reach the primary end point of tolerating 2000 mg of peanut protein 6 weeks after stopping study drug (omalizumab group: 23/29 (79%) vs placebo: 1/8 (12.5%); $P < .01$). Similarly, 22/29 (76%) receiving omalizumab vs 1/8 (12.5%) receiving placebo passed the open OFC to 4000 mg of peanut protein 12 weeks after stopping study drug ($P < .01$). There was no statistically significant difference in frequency of dosing reactions between groups (omalizumab: 7.8% vs placebo: 16.8%; odds ratio, 0.57, $P = .15$), despite the higher peanut doses in the omalizumab group. Most reactions were mild and occurred during the IDE and dose escalation visits, but moderate and severe reactions did still occur in both groups. In addition, 3 patients (2 on omalizumab, 1 on placebo) stopped OIT dosing because of gastrointestinal symptoms; 2/3 underwent an endoscopy and both had biopsies consistent with eosinophilic esophagitis.

Cow's Milk

In 2011, Nadeau et al³³ completed a pilot study of omalizumab in combination with rapid oral milk desensitization in 11 children. They found that 9/11 (82%) could reach 1000 mg milk powder on initial dose escalation (IDE) and 2000 mg by week 16 (primary end point). Omalizumab was stopped at week 16, but daily milk OIT continued. A total of 9 out of 11 passed the DBPCFC to 7250 mg of milk at week 24 and continued daily milk ingestion of greater than 8000 mg/d of various milk products. In terms of safety, all participants had some adverse event (AE) with reactions occurring in 1.8% of the doses. Most (70%) were mild, with 20% moderate and 10% severe. Overall, this study found that omalizumab allowed OIT dosing to be escalated more rapidly but that adverse reactions still occurred with a rate of epinephrine use similar to previous studies without omalizumab.

Wood et al³⁴ performed the first DBPC trial of omalizumab combined with milk OIT. In this study, patients received 4 months of omalizumab or a placebo and then initiated milk OIT (minimum maintenance dose of 520 mg of milk protein = 15 mL). At month 28, omalizumab was stopped and all participants underwent a DBPCFC to 10 g of milk protein. Milk OIT continued for an additional 8 weeks for those who passed this challenge. At month 32, the study evaluated sustained unresponsiveness (SU), defined as the ability to tolerate 10 g of milk protein 8 weeks after stopping milk OIT. This study found no significant differences in the treatment groups on the effectiveness of OIT, defined as tolerating 10 g milk protein at month 28 (88.9% vs 71.4%, $P = .18$), nor SU, (48.1% vs 35.7%, $P = .42$). However, omalizumab did reduce the time needed to reach the maintenance OIT dose (median: 25.9 vs 30 weeks, $P = .01$) and improved safety, with the omalizumab group having fewer doses with symptoms (2.1% vs 16.1%, $P = .005$) and fewer dose-related reactions requiring treatment (0% vs 3.8%, $P < .001$) compared with the placebo group.

Multiple Food

Bégin et al³⁵ conducted a single-center phase 1 clinical trial of omalizumab plus rush multifoed OIT in children with at least 2 of the selected food allergens (cow's milk, egg, peanut, nuts, grains, and sesame seed). Participants received omalizumab for 8 weeks before and 8 weeks after initiation of rush OIT with up to 5 allergens.³⁵ A total of

Table 2
Use of Omalizumab Combined with Oral Immunotherapy for Food Allergy

Author, y	Study design	OMA dosing	Individuals	Key inclusion criteria	Efficacy findings	Safety findings
Peanut						
Schneider et al, ²⁹ 2013	Pilot Study, open-label	Started 12 wk before OIT and continued for a total of 20 wk	N = 13 8-16 y	-Total IgE > 50 to < 2000 ku/L -Peanut IgE > 20 -Peanut SPT > 6 mm -React to ≤ 186 mg cumulative peanut flour	- All reached max dose (500 mg peanut flour, cum 992 mg) on IDE - Twelve wk after stopping OMA, 12/13 passed OFC to 8 g peanut flour	-OIT-related reactions occurred in 2% of doses - 96% of reactions during build-up while on OMA were mild, 4% moderate - 17 reactions occurred during maintenance (off OMA): 59% mild, 29% moderate, 12% severe
Yee et al, ³⁰ 2019	Long-term follow-up study of Schneider et al, ²⁹ 2013	Off OMA during LTFU	N = 12	Previously enrolled in a study by Schneider et al, ²⁹ 2013	-At month 72, 7/12 (58%) continued peanut OIT and 6 (46%) stopped because of adverse reactions -At follow-up, peanut protein dose ranged from 500 mg to 3500 mg	-All patients had ≥ 1 AE: 86% mild, 5% (n = 12) treated with epinephrine - One patient was diagnosed with eosinophilic esophagitis
Brandström et al, ³¹ 2019	Open-label, Phase 2 study (Part 2 of the study- open-label OMA + OIT)	- Initial dose and duration as detailed above (Brandström et al. ²⁷ 2017) - Individualized withdrawal of OMA on the basis of symptoms and CD-sens	N = 23 12-19 y	- Previously enrolled in Part one - Tolerating > 1 g of peanut (280 mg peanut protein) at the open OFC at the end of Part 1 (after OMA for 8-32 wk) - Total IgE 30-1500 kU/L - Anaphylaxis to peanut within the past 5 y or at screening OFC	- All reached the 2800 mg peanut protein maintenance dose - 9/23 (39%) tolerated a 2800 mg peanut protein single-dose OFC 12 wk after stopping OMA	- Mild oropharyngeal and GI symptoms of OIT were common - Systemic reactions occurred with 43 doses (0.3%) with 91% occurring when no longer on full dose OMA - Allergic symptoms returned in 50% of patients after OMA was stopped - One patient was diagnosed with EoE
MacGinnitie et al, ³² 2017	Multicenter, phase 2, DBPC (OMA vs Placebo), plus open-label peanut OIT	-Started 12 wk before OIT -Duration of 19-25 wk on the basis of OIT dose Dosing on the basis of weight and IgE level	N = 37 7-19 y	- Total IgE 50 to ≤ 2000 IU/L - Peanut IgE ≥ 10 kU/L	- OMA group tolerated a higher median peanut dose on IDE - Higher % of the OMA group tolerated 2000 mg peanut protein 6 wk after stopping the study drug (79 vs 12.5%) and 4000 mg 12 wk after stopping the study drug (76 vs 12.5%)	- Frequency of dosing-related reactions was similar, although the OMA group was exposed to much higher peanut doses
Milk						
Nadeau et al, ³³ 2011	Phase 1 pilot study	- Started 9 wk before OIT - Duration of 16 wk If IgE < 700 kU/L, OMA dosed per package insert If IgE > 700 kU/L, the dose was 225 to 300 mg (~0.016 mg/kg/IgE) every 2 to 4 wk	N = 11 7-17 y	- History of acute reaction to milk	- On 9/11 reached 1000 mg milk powder (Cumulative 1992 mg) on IDE and 2000 mg by week 16. - On 9/11 passed the week 24 DBPCFC to cumulative of 7250 mg milk protein = 220 mL milk	Reactions occurred with 1.8% of doses- 70% mild, 20% severe, 10% severe
Wood et al, ³⁴ 2016	DBPC OMA vs placebo, and open-label milk OIT	- Started 4 mo before OIT - Duration of 28 mo - OMA dosed per package insert or using the formula of 0.016 mg/kg/IgE IU	N = 57 7-32 y	- React to < 2 g of milk protein - Milk SPT ≥ 3 mm or milk IgE > 0.35 kU/L - Weight-IgE combination that required a dose < 750 mg	- OMA group reached maintenance faster - No significant difference between the groups in passing the month 28 10 g milk protein OFC nor in the month 32 10 g milk protein SU OFC	OMA group had fewer dose-related reactions, doses requiring treatment, and adverse events compared with milk OIT alone

(continued)

Table 2 (Continued)

Author, y	Study design	OMA dosing	Individuals	Key inclusion criteria	Efficacy findings	Safety findings
Multifood						
Begin et al, ³⁵ 2014	Open-label Phase 1	- Started 8 wk before OIT - Duration of 16 wk OMA dose on the basis of weight and total IgE	N = 25 4–15 y	- Allergy to ≥ 2 foods (milk, egg, peanut, nuts, grains, sesame seed) - React to < 182 mg cumulative food protein - SPT > 3 mm - Food-specific IgE > 0.35 kU/L	- 19/25 (76%) reached the final dose of 1250 mg protein (up to 250 mg protein of each allergen; cumulative of 2380 mg) on IDE - Median time to reach maintenance dose (4 g per allergen) was 18 wk (range: 7–36 wk) - All reached a 10-fold increase in allergen dose by 2 mo	- Most (94%) reactions were mild - 13/25 (52%) had some symptoms on IDE - 5.3% of home doses caused a reaction, with decreased home reactions after 6 mo of therapy - 1 severe reaction during maintenance, treated with epinephrine
Andorf et al, ³⁶ 2018	Phase 2, DBPC OMA vs placebo and open-label OIT Randomized 3:1	- Started 8 wk before OIT - Duration of 16 wk	N = 48 4–15 y	- Allergic to > 1 food (Cashew, walnut, hazelnut, almond, sesame, cow's milk, egg, peanut, soy, or wheat) - React to ≤ 500 mg food protein - SPT ≥ 6 mm - Food-specific IgE > 4 kU/L	Compared with the placebo, the OMA group had: - Greater likelihood of passing week 36 DBPCFC to 2 g protein for ≥ 2 and ≥ 4 foods - Greater median tolerated dose on IDE - Decreased time to reach maintenance	- OMA-OIT group had fewer dosing-related reactions while receiving OMA compared with the placebo-OIT group - No increase in adverse events after stopping OMA - No severe or serious adverse events in either group
Andorf et al, ³⁷ 2019	Phase 2 Open-label wk 0–30 and then randomized parallel-arm blinded phase (1 g or 300 mg food protein OIT vs placebo OIT) (30–36 wk)	- Started 8 wk before OIT - Duration of 16 wk OMA weeks 1–16, multi-OIT weeks 8–30 Dosed per package insert	N = 70 (open-label) N = 60 (blinded phase) 5–22 y	- Allergic to ≥ 2 foods (almond, cashew, egg, hazelnut, milk, peanut, pecan, sesame, shrimp, soy, walnut, wheat) - Reaction to ≤ 500 mg cumulative dose of food protein ≤ 12 mo before enrollment - SPT ≥ 6 mm and/or - Food-specific IgE > 4 kU/L - Total IgE < 2000 kU/L	- 92% in the combined treatment arms vs 69% on placebo could pass ≥ 2 OFCs to ≥ 2 g in week 36 - No significant difference in 300 mg and 1 g doses in maintaining desensitization, but both were more effective than the placebo - 69% in the placebo OIT arm had no objective reactivity 6 wk after OIT discontinuation.	- Overall OMA+multi-OIT was well tolerated with no difference in AE rates between arms - The 1-g group had a higher number of doses treated with epinephrine (n = 4) compared with the 300 mg and 0 mg groups
Azzano et al, ³⁸ 2021	Clinical cohort	- Started ≥ 2 mo before IDE - Doses varied on the basis of asthma dosing and patient factors - OMA is typically discontinued when reached final maintenance OIT dose OIT to up to 6 food allergens	N = 181	- Undergoing OMA-enabled OIT at 1 of 3 academic centers - Recent IgE-mediated reaction or allergy test results $> 95\%$ PPV for IgE-mediated allergy	- OMA dosage per weight alone was associated with progression through IDE	- Occurrence of immediate dosing-related reactions after weaning OMA was associated with a greater ratio of specific IgE to total IgE at baseline

Abbreviations: CD-sens, basophil allergen threshold sensitivity tests; DBPC, double-blind placebo-controlled; DBPCFC, double-blind, placebo-controlled food challenge; EoE, eosinophilic esophagitis; GI, gastrointestinal; IDE, initial dose escalation; IgE, immunoglobulin E; IU, international units; multi-OIT, multiallergen OIT; OFC, oral food challenge; OIT, oral immunotherapy; OMA, omalizumab; PPV, positive predictive value; RCT, randomized control trial; SPT, skin prick test; SU, sustained unresponsiveness.

Table 3
Anti-IgE and Food Allergy Trials in Progress

Name of trial	Study drug	Design and intervention	Population	Allergen(s) of interest	Primary outcome
OutMATCH NCT03881696	Omalizumab Dosing on the basis of weight and total IgE	Phase 3 multicenter, randomized DBPC trial Stage 1: Omalizumab vs placebo SC injection $\times$ 16–20 wk Stage 2: 8 wk of open-label OMA, and then randomized to placebo + multiallergen OIT or OMA + placebo OIT Stage 3: DBPCFC-based treatment - dietary consumption - avoidance - rescue OIT	-Age 1 to 55 y -Peanut allergic (SPT $\geq$ 4 mm, peanut IgE $\geq$ 6 kU/L, reaction to a single dose of $\leq$ 100 mg peanut protein) -Allergic to $\geq$ 2 of 6 other foods (+ SPT, IgE, and symptoms to single dose $\leq$ 300 mg food protein)	Peanut + 2 other allergens: milk, egg, wheat, cashew, hazelnut, walnut	Number of participants by stage 1 treatment who consume a single dose of $\geq$ 600 mg peanut protein without dose-limiting symptoms during the DBPCFC at the end of stage 1 Estimated primary completion date: November 2023
Efficacy and Safety of QGE031 (Ligelizumab) in Patients with Peanut Allergy NCT04984876	QGE031 (Ligelizumab)	52-wk, Phase 3, multicenter, randomized DBPC trial Randomized to ligelizumab 240 mg or 120 mg, or placebo SCq4wks for up to 12 wk. After week 12 DBPCFC, placebo groups cross-over to ligelizumab	- Initially enrolling ages 12–55 y and then will expand to ages 6–55 y -Peanut allergic, defined as peanut IgE $\geq$ 0.35 kU/L, peanut SPT $\geq$ 4 mm, reaction to a single dose of $\leq$ 100 mg peanut protein	Peanut	The proportion of participants who can tolerate a single dose of $\geq$ 600 mg peanut protein without dose-limiting symptoms at week 12 Estimated primary completion date: January 2025

Abbreviations: DBPC, double-blind placebo-controlled; DBPCFC, double-blind placebo-controlled food challenge; IgE, immunoglobulin E; OIT, oral immunotherapy; OMA, omalizumab; SC, subcutaneous; SPT, skin prick test.

13/25 participants (52%) had symptoms on IDE, but 19/25 (76%) were able to reach the highest single dose of 1250 mg (2380 mg cumulative) for each treated food. Home reactions occurred in 5.3% of doses, with most occurring in the first month of therapy. Most (94%) dosing reactions were mild, with 1 severe reaction. The median time to reach the goal maintenance dose of 4000 mg per allergen was 18 weeks (range of 7–36 weeks). In addition, multifood OIT plus omalizumab lead to a significant improvement in health-related QOL at 6, 18, and 24-month follow-up compared with baseline ($p < 0.001$ for each time point).^{61,62} A long-term study that followed these participants for up to a maximum of 62 months found that all participants passed the 2-g OFC to each of their offending food allergens at the end of the follow-up study and egg and milk were the allergens most frequently consumed at a high long-term maintenance dose.⁶³

This same group then conducted a DBPC, randomized phase 2 trial in 48 multifood allergic children aged 4 to 15 years.³⁶ Patients were randomized 3-to-1 to omalizumab or placebo in combination with multifood OIT to 2 to 5 foods. The study drug was given for 16 weeks with multifood OIT starting at week 8. Those on omalizumab tolerated a higher dose of IDE and reached the 2 g maintenance dose per food faster than participants on a placebo. Compared with placebo, a higher proportion of patients on omalizumab passed the week 36 exit DBPCFC, defined as tolerating 2-g protein of at least 2 of their offending foods (83% vs 33%; $P = .004$). There were no serious or severe AEs. There were fewer OIT dose-related reactions in the omalizumab group with no increase in AEs once omalizumab was stopped.

In 2019, a multisite, double-blind, randomized phase 2 study evaluated the sustainability of omalizumab-facilitated multifood OIT.³⁷ Participants underwent open-label omalizumab (weeks 0–16) plus multifood OIT (weeks 8–29) and then underwent week 30 OFCs. They were then randomized to receive 1 g or 300 mg of protein of each food allergen or 0 mg (inactive placebo) and then underwent additional OFCs at week 36. This study found that sustained desensitization after multifood OIT plus omalizumab is best achieved with continued maintenance OIT dosing (either 300 mg or 1 g) compared with discontinuation (85% vs 55%, $P = .03$).

Azzano et al³⁸ reported a cohort of 181 patients who underwent omalizumab-enabled accelerated food OIT for up to 6 food allergens. Omalizumab doses varied on the basis of asthma dosing and patient factors, but all participants received omalizumab for at least 2 months before their IDE. A total of 65% (118/181) had a reaction during their IDE, but only 8 (4.4%) were grade 2 or higher. There were 42% who tolerated the final dose of 1200 mg of total food allergen protein. When evaluating determinants of efficacy, the study found that omalizumab dosage per weight alone was associated with progression through the IDE ($P < .001$) whereas the standard asthma-based dosing using weight and total IgE level was not ($P = .97$). The specific IgE to total IgE ratio was found to be a predictor of immediate OIT reactions during the omalizumab weaning phase.

Trials in Progress

The OutMATCH study (Omalizumab as Monotherapy and as Adjunct Therapy to Multiallergen Oral Immunotherapy in Food Allergic Children and Adults; NCT03881696) is a phase 3 multicenter randomized, DBPC study in participants aged 1 to 55 years who are allergic to peanut and at least 2 other foods (milk, egg, wheat, cashew, hazelnut, or walnut) (Table 3).^{64,65} This study is comprised of 3 stages: stage 1, a comparison of 16 to 20 weeks of omalizumab vs placebo, followed by OFCs with a cumulative dose of up to 6044 mg for each allergen; stage 2, consisting of 8 weeks of open-label omalizumab followed by 1:1 randomization to either of the following: (1) open-label omalizumab plus multiallergen OIT for 8 weeks followed by placebo injections plus multiallergen OIT for 44 weeks; or (2) open-label omalizumab plus placebo OIT for 8 weeks followed by omalizumab plus placebo OIT for 44 weeks, followed by OFCs with a cumulative dose up to 8044 mg for each allergen; and stage 3, the dietary introduction of foods or rescue OIT as needed (Fig 3). The primary outcome is tolerance of a single dose of at least 600 mg of peanut protein (cumulative $\geq$ 1044 mg) at the end of stage I. Key secondary outcomes include a single dose of at least 1000 mg cashew, milk, or egg protein at end of stage 1, a single dose of at least 2000 mg peanut protein and other allergens at end of stage 2, and QOL.

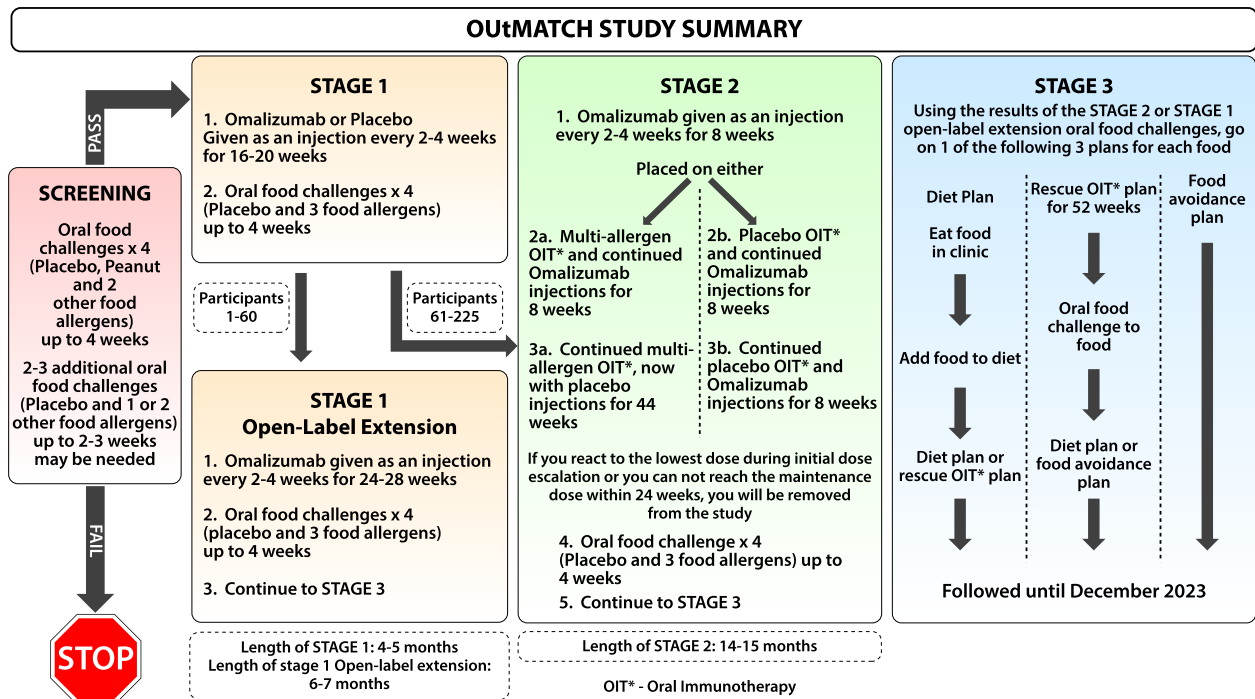


Figure 3. OutMATCH study summary schematic. This figure was published in JACI Global, Volume 1, Robert Wood, R. Sharon Chinthrajah, Amanda Spergel et al, Protocol design and synopsis: Omalizumab as Monotherapy and as Adjunct Therapy to Multiallergen OIT in Children and Adults with Food Allergy (OutMATCH), 225-232, Copyright Elsevier (2022). JACI, Journal of Allergy and Clinical Immunology.

In addition, ligelizumab (QGE031) is currently being studied in a 52-week, phase 3, multicenter, randomized, DBPC study to evaluate the safety and efficacy of 2 dosing regimens of ligelizumab in participants with a peanut allergy (NCT04984876).⁶⁶ The primary outcome is the proportion of participants who can tolerate a single dose of at least 600 mg (1044 mg cumulative) of peanut protein without dose-limiting symptoms at week 12. Key secondary outcomes include the ability to tolerate a single dose of 1000 mg or more of peanut protein at week 12 and week 52, a change in maximum tolerated dose from week 12 to week 52, and a change in QOL.

Clinical Considerations

Whereas there is currently no FDA-approved anti-IgE therapy for food allergy, we are hopeful that that will change in the next few years. Although there are still many unanswered questions, we believe that this could dramatically change the landscape of treatment options for the millions of patients with severe food allergy. The potential advantages of anti-IgE treatments include safety, intermittent dosing, and most importantly, that these treatments will not be food specific, which would be a tremendous advantage for patients with multiple food allergies or those with less common allergies for which allergen-specific treatments are unlikely to be developed. In addition, the use of anti-IgE therapy may enhance the safety of OIT, which is a treatment with the potential to be disease-modifying in a subset of patients. Furthermore, at least with regard to omalizumab, patients may benefit from relief this treatment could provide for many of the comorbidities that are typically associated with food allergy.

Despite this optimism, there are potential downsides that will need to be considered. First, although the cost of biologic therapies may seem prohibitive, we hope that the overall benefits of anti-IgE for the treatment of food allergy will be justified after careful analysis, especially when considering ancillary benefits like QOL and the control of allergic comorbidities. Second, as with most treatments for

allergic diseases, it is not likely that anti-IgE will be a cure, such that the protection provided will likely disappear after treatment is discontinued. For this reason, there are important considerations related to starting this therapy in children and the need for ongoing, possibly lifelong therapy, with a particular need for additional long-term data on adherence, safety, efficacy, and patient-reported outcomes, including impact on QOL. Third, and maybe most important, most previous studies have been limited by excluding individuals with a total IgE level outside of a set range. If the current limits are maintained, many highly atopic individuals who might benefit most from these therapies may be excluded. We are encouraged by the results of the study by Azzano et al,³⁸ noted above, who suggested that dosing omalizumab by body weight alone was more predictive of success than IgE-based dosing. Hence, there is a great need to study these anti-IgE therapies in a broader range of patients, and it is even possible that fixed dosing regimens, such as those that have proven so successful in chronic spontaneous urticaria, could be used for food allergy.

Conclusion

In summary, over the past 20 years, substantial progress has been made in understanding the potential role of anti-IgE therapies for food allergy. We are optimistic that the world of biologics will soon have a major impact on the treatment of food allergy, just as they have had on other allergic conditions. Studies to date have reported that anti-IgE therapy may increase reaction dose thresholds and decrease the time to reach OIT maintenance and OIT dosing-related reactions. At this point, we do not think that there will be any “1 size fits all” treatment for food allergy, and we believe that many patients will still prefer avoidance over any type of treatment. However, if anti-IgE performs as well in the ongoing phase 3 trials given that it has in the preliminary studies to date, these therapies could dramatically reduce the risk of allergic reactions and provide real relief to the millions of patients burdened by their food allergy and the impact that it imposes on their day to day lives.

References

- Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *J Allergy Clin Immunol*. 2018;141(1):41–58.
- Shaker MS, Schwartz J, Ferguson M. An update on the impact of food allergy on anxiety and quality of life. *Curr Opin Pediatr*. 2017;29(4):497–502.
- Bilaver LA, Chadha AS, Doshi P, O'Dwyer L, Gupta RS. Economic burden of food allergy: a systematic review. *Ann Allergy Asthma Immunol*. 2019;122(4):373–380.e1.
- Sicherer SH, Warren CM, Dant C, Gupta RS, Nadeau KC. Food allergy from infancy through adulthood. *J Allergy Clin Immunol Pract*. 2020;8(6):1854–1864.
- National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Food and Nutrition Board, Committee on Food Allergies: Global burden, causes, treatment, prevention, and public policy Oria MP, Stallings VA. *Finding a path to safety in food allergy: assessment of the global burden, causes, prevention, management, and public policy*. Washington, DC: National Academies Press; 2016.
- Marchisotto MJ, Harada L, Kamdar O, Smith BM, Wasserman S, Sicherer S, et al. Food allergen labeling and purchasing habits in the United States and Canada. *J Allergy Clin Immunol Pract*. 2017;5(2):345–351.e2.
- Gupta R, Kanaley M, Negris O, Roach A, Bilaver L. Understanding precautionary allergen labeling (PAL) preferences among food allergy stakeholders. *J Allergy Clin Immunol Pract*. 2021;9(1):254–264.e1.
- Holleman BC, van Os-Medendorp H, van den Bergh H, van Dijk LM, Linders YFM, Blom WM, et al. Poor understanding of allergen labelling by allergic and non-allergic consumers. *Clin Exp Allergy*. 2021;51(10):1374–1382.
- Ahuja R, Sicherer SH. Food-allergy management from the perspective of restaurant and food establishment personnel. *Ann Allergy Asthma Immunol*. 2007;98(4):344–348.
- Karam M, Scherzer R, Ogbogu PU, Green TD, Greenhawt M. Food allergy prevalence, knowledge, and behavioral trends among college students - a 6-year comparison. *J Allergy Clin Immunol Pract*. 2017;5(2):504–506.e5.
- Marrs T, Lack G. Why do few food-allergic adolescents treat anaphylaxis with adrenaline?—Reviewing a pressing issue. *Pediatr Allergy Immunol*. 2013;24(3):222–229.
- Pouessel G, Deschildre A, Castelain C, Sardet A, Sagot-Bevenot S, de Sauve-Boeuf A, et al. Parental knowledge and use of epinephrine auto-injector for children with food allergy. *Pediatr Allergy Immunol*. 2006;17(3):221–226.
- Patriarca G, Schiavino D, Nucera E, Schinco G, Milani A, Gasbarrini GB. Food allergy in children: results of a standardized protocol for oral desensitization. *Hepatogastroenterology*. 1998;45(19):52–58.
- Peters RL, Krawiec M, Koplin JJ, Santos AF. Update on food allergy. *Pediatr Allergy Immunol*. 2021;32(4):647–657.
- Nurmatov U, Dhami S, Arasi S, Pajno GB, Fernandez-Rivas M, Muraro A, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy*. 2017;72(8):1133–1147.
- US Food and Drug Administration. FDA approves first drug for treatment of peanut allergy for children. 2020. Available at: <https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treatment-peanut-allergy-children>. Accessed November 14, 2022.
- Burks AW, Sampson HA, Plaut M, Lack G, Akdis CA. Treatment for food allergy. *J Allergy Clin Immunol*. 2018;141(1):1–9.
- Chu DK, Wood RA, French S, Fiocchi A, Jordana M, Wasserman S, et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. *Lancet*. 2019;393(10187):2222–2232.
- Dantzer JA, Wood RA. Next-generation approaches for the treatment of food allergy. *Curr Allergy Asthma Rep*. 2019;19(1):5.
- Dantzer JA, Kim EH, Chinthrajah RS, Wood RA. Treatment for food allergy: current status and unmet needs. *J Allergy Clin Immunol*. 2023;151(1):1–14.
- Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. *J Allergy Clin Immunol*. 2010;126(6):1105–1118.
- Barzegar S, Rosita A, Pourpak Z, Bermanian MH, Shokouhi R, Mansouri M, et al. Common causes of anaphylaxis in children: the first report of anaphylaxis registry in Iran. *World Allergy Organ J*. 2010;3(1):9–13.
- Leung DYM, Sampson HA, Yunginger JW, Burks AW, Schneider LC, Wortel CH, et al. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med*. 2003;348(11):986–993.
- Rafi A, Do LT, Katz R, Sheinkopf LE, Simons CW, Klaustermeyer W. Effects of omalizumab in patients with food allergy. *Allergy Asthma Proc*. 2010;31(1):76–83.
- Sampson HA, Leung DYM, Burks AW, Lack G, Bahna SL, Jones SM, et al. A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. *J Allergy Clin Immunol*. 2011;127(5):1309–1310.e1.
- 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(5):1123–1129.e2.
- Brandström J, Vetander M, Lilja G, Johansson SGO, Sundqvist AC, Kalm F, et al. Individually dosed omalizumab: an effective treatment for severe peanut allergy. *Clin Exp Allergy*. 2017;47(4):540–550.
- Fiocchi A, Artesani MC, Riccardi C, Mennini M, Pecora V, Fierro V, et al. Impact of omalizumab on food allergy in patients treated for asthma: a real-life study. *J Allergy Clin Immunol Pract*. 2019;7(6):1901–1909.e5.
- 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(6):1368–1374.
- Yee CSK, Albuhairei S, Noh E, El-Khoury K, Rezaei S, Abdel-Gadir A, et al. Long-term outcome of peanut oral immunotherapy facilitated initially by omalizumab. *J Allergy Clin Immunol Pract*. 2019;7(2):451–461.e7.
- Brandström J, Vetander M, Sundqvist AC, Lilja G, Johansson SGO, Melén E, et al. Individually dosed omalizumab facilitates peanut oral immunotherapy in peanut allergic adolescents. *Clin Exp Allergy*. 2019;49(10):1328–1341.
- MacGinnitie AJ, Rachid R, Gragg H, Little SV, Lakin P, Cianferoni A, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. *J Allergy Clin Immunol*. 2017;139(3):873–881.e8.
- Nadeau KC, Schneider LC, Hoyte L, Borrás I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. *J Allergy Clin Immunol*. 2011;127(6):1622–1624.
- Wood RA, Kim JS, Lindblad R, Nadeau K, Henning AK, Dawson P, 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(4):1103–1110.e11.
- Bégin P, Dominguez T, Wilson SP, Bacal L, Mehrotra A, Kausch B, et al. Phase 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using omalizumab. *Allergy Asthma Clin Immunol*. 2014;10(1):7.
- Andorf S, Purington N, Block WM, Long AJ, Tupa D, Brittain E, et al. Anti-IgE treatment with oral immunotherapy in multifoed allergic participants: a double-blind, randomised, controlled trial. *Lancet Gastroenterol Hepatol*. 2018;3(2):85–94.
- Andorf S, Purington N, Kumar D, Long A, O'Laughlin KL, Sicherer S, et al. A Phase 2 randomized controlled multisite study using omalizumab-facilitated rapid desensitization to test continued vs discontinued dosing in multifoed allergic individuals. *EClinicalMedicine*. 2019;7:27–38.
- Azzano P, Paquin M, Langlois A, Morin C, Parizeault G, Lacombe-Barrios J, et al. Determinants of omalizumab dose-related efficacy in oral immunotherapy: evidence from a cohort of 181 patients. *J Allergy Clin Immunol*. 2021;147(1):233–243.
- US Approval. Xolair prescribing information. 2021. Available at: https://www.gene.com/download/pdf/xolair_prescribing.pdf. Accessed March 2, 2023.
- MacGlashan D. Loss of receptors and IgE in vivo during treatment with anti-IgE antibody. *J Allergy Clin Immunol*. 2004;114(6):1472–1474.
- MacGlashan DW, Bochner BS, Adelman DC, Jardieu PM, Trogias A, McKenzie-White J, et al. Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol*. 1997;158(3):1438–1445.
- Saini SS, MacGlashan DW, Sterbinsky SA, Trogias A, Adelman DC, Lichtenstein LM, et al. Down-regulation of human basophil IgE and Fc epsilon RI alpha surface densities and mediator release by anti-IgE-infusions is reversible in vitro and in vivo. *J Immunol*. 1999;162(9):5624–5630.
- Pennington LF, Tarchevskaya S, Brigger D, Sathiyamoorthy K, Graham MT, Nadeau KC, et al. Structural basis of omalizumab therapy and omalizumab-mediated IgE exchange. *Nat Commun*. 2016;7:11610.
- Dantzer JA, Wood RA. The use of omalizumab in allergen immunotherapy. *Clin Exp Allergy*. 2018;48(3):232–240.
- Tsabouri S, Ntrisots G, Koskeridis F, Evangelou E, Olsson P, Kostikas K. Omalizumab for the treatment of allergic rhinitis: a systematic review and meta-analysis. *Rhinology*. 2021;59(6):501–510.
- El-Qutob D. Off-label uses of omalizumab. *Clin Rev Allergy Immunol*. 2016;50(1):84–96.
- Arm JP, Bottoli I, Skerjanec A, Floch D, Groenewegen A, Maahs S, et al. Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic patients. *Clin Exp Allergy*. 2014;44(11):1371–1385.
- Wood RA, Chinthrajah RS, Eggel A, Bottoli I, Gautier A, Woitschlaeger M, et al. The rationale for development of ligelizumab in food allergy. *World Allergy Organ J*. 2022;15(9):100690.
- Gasser P, Tarchevskaya SS, Guntern P, Brigger D, Ruppli R, Zbären N, et al. The mechanistic and functional profile of the therapeutic anti-IgE antibody ligelizumab differs from omalizumab. *Nat Commun*. 2020;11(1):165.
- Benito-Villalva C, de la Rocha-Muñoz A, López-Abente J, Eggel A, Bottoli I, Severin T, et al. Ligelizumab impairs IgE-binding to plasmacytoid dendritic cells more potentially than omalizumab and restores IFN-α production and FOXP3+ Treg generation. *Allergy*. 2023;78(4):1060–1072.
- Nowak-Węgrzyn A, Sato S, Fiocchi A, Ebisawa M. Oral and sublingual immunotherapy for food allergy. *Curr Opin Allergy Clin Immunol*. 2019;19(6):606–613.
- Narisety SD, Frischmeyer-Guerrero PA, Keet CA, Gorelik M, Schroeder J, Hamilton RG, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. *J Allergy Clin Immunol*. 2015;135(5):1275–1282.e1–6.
- Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *J Allergy Clin Immunol*. 2008;121(2):343–347.
- Skiprik JM, Nash SD, Rowley H, Brereton NH, Oh S, Hamilton RG, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol*. 2008;122(6):1154–1160.
- Pajno GB, Caminiti L, Ruggeri P, De Luca R, Vita D, La Rosa M, et al. Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. *Ann Allergy Asthma Immunol*. 2010;105(5):376–381.
- Martorell A, De la Hoz B, Ibáñez MD, Bone J, Terrados MS, Michavila A, et al. Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy. *Clin Exp Allergy*. 2011;41(9):1297–1304.

57. Jones SM, Kim EH, Nadeau KC, Nowak-Wegrzyn A, Wood RA, Sampson HA, et al. Efficacy and safety of oral immunotherapy in children aged 1–3 years with peanut allergy (the Immune Tolerance Network Impact trial): a randomised placebo-controlled study. *Lancet*. 2022;399(10322):359–371.
58. PALISADE Group of Clinical Investigators Vickery BP, Vereda A, Casale TB, Beyer K, du Toit G, et al. AR101 Oral Immunotherapy for Peanut Allergy. *N Engl J Med*. 2018;379(21):1991–2001.
59. Dantzer JA, Wood RA. Omalizumab as an adjuvant in food allergen immunotherapy. *Curr Opin Allergy Clin Immunol*. 2021;21(3):278–285.
60. Fiocchi A, Vickery BP, Wood RA. The use of biologics in food allergy. *Clin Exp Allergy*. 2021;51(8):1006–1018.
61. Otani IM, Bégin P, Kearney C, Dominguez TL, Mehrotra A, Bacal LR, et al. Multiple-allergen oral immunotherapy improves quality of life in caregivers of food-allergic pediatric patients. *Allergy Asthma Clin Immunol*. 2014;10(1):25.
62. Arasi S, Otani IM, Klingbeil E, Bégin P, Kearney C, Dominguez TL, et al. Two year effects of food allergen immunotherapy on quality of life in caregivers of children with food allergies. *Allergy Asthma Clin Immunol*. 2014;10(1):57.
63. Andorf S, Manohar M, Dominguez T, Block W, Tupa D, Kshirsagar RA, et al. Observational long-term follow-up study of rapid food oral immunotherapy with omalizumab. *Allergy Asthma Clin Immunol*. 2017;13:51.
64. US National Library of Medicine. *Omalizumab as monotherapy and as adjunct therapy to multi-allergen oral immunotherapy (OIT) in food allergic children and adults (CoFAR-11)*. National Institute of Allergy and Infectious Diseases (NIAID); 2022. Available at: <https://clinicaltrials.gov/ct2/show/NCT03881696>. Accessed December 4, 2022.
65. Wood RA, Chinthrajah RS, Spergel AKR, Babineau DC, Sicherer SH, Kim EH, et al. Protocol design and synopsis: omalizumab as monotherapy and as Adjunct Therapy to Multiallergen OIT in Children and Adults with Food Allergy (OUMATCH). *J Allergy Clin Immunol Global*. 2022;1(4):225–232.
66. Novartis Pharmaceuticals. A 52 week, multi-center, randomized, double-blind placebo-controlled study to assess the clinical efficacy and safety of ligelizumab (QGE031) in decreasing the sensitivity to peanuts in patients with peanut allergy. 2022. Available at: <https://clinicaltrials.gov/ct2/show/NCT04984876>. Accessed November 17, 2022.