



Omalizumab as monotherapy for food allergy

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Purpose of review

To familiarize the reader with the most recent insights in the use of Omalizumab (monoclonal anti-immunoglobulin E) monotherapy in the treatment of patients with severe food allergy.

Recent findings

The current data from early stage clinical trials show that Omalizumab may be safe and effective by itself in providing desensitization to one or several foods without requiring allergen exposure.

Summary

In the near future, advances in knowledge will guide the adoption and implementation of any new therapy for food allergy and allow the development of a personalized treatment tailored on the specific patient's profile.

Keywords

food allergy, food allergy severity, Omalizumab, precision medicine, quality of life

INTRODUCTION

Food allergy is emerging as a relevant disease [1]. It remains the main etiology of anaphylaxis among children [2], and its prevalence has increased over time [3]. Furthermore, food allergy might negatively impact nutrition and health-related quality of life for both allergic individuals and their families, with an emotional, social, and economic burden [4,5]. Nowadays, the standard of care for food allergy is allergen avoidance and availability of self-injectable epinephrine in the case an anaphylactic reaction occurs. An elimination diet might be difficult and frustrating, in particular for common foods, such as milk and egg. Nevertheless, despite efforts to comply with this diet, accidental exposures leading to adverse reactions are frequent [6]. Therefore, therapies for patients with established food allergies are highly needed. In this perspective, many efforts have been made over time. Currently, the most promising therapeutic options are oral immunotherapy (OIT) and biologicals; among the latter, Omalizumab is the most used either combined with OIT [7] or as monotherapy [8]. Though this is not the only anti-immunoglobulin E (IgE) option (Fig. 1) [9], Omalizumab is currently the only fully-developed molecule in the field. This review aims to provide an update on current evidence about the role of Omalizumab as monotherapy in IgE-mediated food allergy. We will focus on the effects of Omalizumab on the passive increase of the threshold of reactivity to one or several foods out of the context of allergen exposure as in OIT [10,11].

OMALIZUMAB: WHAT IT IS AND HOW IT WORKS

Omalizumab (Xolair) is an anti-IgE humanized monoclonal antibody developed by recombinant DNA techniques (anti-IgE mAb). Specifically, Omalizumab is an immunoglobulin G1 (IgG1), which by binding to the IgE constant Cε3 region of free circulating IgE, prevents the latter from binding to the high-affinity FcεRI receptors on effector cells (primarily basophils and mast cells), interfering with degranulation and release of pro-inflammatory mediators [12]. Additionally, by reducing free circulating IgE, Omalizumab decreases FcεRI expression on these cells, and, therefore, decreases their degranulation. In general, Omalizumab does not bind to FcεRI bound IgE or IgE receptors; this is an important safety aspect for avoiding degranulation by effector cells [12]. Notwithstanding, in rare cases (0.09%), Omalizumab induces an anaphylaxis-like reaction through unknown mechanism(s) [13].

Furthermore, it has been shown that Omalizumab can also reduce the in-vivo expression of FcεRI

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KEY POINTS

- The property of Omalizumab to induce not allergen-specific effects on allergic immune responses makes this biological treatment a potentially attractive candidate for several IgE-mediated diseases including food allergy.
- The current data from early stage clinical trials show that Omalizumab may be effective by itself in providing desensitization to one or several foods without requiring allergen exposure as in oral immunotherapy.
- Further, well designed studies are needed to fill the current gaps in knowledge and guide the adoption and implementation of any new therapy for food allergy.
- Precision medicine'' algorithms are needed to provide patient-tailored (individual) treatments.

on dendritic cells and lead to a reduction in the allergens presentation to T cells. Consequently, it decreases the T helper 2 (Th-2)-mediated allergic pathway activity including decreased IgE production, anergy of B cells, induction of regulatory T cells, and eosinophils apoptosis [14]. In addition to

high-affinity FcεRI receptor, IgE can bind to low-affinity FcεRII receptors (CD23), which can modulate (towards either upregulation or downregulation) IgE synthesis. There is evidence that Omalizumab may downregulate FcεRII, making effector cells insensitive to incoming allergen [15]. Another mechanism by which anti-IgE antibodies decrease allergic reactions is through decreasing IgE production by targeting CD23 or CD23-bound IgE on B cells. For instance, Ligelizumab, a more recently developed anti-IgE antibody, is more effective than Omalizumab in binding CD23-bound IgE [15].

Omalizumab induces a generalized dampening of type 1 allergic immunity as it targets the constant (Fc), not hypervariable, region of IgE. The property of Omalizumab to induce not allergen-specific effects on allergic immune responses makes this biological treatment a potentially attractive candidate for several IgE-mediated diseases also outside the currently approved indications by the European Medicine Agency (EMA) [16] and the US Food and Drug Administration (FDA) [17] (i.e. allergic asthma, chronic idiopathic urticaria and nasal polyps). One such condition is IgE-mediated food allergy.

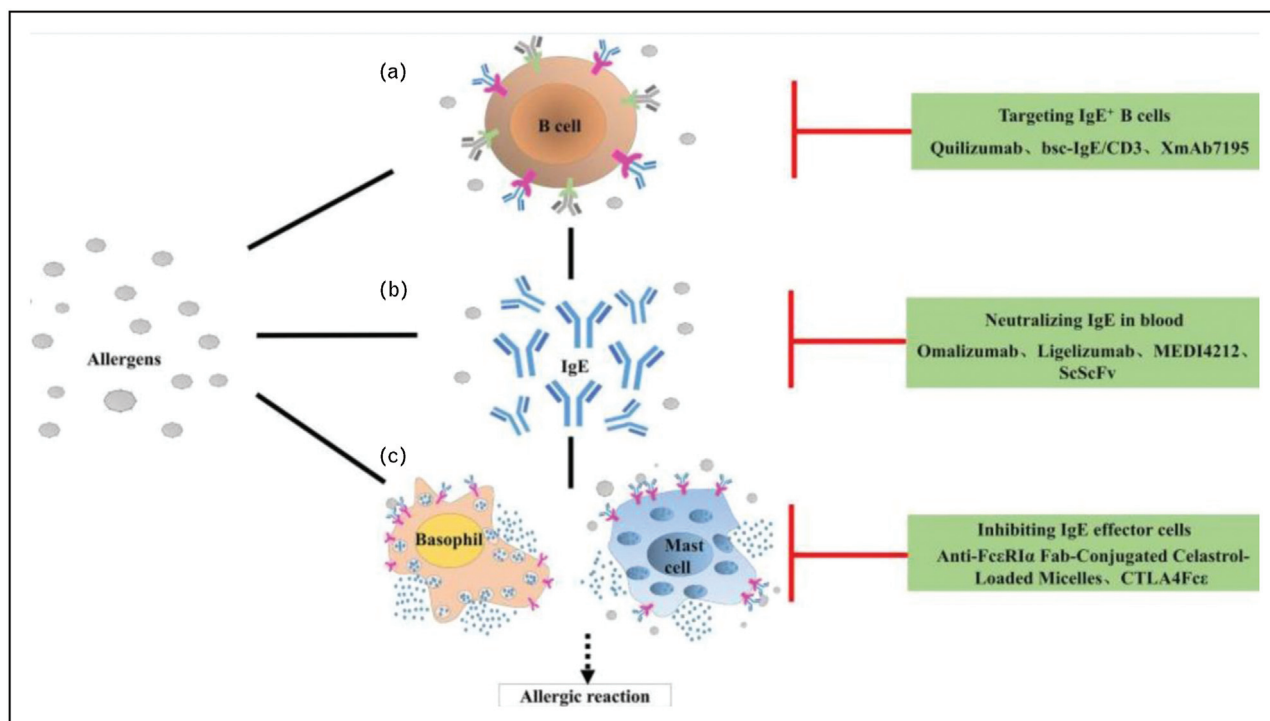


FIGURE 1. Different options for anti-IgE strategy: a. Inhibition of IgE + B cells (Quilizumab). b. Serum IgE neutralization (Immuno adsorption plasma-pheresis, Omalizumab, Ligelizumab, their biosimilars CMAB007 and MEDI4212, and recombinant ScFv (a single-chain antibody targeting IgE, IgE-bound cells, and IgE-secreting cells). c. Inhibition of IgE-effector cells (Anti-FcεRIα Fab-conjugated celastrol-loaded micelles aimed to prevent IgE interaction with mast cells, and kill mast cells, CTLA4FcεFusion protein targeting IgE receptors, FcεRI and FcεRII/CD23. Reproduced from Hu *et al.* [9].

OMALIZUMAB AS MONOTHERAPY FOR FOOD ALLERGY: CURRENT EVIDENCE

The first evidence on the potential clinical benefit of anti-IgE-based approaches in patients with food allergy comes from TNX-901 [18]. TNX-901 was an anti-IgE monoclonal antibody with demonstrated ability to significantly and substantially increase the threshold of reactivity to peanut on oral food challenge (OFC) in 84 peanut-allergic patients in a double-blind, randomized, dose-ranging trial, when used as monotherapy [18]. Notwithstanding, this drug was not further developed for this aim [18]. Subsequently, further data supported the use of Omalizumab as monotherapy in food allergy (as summarized in Table 1). In 2011, a 4-week, double-blind, placebo-controlled, multicenter study in peanut allergic adolescents and adults testing Omalizumab as monotherapy was commenced [19]. Although the study intended to randomize 150 subjects, enrollment was interrupted early on the basis of the recommendation of the Data Safety Monitoring Committee because of the severity of two anaphylactic reactions that occurred during the screening OFCs before the administration of Omalizumab. However, 14 participants (nine into the Omalizumab study arm and five into the

placebo one) completed the trial at the time of study termination and these data were analyzed. Although the predefined efficacy end point was not met, Omalizumab-treated participants experienced an 80.9-fold improvement in the tolerated dose of peanut proteins at the week 24 peanut OFC compared with the baseline peanut OFC, whereas only a 4.1-fold improvement was observed in the placebo group [19].

In 2012, an open-label study showed the efficacy of Omalizumab as monotherapy in 14 peanut-allergic patients (median age of 23 years): after 6 months of treatment, the median cumulative eliciting dose of peanut protein significantly increased from 80 mg (range, 30–380 mg) to 6500 mg (range, 1,830–10,000 mg) [20].

In 2019, a single-center, real-life, retrospective observational study has provided uncontrolled preliminary data in support of Omalizumab as effective monotherapy for food allergy [21^{***}]. 15 out of the 115 patients with severe atopic asthma (Asthma Control Test score < 19 despite high-dose inhaled corticosteroids) received Omalizumab for their asthma per standard-care guidelines, had allergy to at least two foods, and underwent paired OFCs before, and 4 months into, Omalizumab treatment.

Table 1. Summary of findings from the most relevant studies evaluating the use of omalizumab as monotherapy in food allergy

Study (first author, year of publication)	Design and population	Main findings
Sampson <i>et al.</i> 2011 [19]	4-week, double-blind, placebo-controlled, multicenter study in peanut allergic adolescents and adults testing Omalizumab as monotherapy	14 participants (9 omalizumab and 5 placebo) completed the trial. Omalizumab-treated participants experienced an 80.9 fold improvement in the tolerated dose of peanut proteins at the week 24 peanut OFC compared with the baseline peanut OFC, whereas only a 4.1-fold improvement was observed in the placebo group.
Savage <i>et al.</i> 2012 [20]	Open label study in 14-peanut allergic patients (median age, 23 years) undergoing Omalizumab as monotherapy for 6 months	After 6 months of treatment, the median cumulative eliciting dose of peanut protein significantly increased from 80 mg (range, 30–380 mg) to 6500 mg (range, 1,830–10,000 mg)
Fiocchi <i>et al.</i> 2019 [21 ^{***}]	Single-center, single arm, real-life, retrospective observational study in 15 pediatric patients (median, range; 144, 96–276 months) undergoing Omalizumab as monotherapy for 4 months	After 4 months of Omalizumab treatment, all patients experienced an increase in their eliciting threshold to each food tested. Overall, the median (interquartile range) eliciting threshold in milligrams of protein was 460.8 (31–1,740) at baseline, which improved to 8,192 (5,568–10,400) after treatment, representing a statistically significant improvement for egg, milk, baked milk, and wheat. Nine of the 15 were able to tolerate without symptoms a full serving size amount of all the foods tested, two others were able to do so to at least one of the foods tested, and four partially improved. In the 11 patients who asymptotically consumed the full challenge amount, the previously allergenic food was added to the diet. Furthermore, patients improved their health-related quality of life (PedsQL instrument), and reduced symptomatic accidental food allergen exposures

OFC, oral food challenge.

The 15 patients selected for the analysis had clinical histories of immediate reactions to 37 total foods; of these, baseline-eliciting thresholds were measured to 23 total foods including milk, baked milk, egg, baked egg, wheat, and hazelnut. After 4 months of Omalizumab treatment, all patients experienced an increase in their eliciting threshold to each food tested. Overall, the median (interquartile range) eliciting threshold in milligrams of protein was 460.8 [31–1,740] at baseline, which improved to 8,192 (5,568–10,400) after treatment, representing a statistically significant improvement for egg, milk, baked milk, and wheat. Nine of the 15 were able to tolerate without symptoms a full serving size amount of all the foods tested, two others were able to do so to at least one of the foods tested, and four partially improved. In the 11 patients who asymptotically consumed the full challenge amount, the previously allergenic food was added to the diet. Furthermore, patients improved their health-related quality of life as assessed by the generic PedsQL instrument, and reduced symptomatic accidental food allergen exposures [21[¶]].

Although the strength of evidence is not high because of the study design (i.e. small, single-center, single-arm, retrospective study), the close follow-up, the meticulously collected data and paired food challenges provide additional real-world insight into Omalizumab's potential to shift eliciting allergen thresholds and induce clinically meaningful levels of desensitization when used by itself. More recently, these data have been confirmed by the same research group in an oral communication in a larger independent, retrospective cohort of patients with food allergy and concomitant asthma [22].

An ongoing clinical trial called OutMATCHT (Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Children and Adults), sponsored by the National Institutes of Allergy and Infectious Disease through the

Consortium of Food Allergy Research, is testing Omalizumab monotherapy and as an adjunct to multifood OIT in 10 centers, in a randomized, double-blind, placebo-controlled fashion [23]. This study focuses on the effects of Omalizumab during multifood OIT in peanut-allergic patients (Fig. 2). However, in its phase 1 the design is a simple Omalizumab/placebo comparison, with the objective of assessing the ability to consume foods without dose-limiting symptoms during a double-blind placebo-controlled food challenge (DBPCFC) after 16–20 weeks of treatment. The study also includes a 24-week phase 1 extension, with the objective of evaluating if a prolonged Omalizumab treatment increases the probability of patients to introduce foods [23]. The results are expected to shed light on different aspects of Omalizumab in the treatment of food allergy.

CURRENT GAPS AND FUTURE PERSPECTIVES

The current data from early stage clinical trials show that Omalizumab may be effective by itself in providing desensitization to one or several foods without requiring allergen exposure while on treatment. However, large, adequately powered, and rigorous trials that could definitively investigate the efficacy of Omalizumab monotherapy are required since several gaps in the evidence are still to be filled, the main of those are listed below:

- (1) The optimal duration of Omalizumab monotherapy to reach the desensitization.
- (2) The duration of treatment to reach any sustained unresponsiveness.
- (3) The optimal dose for each subject. The majority of studies report on the administration of this drug with a dosage and a frequency (every 2 or 4 weeks) set based on the total serum IgE level and the weight of the individual patient, according

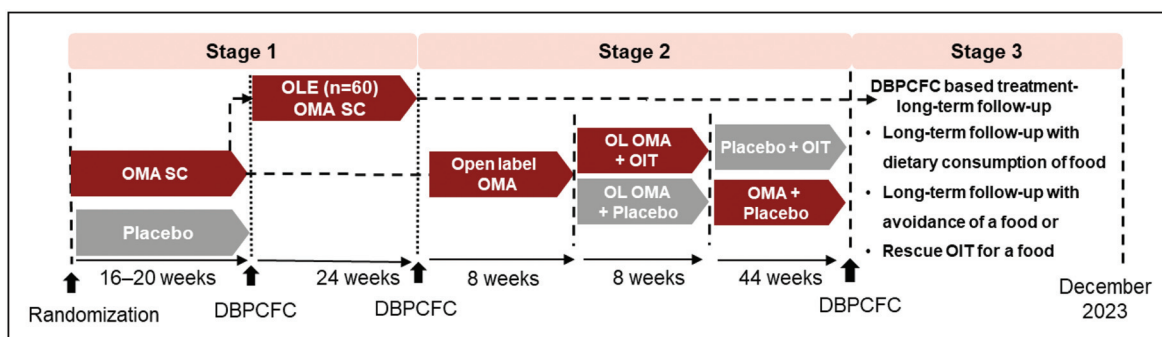


FIGURE 2. Omalizumab as monotherapy and as adjunct therapy to multi-allergen OIT in Food Allergic Participants (OutMATCH): overall design. Reproduced from <https://clinicaltrials.gov/ct2/show/NCT03881696> [21[¶]]. DBPCFC, double-blind placebo-controlled food challenge; long-term, treatment with Omalizumab; OIT, oral immunotherapy; OL, open label; OLE, open label extension; OMA, Omalizumab-facilitated.

to asthma and nasal polyps indication [21[■]]. However, a recent study on a cohort of 181 patients undergoing OIT combined with Omalizumab reports on a dose-related treatment efficacy and suggests that, in the context of OIT and IgE-mediated disease, Omalizumab dosages should be adjusted for body weight alone, independently of total IgE level [24[■]]. In addition, one major drawback of Omalizumab is that, overall, its applicability according to EMA [16] and FDA [17] prescribing information is limited by a weight-dependent maximum level of total IgE up to which it can be administered (i.e. 1500 U/ml). The main reason for an IgE threshold comes from the potential risk that in patients who undergo Omalizumab treatment and have high level of total IgE, considerable concentrations of IgE/Omalizumab immune complexes accumulate in the blood with the risk of renal impairment. To overcome this limit attempts of extracorporeal IgE immunoadsorption preliminary to Omalizumab treatment commencement have been performed for diverse diseases [25], including food allergy [26]. Notwithstanding, Omalizumab has been reported to be used also in subjects with total IgE up to 2,000 IU/mL without any specific safety concern [27[■]].

- (4) Cost-effectiveness.
- (5) Impact on health-related quality of life (patient-related outcomes).
- (6) Specific and sensitive biomarkers to predict the response to the treatment. In this context, a study suggested that basophil allergen threshold sensitivity (CD-sens) can be used to objectively measure Omalizumab treatment efficacy and correlates with the outcome of double-blind placebo-controlled food challenge to peanut [28]. In addition, the ratio of IgE-ab to storage protein Ara h 2/IgE as well as CD-sens to peanut has been suggested to predict the need of a higher Omalizumab dose [28]. More studies are needed.
- (7) Identification of the most suitable candidates (personalized care).
- (8) 'Precision medicine' algorithms for patient-tailored (individual) treatments.

In this perspective, a shared comprehensive definition of food allergy severity useful for different stakeholders involved in the field is currently missing and to this aim results from an international project are highly awaited [DEFinition of Food Allergy SEverity (DEFASE)] [29]. Along the currently published studies, some criteria have been proposed for clinically severe food allergy,

including near fatal reactions requiring 3 or more injections of i.m. epinephrine, an adrenaline i.v. infusion, ventilatory or inotropic support, or elicited by minimal allergenic doses. It has been speculated that most of these patients are also likely to have allergies to multiple food, whereas OIT is strictly food specific and would require consecutive time-consuming protocols. A possible therapeutic option for these patients could be represented by Omalizumab in association with OIT or alone.

CONCLUSIONS

The current evidence supports the use of Omalizumab, alone or combined with OIT, in allergic patients to provide desensitization to one or several foods. However, additional research on the effects of Omalizumab in food allergy not only is likely to shed light on its mechanism of action but also will help health policymakers in considering further integrative options for a food allergy management tailored on the single patient. For instance, it could be speculated that Omalizumab adjunct to OIT may provide incremental benefit in some patients, effective monotherapy with Omalizumab would be a major advance for food-allergic patients, especially those who are polyallergic and/or are averse to oral allergen intake. As such, in August 2018 the FDA granted Breakthrough Therapy Designation for Omalizumab for the prevention of severe allergic reactions following accidental exposure to one or more foods in people with allergies [30].

Adequately powered and rigorously conducted randomized controlled clinical trials are needed to minimize bias and provide high-quality data to guide the adoption and implementation of any new therapy.

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Conflicts of interest

There are no conflicts of interest.

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