

REVIEW

The use of omalizumab in allergen immunotherapy

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Summary

Although omalizumab (anti-IgE) is currently only approved for the treatment of asthma and chronic idiopathic urticaria, it has also been studied as an off-label treatment for numerous allergic conditions, including use as an adjunct to allergen immunotherapy in the treatment of allergic rhinitis, asthma, venom hypersensitivity and food allergy. We conducted a review of publications involving the use of omalizumab with allergen immunotherapy, by searching PubMed with key search terms of “omalizumab” and “immunotherapy.” Omalizumab has been used in combination with inhalant allergen immunotherapy for the treatment of seasonal allergic rhinitis and comorbid asthma. While there have been no randomized controlled trials evaluating the addition of omalizumab to venom IT, several case reports and small patient series have been published on the use of omalizumab with venom IT. Omalizumab has been used in conjunction with oral immunotherapy for the treatment of milk, peanut and egg, as well as other foods in multi-allergen protocols. In conclusion, omalizumab used in conjunction with immunotherapy has shown promising results, especially in the reduction of adverse reactions. At this stage, larger, randomized, placebo-controlled trials are needed to better identify those patients who would benefit the most from the addition of omalizumab to immunotherapy, as well as optimal dosing strategies and duration of treatment.

1 | INTRODUCTION

Immunoglobulin E (IgE) was first described in 1967,¹ and since that time, its critical role in allergic disease has become increasingly clear.^{2,3} IgE binds to the high affinity receptor, FcεRI, on effector cells, particularly basophils and mast cells.⁴ The cross-linkage of IgE while bound to effector cells results in the release of preformed and newly synthesized mediators, leading to hypersensitivity reactions.⁴ Blocking these mediators and, more recently, inhibition of IgE in this allergic cascade has become a target for the treatment of numerous allergic diseases.^{4,5}

Omalizumab (Xolair®; Novartis) is a recombinant DNA-derived humanized IgG1κ monoclonal antibody that selectively binds to human IgE.⁶ In 2003, it was approved for the treatment of severe allergic asthma in adolescents and adults, and more recently, it was approved for the treatment of chronic idiopathic urticaria^{6,7} for

patients age 12 and above and for asthma down to the age of 6 years.⁶ Over the past decade, omalizumab has also been studied as an off-label treatment, or adjunct to treatment, for numerous allergic conditions, including allergic rhinitis, food allergy, atopic dermatitis, eosinophilic gastrointestinal disease, idiopathic anaphylaxis, mastocytosis, and allergic bronchopulmonary aspergillus.⁵

While its mechanism of action in urticaria is not completely understood, with respect to IgE-mediated diseases, the primary mode of action results from the binding of the drug to the heavy-chain constant C_H3 domain of the free IgE molecule at the site of FcεRI receptor.^{8,9} Omalizumab:IgE complexes are formed which results in a significant decrease in free IgE in serum and prevents IgE from binding to effector cells, resulting in decreased mediator release in response to allergen and down-regulation of FcεRI receptors on basophils and mast cells.⁸⁻¹³ Omalizumab can only bind free IgE and cannot cross-link surface-bound IgE, such that it should not

trigger effector cell degranulation; however, anaphylaxis does occur in a small subset of patients with omalizumab injections by mechanisms that remain unclear.¹⁴⁻¹⁶

For asthma, 75-375 mg of omalizumab is administered subcutaneously (SC) every 2-4 weeks. Dose and dosing frequency are determined by serum total IgE level (IU/mL) prior to starting treatment and body weight (kg).⁶ For children age 6-12 years, dosing guidelines allow for treatment of individuals with an IgE of ≥ 30 IU/mL to a max of 1300 IU/mL and a maximum weight of 150 kg. Dosing recommendations for those 12 years and above include patients with an IgE ≥ 30 IU/mL to a maximum of 700 IU/mL and a maximum weight of 150 kg.⁶ Dosing for chronic idiopathic urticaria is 150 or 300 mg SC every 4 weeks and is not based on serum IgE level or body weight. A 1-month supply of omalizumab costs between \$541 and \$2706, with annual costs typically ranging from \$10 000 to 32 000.¹⁷

2 | ALLERGEN IMMUNOTHERAPY OVERVIEW

It is estimated that approximately 25% of the United States population has some form of allergic disease.¹⁸ Allergen immunotherapy (AIT) is the process of providing gradually increasing doses of allergenic proteins with the goal of inducing desensitization.¹⁹ This treatment has the advantage of triggering immunologic changes that can lead to long-term benefits, even when therapy is complete.²⁰ Over the past century, AIT has become an effective treatment for allergic rhinitis, asthma and venom hypersensitivity¹⁹⁻²⁴ and is an emerging treatment option for food allergy.²⁵⁻²⁸ However, the use of AIT has been limited by potential adverse reactions^{19,26,29-32} and poor patient compliance due to the extended duration of treatment.³³ Hence, there is interest in developing safer approaches that will still induce desensitization, ideally in a shorter time frame. Here, we will review studies that have examined the potential value of omalizumab in improving the efficacy and safety of AIT.

3 | INHALANT ALLERGEN IMMUNOTHERAPY + OMALIZUMAB

For the past century, subcutaneous-specific AIT has been effectively used to treat allergic rhinitis (AR) and asthma.^{19,21,23} However, patients typically do not get relief until after months of therapy. Systemic reactions occur in 0.1% of all shot visits, with a significantly increased risk of systemic reactions with cluster or rush build-up protocols.^{31,32} Various clinical trials have examined the use of omalizumab with AIT to determine whether the combination can provide a safer regimen that provides more rapid dose escalation and symptom relief (Table 1).³⁴⁻³⁹

Kuehr et al³⁴ conducted the first clinical trial to investigate the effect of anti-IgE in combination with specific AIT. This was a

randomized, double-blind, placebo-controlled, multi-site study of 221 patients (age 6-17 years) with birch and grass pollen-induced seasonal AR. Subjects were randomized to 1 of 4 treatment groups (A: AIT-birch + placebo, B: AIT-birch + omalizumab, C: AIT-grass + placebo, or D: AIT-grass + omalizumab). After 12 weeks of specific AIT titration, omalizumab or placebo was added for 24 weeks. Symptom load was measured as the sum of daily symptom severity score plus rescue medication use. Combination therapy with omalizumab and AIT reduced symptom load by 48% over the 2 pollen seasons (birch and grass) compared to AIT alone ($P < .001$). When analysed by season, combination therapy reduced symptom load by 50% ($P = .003$) during the birch season and 57% during grass season ($P = .001$) in comparison with relevant AIT monotherapy, while no significant benefit was seen during the first year with birch AIT (symptom load increase by 5%, $P = .43$) or grass AIT (reduced symptom load by 32%, $P = .1$) monotherapy compared to placebo. The authors concluded that that lack of efficacy of AIT-grass alone in the first year of treatment might be overcome by combination with anti-IgE treatment.³⁴ Further, an additional safety analysis by Kamin et al³⁵ found that patients in the placebo group had significantly more AIT injection site redness and swelling than those in the omalizumab group ($P \leq .05$).

Kopp et al³⁶ studied the efficacy and safety of omalizumab + AIT (Depigoid®) in adolescents and adults with seasonal grass pollen allergic rhinoconjunctivitis and asthma. In this randomized, double-blind, placebo-controlled, multi-centre trial, 140 subjects started omalizumab or placebo 2 weeks before initiating AIT using a rush titration protocol. Omalizumab or placebo was continued for 18 weeks. The addition of omalizumab to AIT improved control of both rhinoconjunctivitis and asthma during the first pollen season. One hundred and five patients (80.8%) continued treatment with AIT only during a 2-year extension phase of the study and were found to have no significant difference in mean daily symptom load, asthma control or disease-related quality of life scores between the initial omalizumab group and the initial placebo group during follow-up year 1 or 2, suggesting no prolonged effect of the addition of omalizumab.³⁷ There was a trend of more local reactions in patients in the AIT + placebo group compared to those in the AIT + omalizumab group (16.8% vs 12.3%), but this difference was not significant.^{36,37}

Casale et al³⁸ investigated omalizumab pre-treatment as an adjunct to rush immunotherapy with ragweed allergen. One hundred and fifty-nine adults with ragweed allergic rhinitis were enrolled in a 3 centre, 4-arm, randomized, double-blind, placebo-controlled trial. Patients received pre-treatment with omalizumab or placebo for 9 weeks, followed by 1-day rush immunotherapy with ragweed or placebo and then 12 weeks of AIT plus omalizumab or placebo. Those receiving combination therapy had significantly lower allergy severity scores compared to monotherapy alone ($P = .044$), as well as fewer adverse events during rush AIT ($P \leq .05$). A post hoc analysis showed that the addition of omalizumab to AIT resulted in a five-fold decrease in risk of anaphylaxis during rush AIT (OR, 0.17; $P = .026$).

TABLE 1 Omalizumab and inhalant allergen immunotherapy

Author, year	Study design	Subjects	Safety outcomes	Efficacy outcomes (Omalizumab + specific IT compared to specific IT alone)
Kuehr et al, 2002 (34)	DBPC, open grass or birch SIT	N = 221	Placebo group had significantly more IT injection site redness and swelling than the omalizumab group	Decreased symptom load by 48% over the 2 pollen seasons
Kamin et al, 2010 (35)		Age: 6-17 y Birch or grass pollen AR		Reduced symptom load in birch and grass season compared to relevant SIT alone
Kopp et al, 2009 (36)	DBPC, open SIT	N = 140 Age: 11-46 y AR and co-morbid asthma	Rate of adverse events similar both groups Increased local reactions in the placebo group	Reduced daily symptom load by 39% Improved control of rhinoconjunctivitis, asthma control and asthma quality of life
Kopp et al, 2012 (37)	DBPC, Extension phase with SIT only	N = 128 (year 2) N = 114 (year 3) (same as Kopp 2009)	No significant difference in reactions at IT injection site during extension phase	No difference in symptom load between former omalizumab group and former placebo group in a 2-y follow-up period of IT only
Casale et al, 2006 (38)	DBPC	N = 159 Age: mean 33.3 y Ragweed AR	Omalizumab + IT compared to IT alone: Fewer adverse events during rush IT Fivefold decreased risk of anaphylaxis during rush IT	Improvement in daily allergy severity scores during ragweed season
Massarani et al, 2010 (39)	DBPC	N = 248 Age: mean 38.2 y Cat, dog, and/or dust mite sensitization with persistent asthma	Omalizumab + IT (compared to IT alone): Decreased systemic allergic reactions within 1 h of an injection with IT Decreased reactions during cluster IT Decreased respiratory-related reactions during IT	Increased proportion of patients reaching target maintenance dose Decreased visits needed to achieve maintenance

DBPC, Double-blind, placebo-controlled.

Massarani et al³⁹ examined the effect of omalizumab pre-treatment on the tolerability of AIT in adults with asthma. This randomized, double-blind, placebo-controlled study evaluated 248 adults with symptomatic persistent asthma not adequately controlled with inhaled corticosteroids, and sensitization to dust mite, dog or cat. Patients received omalizumab or placebo for 16 weeks, followed by a 4-week cluster AIT regimen and then 7 weeks of weekly maintenance AIT. Treatment with omalizumab increased the number of patients reaching target maintenance AIT dose (omalizumab group: 87% vs placebo group: 72%) and decreased the number of visits required to achieve the target AIT dose ($P = .004$).³⁹ Overall, treatment was well tolerated. Patients receiving omalizumab had significantly fewer systemic allergic reactions compared to those receiving placebo (17/126 [13.5%] vs 32/122 [26.2%], $P = .006$), including fewer systemic reactions during cluster AIT ($P = .007$). In the week before starting cluster AIT, patients receiving omalizumab had a lower average total asthma symptom score (mean, 0.46 vs 0.69) and lower average daily puffs of rescue beta-agonist (mean, 0.45 vs 0.72, respectively) compared to patients on placebo and fewer patients in the omalizumab group had a respiratory reaction during AIT (placebo: 24/136 [17.6%], omalizumab: 6/139 [4.3%]).

3.1 | Summary and clinical implications of inhalant allergen immunotherapy + omalizumab

Studies to date indicate that the addition of omalizumab as an adjunct or as pre-treatment to AIT can have a greater reduction in AR symptom scores than AIT monotherapy and decreases, but does not eliminate, adverse events, including during rush or cluster protocols. While it is unlikely that omalizumab will be approved as a routine adjunctive treatment for inhalant AIT, this information may be applied to clinical practice for patients who have been prescribed omalizumab for asthma or urticaria. For example, while a patient with severe or unstable asthma may not be a suitable candidate for AIT, this could become a viable and important treatment option once treated with omalizumab.

4 | VENOM IMMUNOTHERAPY + OMALIZUMAB

The prevalence of systemic reactions to an insect sting ranges from 0.4% to 0.8% of children and 3% of adults in the United States,⁴⁰

and insect stings are thought to account for up to 20% of all cases of fatal anaphylaxis.^{24,41} Venom immunotherapy (IT) is effective for preventing systemic allergic reactions to an insect sting²² and is currently recommended for those who have experienced an anaphylactic reaction to an insect sting and have specific IgE to venom allergens.²⁴ Venom IT carries the risk of adverse events for all patients,^{22,24} but there is an increased risk of systemic reactions in patients with a honeybee allergy, elevated baseline serum tryptase or mastocytosis, prior history of a severe reaction to stings and those receiving rush escalation regimens.^{24,41,42} Hence, there has been great interest in finding a treatment regimen that minimizes systemic allergic reactions and improves tolerability of this therapy.

While there have been no randomized controlled trials evaluating the addition of omalizumab to venom IT, several case reports and small patient series have been published on the use of omalizumab with venom IT, using a variety of treatment protocols with regard to both venom IT and omalizumab dosing.⁴³⁻⁵⁰ While some case reports have not shown benefit,⁴⁹ most have suggested that the addition of pre-treatment and/or maintenance omalizumab decreased the risk of systemic reactions during venom IT in high-risk patients,^{46,47} including some individuals with mastocytosis.^{43,48,50}

5 | FOOD ALLERGEN IMMUNOTHERAPY + OMALIZUMAB

Food allergy is now estimated to affect up to 8% of children and 2% to 3% of adults in the United States.^{51,52} Current treatment options include avoidance and emergency medications for treatment of reactions. Effective therapies for food allergies are needed.²⁶ In the 1990s, subcutaneous immunotherapy for peanut allergy was attempted, but had an unacceptably high rate of systemic reactions.^{26,53,54} Subsequent approaches have therefore focused on different routes of delivery (oral, sublingual and epicutaneous) or modification of the allergens to reduce risk but still achieve desensitization.²⁷

Over the past decade, studies have demonstrated promising results for food oral immunotherapy (OIT).²⁷ Protocols vary widely, but most current OIT protocols begin with an initial oral food challenge (OFC), followed by an initial dose escalation day, build-up phase and then maintenance phase.^{25,27} OIT studies have shown effectiveness in desensitization for milk, egg, peanut and wheat.^{25,55-62} However, these studies also have high rates of adverse reactions, ranging from mild, local symptoms, such as oral itching, to severe systemic symptoms, such as anaphylaxis.²⁵⁻²⁷ About 10%-20% of subjects have dropped out of OIT trials due to adverse reactions, most commonly chronic abdominal pain.²⁵⁻²⁷

To mitigate the risks of OIT, there is great interest in developing safer approaches that will still induce desensitization. One approach is to use anti-IgE antibody.⁶³ In 2003, Leung et al published the first study to utilize an anti-IgE monoclonal antibody in food allergy. This randomized, double-blind, placebo-controlled, dose-ranging study showed that talizumab (TNX-901), a humanized

IgG1 monoclonal antibody against IgE similar to omalizumab, increased the threshold peanut dose required to provoke symptoms in patients with peanut allergy from 178 to 2805 mg.⁶⁴ TNX-901 was not further developed, but omalizumab has been studied both as monotherapy for food allergy^{65,66} and as an adjunct to oral immunotherapy, seeking to improve safety, efficacy or both.⁶⁷⁻⁷³ Of note, some of these trials have used open-label omalizumab with either open-label or placebo-controlled OIT, with the primary intent of studying the ability of omalizumab to enhance safety with more rapid OIT dose escalation, while others have used open-label OIT with the omalizumab component of the study being placebo-controlled (Table 2).

5.1 | Milk OIT + Omalizumab

A pilot study of 11 subjects with milk allergy examined the use of omalizumab in combination with OIT.⁶⁷ Subjects received 9 weeks of omalizumab, followed by rush oral desensitization (maximum dose of 1000 mg; cumulative dose of 1992 mg), and weekly dose escalation to a maximum of 2000 mg. At the end of week 16, omalizumab was stopped and milk OIT maintenance was continued. A double-blind, placebo-controlled food challenge (DBPCFC) was performed at week 24. Nine of the 11 subjects reached 1000 mg on the initial dose escalation day and 2000 mg by week 16. All 9 subjects who reached 2000 mg passed the DBPCFC to 3000 mg (cumulative dose of 7250 mg). Reactions occurred in 1.8% of all doses (mean of 3.7 reactions per child), but most were defined as mild (mild: 70%, moderate: 20%, severe: 10%). The study suggested that OIT can be escalated more rapidly with omalizumab as an adjunct, but that adverse reactions still occurred.

Wood et al conducted the first double-blind placebo-controlled trial of omalizumab with milk OIT.^{68,74} Fifty-seven subjects (age 7-32 years) were randomized 1:1 to omalizumab or placebo plus open-label milk OIT. After 4 months of omalizumab/placebo, milk OIT was started with initial dose escalation up to 2.1 mg, followed by dose build-up over 22-40 weeks and then maintenance dosing through month 28 (minimum dose of 520 mg of milk protein). At month 16, treatment was unblinded, placebo was stopped and omalizumab was continued for another year. At month 28, omalizumab was discontinued and all subjects underwent a DBPCFC to 10 g of milk protein. Those passing the OFC continued milk OIT for 8 weeks. Milk OIT was then stopped and 8 weeks later, they had a 10-g OFC to evaluate sustained unresponsiveness (SU). The study found no significant differences in any measure of efficacy. About 88.9% of the omalizumab-treated patients and 71.4% of the placebo-treated patients passed the 10 g "desensitization" OFC ($P = .18$), and SU was seen in 48.1% of the omalizumab group and 35.7% of the placebo group ($P = .42$). However, the omalizumab group required significantly less time (median, 25.9 vs 30 weeks, $P = .01$) and milk OIT doses (median, 198 vs 225, $P = .008$), to achieve maintenance, and had significant reductions in adverse reactions, including the percentage of doses with symptoms (2.1% vs 16.1%, $P = .005$) and dose-related reactions requiring treatment (0% vs 3.8%, $P = .0008$). It was

TABLE 2 Omalizumab and food immunotherapy

Author, year	Study design	Subjects	Safety outcomes	Efficacy outcomes
Milk				
Nadeau et al, 2011 (67)	Phase 1 Pilot study	N = 11 Age: 7-17 y	Adverse reactions: 1.8% of all doses (70% mild, 20% moderate, 10% severe) 3.7 reactions/child	Desensitization: 9/11 (82%) subjects reached goal 2000 mg by week 16 & passed OFC to 3000 mg (8 wk after stopping omalizumab)
Wood et al, 2016 (68)	DBP, open-label milk OIT	N = 57 Age: 7-32 y	Omalizumab group vs milk OIT alone: Decreased adverse reactions Decreased doses with symptoms Decreased dose related reactions requiring treatment	Desensitization: No significant difference in groups SU: No significant difference Omalizumab group required less time to achieve maintenance
Peanut				
Schneider et al, 2013 (70)	Open-label pilot study	N = 13 Age: 8-16 y	Adverse reactions: 2% of doses (87.5% were mild) No severe reactions occurred while receiving omalizumab	Desensitization: 12/13 (92%) patients reached 4000 mg maintenance dose in 8 wk and passed OFC to 8000 mg
MacGinnitie et al, 2017 (71)	DBPC	N = 37 Age: 6-19 y	Adverse reactions: No significant difference between groups Three subjects (2 omalizumab; one placebo) had persistent GI symptoms and withdrew (2 omalizumab group; 2 placebo-group)	79% of omalizumab group tolerated 2000 mg of peanut 6 wk after stopping omalizumab compared to 12.5% of placebo group 76% of omalizumab group tolerated 4000 mg peanut 12 wk after stopping omalizumab, compared to 12.5% in placebo group Higher median peanut dose tolerated on the initial DE day in the omalizumab group
Multi-food				
Begin et al, 2014 (73)	Open-label phase 1	N = 25 Age: 4-15 y	Adverse reactions: 94% of all reactions were mild 52% of patients had a reaction on DE day 5.3% of home doses triggered reaction	19/25 (76%) reached 1250 mg of each food on DE day Median time to maintenance dose of 4000 mg: 18 wk All reached a 10-fold increase in dose of all their allergens by 2 mo of therapy

DE, dose escalation; SU, sustained unresponsiveness.

concluded that the use of omalizumab in conjunction with milk OIT improved safety, but not efficacy.

In a small study of children who had not previously tolerated conventional milk or egg OIT, Martorell-Calataud et al⁶⁹ treated 9 patients with egg allergy and 5 patients with milk allergy with omalizumab before re-instilling OIT. While 100% were successfully desensitized with omalizumab, 3/5 (60%) on milk OIT and 3/9 (33%) on egg OIT had increased reactivity after cessation of omalizumab.

5.2 | Peanut OIT + Omalizumab

Thirteen peanut allergic children (age 8-16 years) participated in an open-label pilot study of omalizumab plus peanut OIT.⁷⁰ All participants received omalizumab (weeks 0-12), followed by a 1-day rush oral desensitization of up to 500 mg peanut flour (cumulative dose of 992 mg). Dose increases up to 4000 mg peanut flour continued over weeks 12-20. At week 20, omalizumab was discontinued and

peanut OIT continued. Twelve weeks after stopping omalizumab, subjects had a DBPCFC to a cumulative dose of 8000 mg of peanut. All subjects reached the 500 mg dose on the dose escalation day. One subject withdrew at week 15 due to persistent nausea and vomiting. The remaining 12 subjects reached the 4000 mg peanut OIT dose, in a median of 8 weeks and passed an OFC to a cumulative dose of 8000 mg of peanut flour. Reactions occurred with 2% of peanut OIT doses. The majority of reactions were mild (87.5%) and occurred during weekly dose escalation (65%). Seventeen of 72 reactions (24%) occurred during the maintenance phase, following discontinuation of omalizumab (59% mild, 29% moderate and 12% severe). No severe reactions occurred while on omalizumab.

MacGinnitie et al⁷¹ published the first randomized, double-blind, placebo-controlled, multi-centre study of the efficacy of omalizumab as an adjunct to peanut OIT. Thirty-seven patients (age 7-19 years) were randomized 3.5:1 to omalizumab or placebo. After 12 weeks of treatment with omalizumab or placebo, patients participated in a rapid

1-day oral desensitization of up to 250 mg peanut protein, followed by weekly dose increases up to 2000 mg. Subjects tolerating 2000 mg of peanut protein had an open challenge to 4000 mg of peanut protein 12 weeks after their last dose of omalizumab or placebo. If they passed the challenge, they continued on 4000 mg of peanut protein daily. The median peanut dose tolerated on the initial desensitization day was >10 times higher for the omalizumab treated group compared to the placebo group (omalizumab group: 250 mg; placebo group: 22.5 mg, $P = .00027$). About 79% (23/29) of those in the omalizumab group tolerated 2000 mg of peanut 6 weeks after stopping omalizumab compared to 12.5% (1/8) of those in the placebo group ($P < .01$). Similarly, 12 weeks after stopping omalizumab, 76% (23/29) of patients in the omalizumab group passed the 4000-mg peanut food challenge, compared to 12.5% (1/8) in the placebo group ($P = .002$). There was no significant difference in adverse reactions between groups, despite the omalizumab group receiving higher peanut doses (OR, 0.57; $P = .15$). Three subjects had persistent gastrointestinal symptoms consistent with eosinophilic esophagitis and withdrew from the study (2 were omalizumab-treated, 1 placebo-treated). The authors concluded that omalizumab improves safety and tolerability of rapid peanut OIT up dosing and that in most cases, desensitization is maintained once omalizumab is discontinued.

5.3 | Egg OIT + Omalizumab

There are no clinical trials evaluating the addition of omalizumab to egg OIT. Lafuente et al⁷² published a case series of 3 egg allergic children who had possible recurrence of symptoms after discontinuation of omalizumab in egg OIT. Two of the three patients failed an initial attempt at egg OIT without omalizumab. Patient 3 did not attempt egg OIT without omalizumab. All 3 patients received omalizumab and then tolerated egg OIT (up to 50 mL of raw egg white). Omalizumab was discontinued and 3-4 months later, the patients developed symptoms when eating a previously tolerated dose of egg. Omalizumab was re-started. Two of the patients underwent a repeat challenge and tolerated one whole egg omelette 2 months after re-starting omalizumab.

5.4 | Multi-food OIT + Omalizumab

At least 30% of food allergic children have clinical reactivity to more than one food.⁵¹ Hence, there is interest in treating multiple food allergies simultaneously.²⁶ Begin et al⁷³ conducted an open-label, phase 1 study of rush OIT plus pre-treatment with omalizumab. 25 patients (age 4-15 years) received 8 weeks of omalizumab, followed by rapid oral desensitization to up to 5 food allergens (up to 1250 mg total; 250 mg of each food protein) and then bi-monthly dose escalation. About 76% (19/25) of patients were able to reach the full 1250 mg of food protein total on the initial dose escalation day. The median time to reach maintenance dose (4000 mg per allergen) was 18 weeks (7-36 weeks). About 94% of all reactions were mild. About 52% of patients experienced a reaction on the initial dose escalation day, but all were mild. About 5.3% of home doses

caused a reaction, most occurring in the first few months of treatment. This was the first study to demonstrate that multi-food OIT using omalizumab appears to be well tolerated and decreases the time needed to reach maintenance. Numerous other studies of multi-food OIT, and omalizumab are ongoing at this time.

5.5 | Summary and clinical implications of omalizumab and food allergy

To date, the use of omalizumab with food OIT has been examined by small pilot studies, 2 small double-blind placebo-controlled trials and case reports. These studies indicate that the addition of omalizumab to OIT can decrease both the time required to reach maintenance dosing and adverse events. Additional research could lead to an indication for the use of omalizumab with OIT, especially if pre-treatment biomarkers could be developed to best identify those patients who would benefit the most from the addition of omalizumab to OIT.

6 | DISCUSSION

The use of omalizumab as an adjunct to immunotherapy has been utilized in the treatment of asthma, allergic rhinitis, venom hypersensitivity and food allergy. Studies to date indicate that omalizumab can markedly decrease the time required to reach AIT maintenance dosing and decreases, but does not eliminate, adverse events. However, larger, randomized, controlled trials are still needed to better understand both safety and efficacy. With these larger trials, it might also be possible to better identify those patients who would benefit most from the addition of omalizumab to AIT, especially for food allergy, including both clinical history and specific biomarkers.

It is also important to recognize that the optimal dosing and duration of omalizumab to use with immunotherapy is unknown. Most studies determined the omalizumab dose based on the guidelines for asthma,^{34-36,38,39,46,49,66,69,70,72,73} while others used a modified regimen.^{43,44,48,67,68,71} With regard to duration, many studies added omalizumab only as pre-treatment, with initiation weeks to months prior to AIT. Others have continued the combination therapy through maintenance. Given the cost of this medication, it is crucial to determine the optimal treatment duration in order to maximize effect and minimize cost. No studies to date have been of sufficient size to conduct accurate cost-benefit analyses as have been carried out with asthma, and further research regarding this topic is clearly needed.

In addition to cost, another limitation with the use of omalizumab relates to the exclusion of many patients based on weight and/or total serum IgE.^{34,36,38,64,66,68,70,71} Many of the studies to date do not specify how many potential subjects were excluded based on this criteria, but there is no doubt it could have a significant impact, potentially even having its greatest affect the most highly allergic patients who could theoretically benefit most. As an example, in the study of omalizumab combined with milk OIT, Wood et al⁶⁸ reported that 262 patients were assessed for eligibility and

19 were excluded due to IgE level, even though this study used a modified dosing table allowing total IgE levels as high as 1300 IU/mL. When asthma is considered, both weight and IgE can have a significant effect on patient eligibility, as was demonstrated in the ICATA study, a randomized trial of omalizumab for asthma in inner-city children.⁷⁵ In this study, 273 patients (47% of those screened) were excluded because the subject's weight and/or IgE level were outside omalizumab dosing recommendations.

In summary, immunotherapy has been successfully used for the treatment of asthma, allergic rhinitis, venom hypersensitivity and food allergy; however, safety and time to maintenance have limited its use in some patients. Over the past 15 years, studies of omalizumab used in conjunction with immunotherapy have shown promising results. At this stage, larger, randomized, placebo-controlled trials are needed to better identify those patients who would benefit most from the addition of omalizumab to immunotherapy, as well as optimal dosing strategies and duration of treatment.

CONFLICT OF INTEREST

Robert Wood has received research support from the National Institutes of Health, DBV, Astellas, HAL-Allergy and Aimmune. Jennifer Dantzer has nothing to declare.

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