



Update on omalizumab in allergen immunotherapy

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Purpose of review

To review the most relevant studies in the advancing field of omalizumab in allergen immunotherapy.

Recent findings

Omalizumab has been used in combination with inhalant, venom, and food allergen immunotherapy. These studies suggest that omalizumab can decrease the time required to reach maintenance dosing and adverse events. However, severe adverse events do still occur. Limited long-term data suggests that there is a risk for increased reactivity after stopping omalizumab.

Summary

Omalizumab in conjunction with immunotherapy has shown promising results for the treatment of allergic rhinitis, venom hypersensitivity, and food allergy, especially in the reduction of adverse events. Larger randomized, placebo-controlled trials are needed to better understand optimal dosing and duration, cost–benefit analysis, ideal patients, and long-term benefits. This combination therapy has the potential to improve treatment, particularly for high-risk patients.

Keywords

allergic rhinitis, anti-IgE, food allergy, immunotherapy, omalizumab

INTRODUCTION

Atopic conditions, including asthma, atopic dermatitis, hay fever, and food allergy, are among the most common chronic conditions in children that often persist into adulthood [1–3]. These atopic conditions can have a significant impact on families and society, including impaired quality of life and increased direct and indirect costs [4^a,5–6]. Management can include avoidance of known triggers, pharmacotherapy, and immunomodulatory therapies.

Allergen immunotherapy (AIT) involves the administration of gradually increasing doses of allergenic proteins at repeated intervals with the goal of inducing desensitization [7]. This treatment has the advantage of causing immunologic changes that can lead to long-term benefits, even when therapy has stopped, which makes this therapy attractive to many patients [8,9]. Various routes of administration have been explored for the various conditions. AIT has become an effective treatment for allergic rhinitis, asthma, and venom hypersensitivity [7,8,10–14] and is an emerging treatment option for food allergy [15^a,16–18,19^a]. The use of AIT has been limited by potential adverse reactions [7,10,20–22] and poor adherence because of cost and inconvenience [23–25]. For that reason, there is a need to develop safer approaches that will mitigate the risks and/or reduce the time to desensitization.

Omalizumab (Novartis, Basel, Switzerland) is a humanized monoclonal antibody that binds to the CH3 domain of the Fc portion of IgE and prevents IgE from binding to the high-affinity IgE receptor FcεRI [26,27]. Omalizumab:IgE complexes are formed, which leads to a significant decrease in free IgE, inhibition of the IgE allergic pathway and down-regulation of FcεRI receptors on basophils and mast cells [28,29]. In 2003, omalizumab was approved for the treatment of severe asthma in adolescents and adults. To date, labelling has been expanded to chronic idiopathic urticaria, nasal polyps, and asthma in children down to the age of 6 years [30]. Over the past decade, omalizumab has also been studied as an off-label treatment for numerous diseases in which IgE may have a role, such as food allergy, rhinitis, and anaphylaxis [15^a,31–33]. Here we will review recent studies that have examined the potential benefit of omalizumab in improving the safety and efficacy of

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KEY POINTS

- Omalizumab combined with inhalant SCIT, VIT, or food allergen OIT can decrease time to reach maintenance dosing and dosing-related adverse events.
- There may be an increased risk of reactions or loss of tolerance after stopping omalizumab.
- Additional studies are needed to determine the optimal dose and duration of treatment, identify patients who would benefit most, and understand long-term safety and efficacy outcomes.

AIT for food allergy, allergic rhinitis, and venom hypersensitivity.

FOOD ALLERGEN IMMUNOTHERAPY WITH OMALIZUMAB

Food allergies have become a significant public health burden and affect up to 8% of children and 2–3% of adults in the United States [19[■],34,35]. Many persist or have low rates of resolution [34]. Current standard of care includes avoidance and emergency medications for treatment of acute reactions, which has limitations. Hence, effective and well tolerated therapies for food allergies are needed [21]. Over the past several decades, a substantial amount of research has focused on several forms of food immunotherapy [36]. In the 1990s, subcutaneous immunotherapy (SCIT) was attempted but injections lead to repeated systemic reactions in most patients [37,38]. Hence, subsequent approaches have utilized different routes of delivery (oral, sublingual, and epicutaneous) [15[■],39]. Studies have shown promising results for oral immunotherapy (OIT) with the ability to raise the threshold of reactivity; however, there are high rates of reactions ranging from mild to severe anaphylaxis that can occur during any phase of treatment [40,41]. In January 2020, the first treatment for peanut allergy was approved by the Food and Drug Administration (peanut OIT) [42]. Although this is encouraging, individuals must continue to avoid peanut and life-threatening reactions are still possible to larger amounts of peanut and the treatment itself. So, although immunotherapy has become an established treatment for inhalant and venom allergy, it has yet to become the routine management of food allergy [40]. There is great interest in developing safer approaches that will decrease the risks and/or reduce the time to desensitization. Newer approaches have attempted to modify the allergen and/or utilized an immunomodulatory agent, with the most studied being anti-IgE [15[■],39].

In 2003, Leung *et al.* [43] completed the first trial to utilize an anti-IgE monoclonal antibody (TNX-901, talizumab) as treatment for food allergy. This randomized, double-blind, placebo-controlled (DBPC) study showed that TNX-901 increased the peanut dose required to cause symptoms from 178 to 2805 mg. This drug was not further developed but remains an important proof of principle study. Omalizumab has since been studied as monotherapy [44] and as an adjunct to food allergen OIT [45–50[■],51,52[■],53–55,56[■],57[■]]. These trials have varied in study design (open label vs. DBPC), OIT dosing, and omalizumab dosing and duration. To date, clinical trials have primarily focused on milk, peanut, and multiallergen OIT [58[■]]. Here, we will review key studies that have examined the potential benefit of omalizumab in improving safety and efficacy of food allergen OIT (Table 1).

MILK

In 2011, an initial pilot study of 11 patients receiving 9 weeks of omalizumab followed by rush milk OIT showed that 9 of 11 (82%) could reach 1000 mg on initial dose escalation (IDE) and 2000 mg by week 16 and then passed a DBPCFC to 7250 mg of milk [45]. This study suggested that the addition of omalizumab to OIT allowed a more rapid dose escalation but that reactions did still occur with 1.8% of doses.

Wood *et al.* [46,59] conducted the first double-blind placebo-controlled trial of omalizumab with milk OIT. Fifty-seven patients (age 7–32 years) were randomized 1:1 to open-label milk OIT with omalizumab or placebo. After 4 months of omalizumab/placebo, patients were treated with milk OIT for 24 months (minimum maintenance dose of 520 mg of milk protein). This study found that the addition of omalizumab reduced dose-related symptoms (2.1 vs. 16.1%, $P = 0.005$) and dose-related reactions requiring treatment (0 vs. 3.8%, $P < 0.001$). In addition, the omalizumab group required less time to reach maintenance (median: 25.9 vs. 30 weeks, $P = 0.01$). However, there were neither significant differences between groups on final effectiveness of OIT as determined by the 10 g OFC at month 28 (89 vs. 71%, $P = 0.018$) nor the 10 g sustained responsiveness OFC at month 32 (48 vs. 36%, $P = 0.42$).

Two smaller studies have evaluated the safety and efficacy of omalizumab with milk OIT and found that the addition of omalizumab appeared to increase the tolerated dose but adverse reactions did still occur [47,48]. However, in one study, three of five (60%) on milk OIT and three of nine (33%) on egg OIT had increased reactivity after stopping omalizumab [48].

Table 1. Milk, peanut, and multifoed immunotherapy combined with omalizumab

Author, year [ref]	Study design	Participants	Omalizumab dosing	Goal OIT maintenance dose	Efficacy outcomes	Safety outcomes
Milk						
Nadeau <i>et al.</i> , 2011 [45]	Phase 1 pilot study	N: 11 Age: 7–17 years	Started 9 weeks prior to OIT and continued for 16 weeks (end of weekly dose escalation)	2000 mg	Nine of 11 reached 2000 mg, passed DBPCFC to 7250 mg 8 weeks after stopping OMB, and continued daily milk ingestion >8 g/day	Reactions with 1.8% of doses (mild: 1.3%, moderate: 0.3%; severe: 0.1%) Two received epinephrine at home during maintenance Compared with placebo group, the OMB-OIT group had decreased: Adverse reactions, Doses with symptoms, Dosing reactions requiring treatment
Wood <i>et al.</i> , 2016 [46,59]	DBPC, open-label milk OIT	N: 57 Age: 7–32 years	Started 4 months prior to OIT and continued for 28 months	Goal: 3.8 g Minimum: 520 mg milk protein	No significant difference in groups in passing 10g OFC at 28 months or the 10g SU OFC at 32 months. - OMB-OIT group required fewer weeks to reach maintenance	Build-up while on OMB was well tolerated Six patients had anaphylactic symptoms 2.5 to 4 months after stopping OMB No serious adverse events -0.012 AEs per dose per child during build-up and 0.028 during maintenance
Martorelli-Calatayud <i>et al.</i> , 2016 [48]	Case series	N: 14 [5 milk allergic, 9 egg allergic] Age: 3–13 years	Started 9 weeks prior to OIT and stopped 2 months after reaching the final dose of build-up	Milk: 6.6 g protein (200 ml CM) Egg: 1.8 g egg protein (1.5 ml liquid raw egg white)	All reached goal OIT dose Six patients (43%) had decreased tolerance after stopping OMB (one dropped out)	Build-up while on OMB was well tolerated Six patients had anaphylactic symptoms 2.5 to 4 months after stopping OMB No serious adverse events -0.012 AEs per dose per child during build-up and 0.028 during maintenance
Takahashi <i>et al.</i> , 2017 [47]	RCT OMB-OIT vs. untreated	N: 16 Age: 6–14 years	Started 8 weeks prior to OIT and discontinued week 24	200 ml fresh CM	During CM-OFC at week 32, OM-OIT group had higher median tolerated dose compared with untreated (2080 vs. 0 mg)	Build-up while on OMB was well tolerated Six patients had anaphylactic symptoms 2.5 to 4 months after stopping OMB No serious adverse events -0.012 AEs per dose per child during build-up and 0.028 during maintenance
Peanut						
Schneider <i>et al.</i> , 2013 [49] Yee <i>et al.</i> , 2019 [50▪▪]	Pilot study, open-label Long-term follow-up	N: 13 Age: 8–16 years	Started 12 weeks prior to OIT. Stopped at week 20 (end of build-up)	4000 Yee mg peanut flour	Twelve of 13 reached goal maintenance dose and passed OFC to 8 g peanut flour at week 32. Seven of 12 continued peanut OIT at month 72	Reactions with 2% of doses (88% mild) Build-up: 49 reactions, 96% mild; 4% moderate Maintenance (off OMB): 17 reactions (59% mild, 29% moderate, 12% severe) LTFU: all had at least one AE (most mild, but 5% treated with epinephrine) - One person diagnosed with EoE

Table 1 (Continued)

Author, year [ref]	Study design	Participants	Omalizumab dosing	Goal OIT maintenance dose	Efficacy outcomes	Safety outcomes
Brandström <i>et al.</i> , 2019 [51,52 [■]]	Open-label phase 2 trial	N: 23 Age: 12–19 years	Started 8–12 weeks prior to OIT. Dose reduced and then stopped based on symptoms and CD-sens	2800 mg of peanut protein	All reached goal maintenance dose Nine of 23 (39%) passed on open OFC with 2800 mg 12 weeks after stopping OMB	-Mild OP and GI reactions were common Forty-three systemic reactions (0.3% of doses; 20 mild, 22 moderate, 1 severe) Four occurred while on full dose OMB One person diagnosed with EoE
MacGinnitie <i>et al.</i> , 2017 [53]	DBPC, open-label peanut OIT	N: 37 Age: 7–19 years	Started 12 weeks prior to OIT. Stopped week 19–25 depending on OIT dose.	2000 mg of peanut protein	Compared with placebo, OMB-OIT group: Higher median peanut dose tolerate on IDE Higher proportion tolerated 2 g of peanut 6 weeks after stopping OMB and 4 g of peanut 12 weeks after stopping OMB	Three subjects (2 OMB; one placebo) had persistent GI symptoms and withdrew (2/3 biopsies-proven EoE) No significant difference between groups in AE
Multifood Bégin <i>et al.</i> , 2014 [54]	Phase 1 open label	N: 25 Age: 4–15 years	Started 8 weeks prior to OIT. Stopped 8 weeks after IDE	4000 mg protein of each allergen (up to five allergens)	Nineteen of 25 (76%) reached max of 1250 mg of protein on IDE Median time of 18 weeks to reach maintenance All tolerated a 10-fold increase of all their allergens by 2 months of OIT	94% of reactions were mild. One severe reaction. Median home dosing reaction rate of 3.2 per 100 doses
Andorf <i>et al.</i> , 2018 [55]	Phase 2 DBPC, open-label OIT	N: 48 Age: 4–15 years	Started 8 weeks prior to OIT and stopped at week 16.	2000 mg protein of each allergen (up to 5 allergens)	Compared with placebo, OMB group: - Greater proportion passed DBPCFC to 2g protein for ≥2 foods (83% vs. 33%) & ≥4 foods (77% vs. 0%) - Less time required to achieve maintenance (HR: 5.35) - Greater median tolerated dose on IDE	- No serious or severe AEs - Lower rate of dosing-related AEs while receiving OMB-OIT compared with placebo-OIT - No increase in AEs during period of OMB withdrawal

CM, cow's milk; EoE, eosinophilic esophagitis; GI, gastrointestinal; IDE, initial dose escalation; ITFU, long-term follow-up; OFC, oral food challenge; OMB, omalizumab; OP, oropharyngeal; SU, sustained unresponsiveness.

PEANUT

Several studies have explored the effect of omalizumab on peanut OIT (Table 1). A pilot study in 13 peanut allergic children utilized omalizumab as pretreatment for 12 weeks, followed by a 1-day rush IDE and then build-up OIT over weeks 12–20 [49]. At week 20, omalizumab was stopped and peanut OIT continued. This study showed that all could reach the goal 500 mg dose on IDE and 12 of 13 (92%) tolerated 8 g 12 weeks after stopping omalizumab. Reactions did occur, mostly mild but with two severe reactions after stopping omalizumab. An extended follow-up showed that 7 of 13 (54%) were consuming dietary peanut at month 72 [50^{***}].

Brandström *et al.* [51,52^{***}] used a novel approach to omalizumab dosing in a one-armed phase 2 trial of peanut OIT facilitated by individually dosed omalizumab. Omalizumab dosing was determined by basophil allergen threshold sensitivity (CD-sens) and symptoms. All reached the maintenance dose of 2800 mg of peanut protein, but only 9 of 23 (39%) were able to tolerate this dose 12 weeks after stopping omalizumab. Mild reactions were common and systemic reactions occurred with 0.3% of doses (with 91% occurring after full-dose omalizumab was stopped). After omalizumab was stopped, symptoms returned in 50% of patients with six individuals unable to stop omalizumab and six dropping out. In addition, one patient developed biopsy-proven eosinophilic esophagitis (EoE).

The PRROTECT study (Peanut Reactivity Reduced by Oral Tolerance in an Anti-IgE Clinical Trial) was the first randomized, DBPC multicenter study of the efficacy of peanut OIT combined with omalizumab [53]. Those receiving omalizumab were able to tolerate more than 10 times the protein dose during IDE compared with the placebo group (250 vs. 22.5 mg, $P < 0.01$). In addition, the omalizumab group was more likely to tolerate the target dose of 2000 mg of peanut protein 6 weeks after stopping omalizumab or placebo [omalizumab group: 23/29 (79%) vs. placebo: 1/8 (12.5%); $P < 0.01$] and 4000 mg 12 weeks after stopping [omalizumab group: 22/29 (76%) vs. placebo group: 1/8 (12.5%); $P < 0.01$]. Most reactions were mild but moderate and severe reactions did still occur in both groups. Also, two individuals developed biopsy-proven EoE.

MULTIFOOD

The use of omalizumab may have the greatest use in patients who are multifoody allergic. The first study of multifoody OIT combined with omalizumab was examined in a phase 1 trial of rush OIT in children [54]. Participants completed rush OIT to peanut and up to four other food allergens. Approximately half

had some symptoms during IDE, but 19 of 25 (76%) were able to tolerate the maximum dose of 1250 mg of total food protein. All tolerated a 10-fold increase of all of their allergens by 2 months of OIT. Reactions still occurred but 94% were mild.

Andorf *et al.* [55] conducted a DBPC, phase 2 trial in which children were randomized to multifoody OIT with two to five foods combined with omalizumab ($n = 36$) or placebo ($n = 12$). The omalizumab group tolerated a higher median dose on IDE and reached maintenance faster than the placebo group. In addition, a higher proportion of the omalizumab group passed the DBPCFC to at least 2 of their offending foods (83 vs. 33%; $P = 0.004$). Compared with placebo, the omalizumab group had fewer OIT dose-related reactions with no increase in adverse events during omalizumab withdrawal. In a follow-up study, authors concluded that sustained desensitization after omalizumab-assisted OIT is best maintained with continued maintenance OIT dosing (either 300 or 1 vs. 0 mg) [56^{*}].

SUMMARY OF FOOD ALLERGEN OIT WITH OMALIZUMAB

This has been an expanding area of research over the past two decades with several studies currently active (Table 2). To date, studies of food allergen OIT combined with omalizumab indicate that combination therapy can accelerate the build-up phase and decrease adverse events with a possible improvement in efficacy. However, many points need to be clarified. Additional research is needed on the optimal omalizumab dosing. A recent study indicated that in food allergy OIT, omalizumab should be adjusted for weight alone and not weight and IgE as done in most studies [57^{***}]. Finally, more research is needed to understand if combination therapy improves long-term outcomes.

INHALANT ALLERGEN IMMUNOTHERAPY WITH OMALIZUMAB

Subcutaneous allergen immunotherapy (SCIT) was first introduced over 100 years ago [60] and has been used to treat allergic rhinitis and asthma [7,10,11]. Although this treatment can be efficacious, patients typically do not get relief until months after the start of therapy. In addition, benefits must be weighed against the risks of systemic reactions (0.1–0.2%) and rarely fatal anaphylaxis [61–63], with the degree of severity being impacted by the administration protocol (rush, cluster), individual susceptibility, and features of the extracts [63–65]. For this reason, various clinical trials have examined the use of omalizumab with SCIT to improve symptoms,

Table 2. Oral immunotherapy and omalizumab trials in process

Study	Allergen	Purpose
E-B-FAHF-2, Multi-OIT and Xolair (Omalizumab) for Food Allergy NCT02879006	Multifood	Examine the use of E-B-FAHF-2 Chinese herbal therapy in combination with multifood OIT and omalizumab to help children and adults achieve desensitization and sustained unresponsiveness to food allergens
Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Participants (OUMATCH) NCT03881696	Multifood	Phase 3 DBPC multisite study that aims to determine the safety and efficacy of omalizumab alone or in combination with multiallergen OIT (peanut with two other foods)
Omalizumab to Accelerate a Symptom-driven Multifood OIT (BOOM) NCT04045301	Multifood	Phase 2b, multicenter randomized controlled trial comparing two doses of omalizumab to placebo in subjects with multiple food allergies undergoing multifood OIT
Clinical Study Using Biologics to Improve Multi OIT Outcomes NCT03679676	Multifood	Phase 2, single-center, multiallergen OIT study in participants with allergies to peanut with one to two additional foods that will compare efficacy of omalizumab vs. placebo or dupilumab plus OIT

OIT, oral immunotherapy.

decrease time to maintenance, and enhance safety in high-risk patients (Table 3) [66–72].

The first clinical trial to investigate the effect of anti-IgE with specific AIT was conducted more than 10 years ago by Kuehr *et al.* [67]. In this randomized DBPC, multisite study, 221 patients, age 6–17 years, with birch and grass pollen-induced seasonal allergic rhinitis were randomized to one of four treatments. After 14 weeks of birch or grass pollen SCIT, each group was randomized to receive placebo or omalizumab for 24 weeks. Treatment with SCIT with omalizumab reduced symptom load by 48% over the two pollen seasons (birch and grass) compared with SCIT alone ($P < 0.001$). Combination treatment also reduced symptom severity, the need for rescue medication, and days with allergy symptoms compared with SCIT alone ($P < 0.001$). An additional safety analysis found that patients in the omalizumab group had less SCIT injection site redness and swelling than those in the placebo group ($P \leq 0.05$) [68].

Omalizumab has also been studied as pretreatment to SCIT [69–73]. Kopp *et al.* [69] studied SCIT (Depigoid; Laboratorios LETI SI, Tres Cantos, Spain) with omalizumab in adolescents and adults with grass pollen allergic rhinitis and asthma. In this randomized, DBPC trial, 140 patients received placebo or omalizumab for 2 weeks and then initiated SCIT using a rush protocol. Omalizumab or placebo was continued for 18 weeks. Combination therapy reduced daily symptom load by 39%, improved control of rhinoconjunctivitis, asthma control, and asthma quality of life but no significant

difference in local reactions. An extension phase of the study found that these effects were limited to the combined treatment period [70].

Casale *et al.* [71] enrolled 159 adults with ragweed allergy in a three-center, four-arm, randomized, DBPC trial. Patients received 9 weeks of pretreatment with omalizumab or placebo, followed by 1 day rush up dosing protocol of ragweed SCIT and then 12 weeks of SCIT with omalizumab or placebo. Combination therapy had significantly lower allergy severity scores compared with monotherapy alone and fewer adverse events during rush AIT. A post hoc analysis found that the addition of omalizumab resulted in a five-fold decrease in risk of anaphylaxis caused by ragweed SCIT (SCIT alone: 25.6% vs. SCIT with omalizumab: 5.6%; $P = 0.03$). The authors also found that *in vitro*, the combination of ragweed SCIT and omalizumab lead to prolonged inhibition of allergen-IgE binding compared with either treatment alone [73].

Massanari *et al.* [72] conducted first study to evaluate the efficacy of omalizumab in improving the safety and tolerability of SCIT in a high-risk population of adults with persistent asthma whose symptoms were not adequately controlled with inhaled corticosteroids. In this DBPC trial, patients received SCIT (cluster build-up) after premedication with omalizumab or placebo [72]. More patients reached the target maintenance SCIT dose in the omalizumab group compared with placebo (87 vs. 72%; $P = 0.004$). The addition of omalizumab decreased the number of visits required to achieve the target SCIT dose ($P = 0.004$). The systemic

Table 3. Inhalant allergen immunotherapy combined with omalizumab

Author, year [ref]	Study design	Participants	Omalizumab dosing	Efficacy outcomes (Omalizumab with SCIT compared to SCIT alone)	Safety outcomes
Kuehr <i>et al.</i> , 2002 [67] Kamin <i>et al.</i> , 2010 [68]	DBPC, open grass or birch SCIT (four treatment arms)	N = 221 Age: 6–17 years Birch or grass pollen AR	Started after 12 weeks of SCIT and continued for 24 weeks	Decreased symptom load by 48% over birch and grass seasons - When analyzed by season, OMB-relevant SCIT and OMB alone both had a greater reduction in symptom load compared with season relevant SCIT alone	- Fewer SCIT injection site redness and swelling
Kopp <i>et al.</i> , 2009 [69] 2013 [70]	DBPC, open SCIT Extension phase with SCIT alone	N = 140 Age: 11–46 years AR and asthma	Started 2 weeks prior to SCIT initiation and continued for 18 weeks	Reduced daily symptom load by 36% - Improved rhinoconjunctivitis, asthma, and asthma quality of life - No difference in symptom load between groups in 2-year follow-up period of SCIT alone	Similar rate of adverse events Increased local reactions in the placebo group No significant difference in SCIT injection site reactions during follow-up.
Casale <i>et al.</i> , 2006 [71]	DBPC, four-arm (placebo or OMB combined with IT or placebo IT)	N = 159 Age: mean: 33 years Ragweed AR	Started 9 weeks prior to SCIT initiation and continued for a total of 21 weeks	ITT analysis showed improvement in daily allergy severity scores during ragweed season ($P = 0.044$)	Decrease rate of adverse events in OMB-SCIT compared with those receiving SCIT alone (33 vs. 56%). Five-fold decrease in risk of anaphylaxis caused by rush IT
Massanari <i>et al.</i> , 2010 [72]	DBPC, open label SCIT	N = 248 Age: mean 38.2 years Persistent asthma + cat, dog, and/or HDM allergy	Started 13 weeks prior to SCIT initiation with 3 weeks of cluster SCIT with OMB or placebo overlap	Increased proportion of patients reaching target SCIT maintenance dose Decreased visits need to reach SCIT target dose	Decreased systemic reactions but not completely protective (13.5% of OMB group experienced a SAR). Decreased need for rescue medication during SCIT Similar rate of local reactions
Lambert <i>et al.</i> , 2014 [74]	Open-label case series	N = 6 Age: 11–21 years Severe persistent asthma with HDM allergy	Initiated prior to SCIT to improve asthma control. After median of 8 months, SCIT to HDM was started. OMB discontinuation varied (median: 8 months)	Used cluster SCIT to reach maintenance dose in 4 days - Asthma control improved in five of six patients able to continue OMB with SCIT	Five of six patients had no severe side effects of SCIT One of six discontinued SCIT because of uncontrolled asthma SCIT tolerated even after OMB was discontinued

AR, allergic rhinitis; DBPC, double-blind, placebo-controlled; IT, intent to treat; OMB, omalizumab; SCIT, subcutaneous immunotherapy.

reaction rate was reduced from 26.2% in the placebo with SCIT group to 13.5% in the omalizumab with SCIT group ($P=0.006$), including fewer systemic reactions during cluster SCIT ($P=0.017$).

More recently, Lambert *et al.* [74] used omalizumab to induce asthma control in six patients (aged 11–21 years) with severe asthma and then initiated combination therapy with house dust mite SCIT by cluster regimen. For five of six patients, asthma improved during combined treatment with SCIT and omalizumab and SCIT was well tolerated. These patients were also able to decrease their inhaled corticosteroid dose.

SUMMARY OF INHALANT ALLERGEN IMMUNOTHERAPY WITH OMALIZUMAB

There is evidence that omalizumab combined with SCIT compared with SCIT alone can lead to a greater reduction in allergic rhinitis symptom score and can decrease adverse events and time to maintenance. However, cost of omalizumab limits its widespread use. Combination therapy may be indicated in select patients, such as those who are polysensitized or highly sensitive, or could be applied in those who have been prescribed omalizumab for asthma, urticaria, or nasal polyps.

VENOM IMMUNOTHERAPY WITH OMALIZUMAB

The prevalence of systemic reactions to an insect sting ranges from 0.5 to 3.3% in United States reports and 0.3 to 7.5% in European reports and our thought to account for up to 20% of all cases of fatal anaphylaxis [14,75]. Venom immunotherapy (VIT) is the most effective method for preventing allergic reactions to an insect sting and is indicated in individuals with a history of a systemic reaction to an insect sting and presence of venom-specific IgE by skin or in-vitro testing [14,76]. VIT carries the risk of adverse events in all patients with increased risk associated with rapid dose increase, high basal tryptase level, honeybee VIT, and basophil activation [77,78[■],79[■]]. When there are repeated reactions to VIT, an alternative approach that can be considered is the use of omalizumab [79[■]].

There have been no randomized controlled trials on the use of omalizumab combined with VIT; however, several case reports and small patient series have been published that use a variety of protocols with regards to omalizumab dosing and VIT [80–88]. In general, the addition of omalizumab reduces systemic reactions and allows the patient to reach the maintenance dose [80,81,85], including some individuals with mast cell disease

[80,82,86,88]. However, this is not always effective and one report did not show a benefit of combination therapy [87].

CONCLUSION

Available data suggests that omalizumab could be a valuable option as add-on treatment with AIT for respiratory, venom, or food desensitization. It may be of particular benefit during build-up phase when it might assist in reducing time required to reach maintenance and when adverse events are more common. However, the routine use of omalizumab as add-on therapy is limited by the high cost and the lack of long-term data on efficacy and safety. More studies are needed to compare combination therapy with AIT alone and omalizumab monotherapy. Furthermore, the optimal dosing of omalizumab is unknown. Most studies have utilized dosing based on IgE and weight, both of which can have a significant impact on a person's eligibility. A recent study concluded that with OIT, omalizumab should be adjusted for body weight alone [57[■]]. Further studies are needed to determine the optimal dose, duration, and timing. In addition, more clinical studies are needed to identify patients who would benefit most from combination therapy and determine long-term outcomes.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- of outstanding interest

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