Curr Treat Options Allergy (2018) 5:155–165
DOI 10.1007/s40521-018-0170-8

Anaphylaxis (M Sánchez-Borges, Section Editor)

Use of a Combination of Allergen Immunotherapy and Omalizumab for Prevention of Anaphylaxis

Cristoforo Incorvaia, MD[1,*]
Irene Martignago, MD[2]
Erminia Ridolo, MD[2]

Address
[*,1]Cardiac/Pulmonary rehabilitation, ASST Pini-CTO, Via Bignami 1, 20126, Milan, Italy
Email: cristoforo.incorvaia@asst-pini-cto.it
[2]Department of Clinical & Experimental Medicine, University of Parma, Parma, Italy

Published online: 23 April 2018

This article is part of the Topical Collection on *Anaphylaxis*

Keywords Respiratory allergy · Hymenoptera venom allergy · Food allergy · Immunotherapy · Systemic reactions · Anaphylaxis

Abstract

Purpose of review Allergen immunotherapy (AIT) is aimed at the etiological treatment of respiratory allergy and Hymenoptera venom allergy, while it is still under investigation for food allergy. The incidence of anaphylactic reactions to AIT is generally low, but may hamper its completion and makes needed preventive treatment.
Recent findings Several studies focused the attention on the use of the anti-IgE antibody omalizumab to prevent anaphylaxis in patients at high risk of systemic reactions, that is especially elevated during food allergy AIT and, in certain circumstances, during venom immunotherapy (VIT).
Summary We performed a systematic review to analyze the use of omalizumab to prevent anaphylaxis during the course of AIT. The administration of omalizumab prior to AIT proved to improve the safety, reducing the rate of systemic adverse reactions. Double-blind placebo-controlled trials are rare and most of the available studies are case/small series reports. Further studies are needed to demonstrate the indication of omalizumab treatment in AIT.

Introduction

Allergen immunotherapy (AIT) is the only disease-modifying treatment in allergic disorders, such as rhinitis, asthma, and Hymenoptera venom allergy [1], while it is still a research field in food allergy. AIT consists in administering increasing doses of allergen extracts containing the specific allergens, in order to induce an immune tolerance to such allergens, as driven by allergen-specific regulatory T (Treg) and regulatory B (Breg) cell generation, with production of allergen-specific IgG4 antibodies, as well as to the action on type II immune cells (TH2 cells), type 2 innate lymphoid cells (ILC2), and type 2 cytotoxic T cells [2•]. Safety and efficacy of AIT are different according to the kind of allergic disease and sometimes the risk of anaphylaxis is not negligible. Such risk emerged in the 1980s, with a series of fatal reactions to subcutaneous immunotherapy (SCIT) in the USA and UK [3••]. In the following years, the major risk for fatalities was acknowledged in the presence of asthma at the time of the injection of the allergen extract, and recent studies showed that an accurate check of adequate asthma control makes life-threatening reactions significantly more infrequent [4•]. Nevertheless, differently from sublingual immunotherapy (SLIT), with which systemic reactions are very rare, SCIT is still concerned by a risk, even though not high, of anaphylaxis [4•]. The possibility to reduce such risk by pretreatment with drugs able to block the reactivity was evaluated. Antihistamines showed an ability to prevent skin reactions but not anaphylaxis [5], while omalizumab has the characteristics to achieve this goal. Omalizumab is a humanized antibody able to bind free IgE and reduce cell-bound IgE and high-affinity FcεRI receptors, causing a decrease in mediator release and, consequently, in allergic reactivity. Omalizumab induces a reduction in free IgE within 48 h from the first subcutaneous administration and in clinical symptoms within a week [6]. Thus far, omalizumab is approved for the treatment of severe allergic asthma and of chronic spontaneous urticaria, with different doses and schemes of administration. Its use in other atopic-associated diseases, such as nasal polyposis, atopic dermatitis, eosinophilic esophagitis, anaphylaxis, and allergen immunotherapy, has been investigated but is still off-label. A particular field of scientific interest is the possible use of omalizumab in increasing the safety profile of AIT, especially concerning anaphylactic reactions. Downregulation of FcεRI in mast cells and the consequent decreased activation of these cells are the speculated mechanism by which omalizumab could reduce the risk of anaphylaxis.

Allergen immunotherapy with inhalant allergens

In patients with allergic rhinitis (AR) and/or allergic asthma, AIT can be administered by SCIT or SLIT treatment [7]. During a 5-year study including 28.9 million injection visits in USA, 4 fatalities were recorded [8•]. In a recent European study performed on 4316 patients, the rate of systemic reactions was 2.1% and no fatalities were reported [9]. The risk of anaphylaxis is related especially to the disregard in following the manufacturer recommendations about administration's schedule, the co-presence of a mast cell disorder and of an uncontrolled asthma [10]. While the first condition is manageable, asthma, mastocytosis, and other mast cell disorders can represent a contraindication for AIT. Asthma control can be difficult to reach in about 4% of adult asthmatic patients [11]. Omalizumab is a possible add-on therapy in patients with severe asthma at 4 and 5 stage according to GINA guidelines [12]. Studies investigating the efficacy on seasonal allergy by adding omalizumab to AIT are available, as reviewed by Stock et al. [13], but to the purpose of the present analysis, only the use of omalizumab in AIT-treated patients with an endpoint focused on safety is concerned [14•, 15–18]. The main risk assessed

in these studies was the control of asthmatic symptomatology, but an increased safety profile with regard to anaphylaxis was demonstrated. It is worth mentioning the case report by Stelmach et al., who were able to perform AIT for house dust mites (HDM) in an 11-year-old boy who experienced anaphylaxis during a previous SCIT treatment and was affected by severe uncontrolled asthma [18]. The patient was treated with omalizumab 300 mg every 4 weeks for 6 months before initiating SCIT for HDM; the maintenance dose was reached with no side-effect and with a good control of asthma symptoms. Also, in patients with AR, systemic adverse reactions are made unlikely by omalizumab treatment. Casale et al. were able to demonstrate a fivefold decrease in risk of anaphylaxis associated to a rush schedule of SCIT in 159 patients with ragweed pollen-induced AR [14•]. Importantly, in the randomized, placebo-controlled trial by Massanari et al. on 248 subjects undergoing AIT and randomized to be treated with omalizumab (126) or placebo (122), patients receiving omalizumab had significantly fewer systemic allergic reactions to AIT than those receiving placebo (13.5 vs 26.2%, $P = 0.017$) and had fewer respiratory-related systemic allergic reactions (6 in omalizumab treated vs 24 in placebo treated); 87.3% of omalizumab-treated patients were able to reach the target maintenance immunotherapy dose compared with 72.1% of placebo-treated patients, $P = 0.004$ [17].

Venom immunotherapy

Venom immunotherapy (VIT) for patients with systemic reactions to Hymenoptera stings is available only by subcutaneous route and is safer than AIT with inhalant allergens. In fact, no fatalities have ever been reported in literature and the risk of anaphylaxis is generally low, varying from 0.5 to 14.2% [19•, 20]. Anaphylactic reactions occur more frequently during the build-up phase of VIT and especially in patients with honeybee venom allergy [21]. Another individual risk factor for anaphylaxis is the association with a clonal mast cell disorder [20, 21]. When systemic adverse events occur during VIT, the schedules (timeline and build-up doses) are usually modified and adapted to the patient, to obtain a complete tolerability and reach the maintenance dose, that is needed to achieve a complete protection from insect stings. In clinical practice, however, some patients do not tolerate VIT even after these adjustments and it is required to interrupt VIT.

In the latest decade, several authors used omalizumab to overcome this hurdle, obtaining good results [22–32]. Use of anti-IgE treatment in patients who had anaphylaxis during VIT is documented by case report or small series, while no systematic study has been conducted thus far. The published case reports are listed in Table 1. All authors, except one, successfully administered omalizumab in patients with a previous failure due to systemic reactions in build-up or maintenance phases of a VIT protocol. Differences among the reported experience regard (1) dose of omalizumab administered, (2) time between the first omalizumab administration and onset of VIT, (3) VIT protocol (rush, ultra-rush or their modifications), (4) venom preparation used, (5) time between onset and stopping of omalizumab treatment, and (6) presence of mast cell disorders.

Table 1. Case reports on effect of omalizumab in patients with systemic reactions to VIT

Authors [ref.]	Venom	VIT intervals	Duration of om. treatment before VIT	VIT schedule	Omalizumab dose	Mastocytosis	Adverse effects	Time length of Om. treatment
Schulze [22]	Honeybee	14 days	2 weeks	Ultra-rush	300 mg	No	None	Stopped after 12 months with no further adverse reaction
Wedi [23]	Honeybee	NA	1 week	Ultra-rush	150 mg	Yes	None	Stopped after 5 months with no further adverse reaction
Kontou-Fili [24]	Honeybee	30 days	1 h	Modified rush	300 mg	Yes	None	Anaphylaxis after reduction to 150 mg, no more adverse reaction with 300 mg
Averbeck [25]	Vespula	NA	4 weeks	Ultra-rush	300 mg	No	None	Stopped after 7 months with no further adverse reaction
Rerinck [26]	Honeybee	NA	4–6 weeks	Ultra rush	150 mg	NA	None	Stopped after 8 months with no further adverse reaction
Soriano Gomis [32]	Honeybee	Suspended	2 weeks	Ultra-rush	300 mg	No	Anaphylaxis during build-up phase	No other attempt with Om. or VIT
Galera [27]	Honeybee	30 days	15 min before and 15 min after	Rush	150 mg	NA	None	Anaphylaxis after reduction to 75 mg, no more adverse reaction with 300 mg.
da Silva [28]	Honeybee	28 days	2 weeks	Ultra- rush	300 mg	Yes	LLR	Suspended after 6 months with no further adverse reaction
Palgan [29]	Vespula	28 days	1 day	Rush	150 mg	No	None	Om. treatment continued
Boni [30]	Honeybee	NA	2 days	Rush	450 mg	No	None	Om. treatment continued

Om. omalizumab

Most patients requiring omalizumab treatment are middle-aged men, allergic to honeybee venom, and, in about half of the cases, suffering from mast cell clonal disorders. The unsuccessful experience concerned a 27-year-old man allergic to honeybee venom who developed recurrent systemic adverse reactions during the build-up phase of VIT with two different protocols. Basal tryptase was reported as normal (2.2 μg/L). The patient was treated for 6 months with 300 mg of omalizumab once a month, but experienced again anaphylaxis at the dose of 10 μg of bee venom during an ultra-rush VIT. No further attempts of VIT were tried [26]. Authors speculated that the failure of omalizumab in achieving protection from anaphylaxis was secondary to the use of an ultra-rush protocol for VIT. However, in other case reports, the goal to protect from systemic reactions was achieved performing this kind of VIT protocol [22, 23, 25, 26, 28, 31]. Omalizumab was also used in two cases of anaphylaxis to immunotherapy for fire ant venom allergy, both treated with the 150-mg dose, based on IgE level and weight. The treatment allowed to restart and continue immunotherapy without further systemic reactions [33, 34].

Even though almost all studies demonstrated a good safety profile, the different variables among the reports make difficult to affirm the certain utility of omalizumab in patients at high risk of anaphylaxis in course of VIT. Randomized controlled studies should provide definite demonstration, but ethical reasons oppose to perform such studies in subjects who could experience life-threatening adverse reactions.

Food allergy immunotherapy

Food allergy is a critical issue for allergists especially due to the lack of effective causal treatments. In fact, the only therapies currently available are avoidance diets and, in case of emergency, auto-injectable adrenaline [35]. AIT for food allergy is an important field of research, and different routes of administration have been investigated, but no product has been approved by authorities for clinical practice thus far [36]. The most successful route seems to be oral immunotherapy (OIT), that consists in consuming the allergenic food in a vehicle, with gradually increasing amounts, using a start-off dose below the threshold symptom-triggering amount, in order to achieve desensitization or tolerance [37]. Adverse reactions are quite common and can concern up to 50% of treated patients. In a study on 352 patients, 95 adverse reactions (27%) required adrenaline treatment [38]. Moreover, often the maximum tolerated dose is under the target dose, and this does not allow patients to consume the allergenic food, but only protects them from inadvertent exposure [39•]. To overcome these issues, several studies have been conducted on capacity of omalizumab to prevent or reduce systemic reactions to OIT with peanut, egg, milk, and multiple foods. The main data are reported in Table 2.

As far as prevention of anaphylaxis to foods is concerned, the first double-blind, placebo-controlled (DBPC) trial on the utility of anti-IgE therapy in food allergy was conducted in 2003 using the anti-IgE antibody TNX-901 (talizumab) in 84 patients with allergic reactions to peanut. By oral challenge, the mean increases in threshold amounts of peanut were 710 mg in the placebo group, 913 mg in the group given 150 mg of TNX-901, 1650 mg in the group given 300 mg of TNX-901, and 2627 mg in the group given 450 mg of TNX-901,

Table 2. Studies on the effects of omalizumab on reactions to oral food immunotherapy

Author [ref.]	Year	Patients, Sex, Mean age	Food	Study design	Omalizumab Dose	Length of Om. therapy before OIT	Food tolerated dose	Adverse Effects during OIT	Comment
Sampson [40]	2011	14 f, 8 M, 21.4 yr	Peanut	DBPC	0.016 mg/kg/IgE monthly or fortnightly	24 weeks	50 mg	Mild to moderate AE in 76.5% O. group	4 pts. tolerated ≥ 1000 mg peanut flour
Schneider [41]	2013	13 f, 8 M, 10 years	Peanut	DBPC	According to IgE level and weight (European Guidelines)	12 weeks	8000 mg	1 pt.: nausea and vomiting at 1250 mg	After suspension of Om. 12 weeks 2 pts. required adrenaline
MacGinnitie [42]	2016	37 f, 22 M, 10 years	Peanut	DBPC	0.016 mg/kg/IgE monthly or fortnightly	12 weeks	2000 mg in 23 pts	Grade 2 anaphylaxis in 4 pts. in Om. group	Maintained tolerance following Om. suspension
Savage [43]	2012	14, NA, NA	Peanut	Open-label	According to IgE level and weight (US Guidelines)		Mean increased 56-fold threshold	3 of 10 pts. that concluded the trial received adrenaline	Effective, but severe reactions in 30% of OIT
Nadeau [44]	2011	11, NA, NA	Milk	Observational	0.016 mg/kg/IgE monthly or fortnightly	9 weeks	9 pts. 2000 mg, 1 pt. 1200 mg	1 pt. received adrenaline, but completed the trial	1 pt. withdrew because of abdominal pain
Wood [45]	2016	57, NA, NA	Milk	DBPC	0.016 mg/kg/IgE monthly or fortnightly	10 weeks	24 Om.-treated pts. reached 10 g	2,1% of AE in Om. group vs. 16,1% in placebo group	2 pts. in Om. group received adrenaline vs. 9 pts. in placebo group
Martorell-Calatayud [46]	2016	5, NA, NA	Milk	Observational	NA	9 weeks	2 pts. reached 200 ml	1 pt. had grade 1 anaphylaxis, 1 pt. had 2 grade	2 pts. had anaphylaxis after Om. discontinuation
Takahashi [47]	2015	1, M, 5 f NA	Milk	Case-report	150 mg every 2 weeks	8 weeks	200 ml	None	No reactions after Om. discontinuation
Martorell-Calatayud [46]	2016	9, NA, NA	Egg	Observational	NA	9 weeks	33 ml	2 pts. had grade 2 anaphylaxis	4 pts. had anaphylaxis after Om. discontinuation
La Fuente [48]	2014	3 F, 9.6 years	Egg	Case-report	According to IgE level and Weight (European Guidelines)	8 weeks	50 ml	None	2 pts. had anaphylaxis after Om. discontinuation
Begin [49]	2014	25 m, 7 f NA	Multiple foods	Open-label	According to IgE level and Weight (US Guidelines)	9 weeks	4 g	5.3% of pts., of which 94% were mild	Reaction rate dropped by 70% after 6 months of therapy

Om. omalizumab, *AE* adverse events

the difference in favor of the 450 mg being highly significant ($p = 0.001$) [39•]. Similar results for peanut OIT were confirmed by 3 DBPC studies, one on 14, one on 13 and a larger one on 37 patients [40–42], and by an open-label trial on 14 subjects [43]. In the latter study, the kinetics of mast cells and basophils after therapy with omalizumab was also analyzed. The authors found that in basophils, but not in mast cells, suppression is necessary to achieve a clinical response to omalizumab, highlighting a role for basophils in anaphylaxis to foods [43]. The most investigated food as to prevention of anaphylaxis by omalizumab is cow's milk. The first study dates back to 2011 and was performed on 11 children pre-treated for 9 weeks with omalizumab. Nine of them tolerated a daily dose of 2000 mg of milk; one, who needed adrenaline treatment during OIT, reached 1250 mg; and one withdrew voluntarily the study [44]. A first DBPC study proved a significant decrease in adverse reactions in omalizumab-treated patients compared to the placebo group, but no significant efficacy of OIT was detected [45]. Moreover, 2 small series reports investigated whether the obtained tolerance is maintained after omalizumab discontinuation [46, 47], reporting contrasting results, probably due to the small samples. In 3 cases, omalizumab was resumed reaching again tolerance at the same threshold dose [47]. Negative outcomes could be explained by the absence of Foxp3+ allergen-specific Treg cell production after milk OIT, as observed by Bedoret et al. [50].

Concerning egg allergy, only case reports are available [46, 48]. In the first report, 9 subjects were treated with omalizumab for 9 weeks before egg OIT. During the dose-increase phase, 2 patients had moderate systemic symptoms that did not require adrenaline. All patients achieved a tolerance to 33 ml of raw white egg, but 4 of them developed third–fourth grade anaphylaxis after omalizumab discontinuation [46]. In the second report, the outcome was comparable, with recurrence of anaphylaxis after the suspension of anti-IgE treatment, even though tolerance had been reached [48].

A further study investigated the use of omalizumab in multiple foods OIT. Twenty-five subjects received treatment for 9 weeks before OIT, registering only one severe anaphylactic reaction. Of the remaining 400 adverse reactions, 94% were mild. The authors did not provide data following omalizumab discontinuation [49].

Globally, OIT preceded by omalizumab treatment seems able to reduce, but not eliminate, the risk of anaphylaxis, as well as to start the treatment with a higher initial dose and to increase the allergen threshold dose. After its discontinuation, when tolerance is reached, severe systemic adverse reactions can occur in a not-negligible number of patients. Some authors showed that, once omalizumab is re-administered, the therapy remains effective and safe.

Two studies for peanut OIT and one for milk are currently ongoing to better understand the safety of omalizumab after its discontinuation [51].

Conclusion and future perspective

Omalizumab has been used as adjuvant therapy during AIT for respiratory allergy, Hymenoptera venom, and food allergy, with overall good results concerning safety. In case of respiratory allergy, omalizumab was shown to reduce the risk of systemic reactions up to 5 times [14•] and to allow to

administer AIT in patients who previously experienced anaphylactic reactions to the treatment [17].

As to VIT, a number of case reports highlighted the ability of omalizumab to increase safety, even in patients at high risk of anaphylaxis based on the use of honeybee venom, that is known to be far less tolerated than vespid venom [22–24], or the presence of mast cell clonal disorders as comorbidity [20, 23, 28].

Omalizumab therapy as pre- and co-treatment during OIT decreased the risk of anaphylaxis, without eliminating it but permitting to achieve higher tolerated doses in a shorter time, as demonstrated also by DBPC studies [51].

Hitherto, some critical points for the use of omalizumab as add-on therapy for AIT need to be addressed and clarified.

Optimal dose of omalizumab

In some studies, omalizumab was administered according to weight and IgE levels, as for severe asthma treatment, while in others, a fixed dose was used. Indeed, limiting to asthma-related criteria could result in the exclusion of several subjects from this therapy, while fixed dosage could be under- or over-dosed in others.

Timing pre-AIT treatment onset

In all studies, omalizumab has been administered months before the initiation of AIT, but the time interval was very variable, ranging from 2 to 12 weeks.

Duration of treatment

In all studies, omalizumab was continued during the first months of AIT, but the timing of discontinuation, when occurring, was also variable.

Patients to be treated

Most studies investigated the use of omalizumab only in patients with previous adverse reactions to AIT for both respiratory and Hymenoptera venom allergy, while the risk of anaphylaxis in OIT is quite elevated for food allergic patients not treated previously. Biological or clinical markers to identify which patients can benefit from a pre-/co-treatment with omalizumab need to be identified.

Cost-effectiveness

The cost of omalizumab therapy is different in each country and depends on doses and length of treatment. It is not possible to analyze the cost-effectiveness of omalizumab in AIT with the data available thus far.

In the light of these considerations, larger randomized placebo-controlled trials are needed to clarify all these uncertain points in order to standardize this promising therapy. It is our opinion that VIT deserves particular efforts due to the influence of systemic reactions on treatment outcome. In fact, the occurrence of repeated systemic reactions alters the disease-modifying effect of VIT, as shown by the large difference in reactions to re-sting following VIT discontinuation, that concerned 46% of patients with systemic reactions to VIT compared with 8% of patients with no systemic reactions to treatment [52•]. Also, food allergy, provided AIT will be acknowledged by consensus documents and guidelines, is worthy to be considered for omalizumab treatment, because at

present there are no curative therapies available in routine practice and OIT is an efficacious experimental approach but is associated with high rates of allergic reactions [53].

Compliance with Ethical Standards

Conflict of Interest

Dr. Cristoforo Incorvaia has been a scientific consultant for Stallergenes Greer.
Dr. Irene Martignago and Prof. Erminia Ridolo declare that they have no competing interests.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Pajno GB, Nadeau KC, Passalacqua G, Caminiti L, Hobson B, Jay DC, et al. The evolution of allergen and non-specific immunotherapy: past achievements, current applications and future outlook. Expert Rev Clin Immunol. 2015;11(1):141–54.
2.• Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. J Allergy Clin Immunol. 2014;133(3):621–31.

A comprehensive and detailed review on the mechanisms underlying the clinical outcome of AIT.

3.•• Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica GW, et al. International consensus on allergy Immunotherapy. J Allergy Clin Immunol. 2015;136(3):556–68.

The updated international consensus document covering all the issues of AIT.

4.• James C, Bernstein DI. Allergen immunotherapy: an updated review of safety. Curr Opin Allergy Clin Immunol. 2017;17(1):55–9.

A recent and complete analysis on safety of AIT

5. Gorska L, Chelminska M, Kuziemski K, Skrzypski M, Niedoszytko M, Damps-Konstanska I, et al. Analysis of safety, risk factors and pretreatment methods during rush hymenoptera venom immunotherapy. Int Arch Allergy Immunol. 2008;147(3):241–5.
6. Incorvaia C, Mauro M, Russello M, Formigoni C, Riario-Sforza GG, Ridolo E. Omalizumab, an anti-immunoglobulin E antibody: state of the art. Drug Des Devel Ther. 2014;8:197–207.
7. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R, et al. EAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. Allergy. 2017 Sep 23; **[Epub ahead of print]**
8.• Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. Risk factors for fatal and nonfatal reactions to subcutaneous immunotherapy: national surveillance study on allergen immunotherapy (2008–2013). Ann Allergy Asthma Immunol. 2016;116:354–9.

The important demonstration that uncontrolled asthma is the major risk factor for severe systemic reactions to AIT.

9. Calderon MA, Vidal C, Rodriguez del Rio P, et al. On behalf of the EASSI doctors' group. European survey on adverse systemic reactions in allergen immunotherapy (EASSI): a real-life clinical assessment. Allergy. 2017;72:462–72.
10. Pitsios C, Demoly P, Bilo MB, Gerth van Wijk R, Pfaar O, Sturm GJ, et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy. 2015;70:897–909.
11. Hekking PP, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. J Allergy Clin Immunol. 2015;135(4):896–902.
12. http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention. Accessed 09–13-2017.
13. Stock P, Rolinck-Werninghaus C, Wahn U, Hamelmann E. The role of anti-IgE therapy in combination with allergen specific immunotherapy for seasonal allergic rhinitis. BioDrugs. 2007;21(6):403–10.
14.• Casale TB, Busse W, Kline JN, Ballas ZK, Moss MH, Townley RG, et al. Omalizumab pretreatment

decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. J Allergy Clin Immunol. 2006;117:134–40.

The first demonstration of the ability of omalizumab to reduce systemic reaction to AIT with inhalant allergens.

15. Kopp MV, Hamelmann E, Zielen S, Kamin W, Bergmann KC, Sieder C, et al. Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma. Clin Exp Allergy. 2009;39(2):271–9.
16. Kamin W, Kopp MV, Erdnuess F, Schauer U, Zielen S, Wahn U. Safety of anti-IgE treatment with omalizumab in children with seasonal allergic rhinitis undergoing specific immunotherapy simultaneously. Pediatr Allergy Immunol. 2010;21(1 Pt 2):160–5.
17. Massanari M, Nelson H, Casale T, Busse W, Kianifard F, Geba GP, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. J Allergy Clin Immunol. 2010;125:383–9.
18. Stelmach I, Sztafińska A, Woicka-Kolejwa K, Jerzyńska J. Omalizumab in the prevention of anaphylaxis during immunotherapy: a case report. Postepy Dermatol Alergol. 2014;31(3):191–3.
19.• Dhami S, Zaman H, Varga EM, Sturm GJ, Muraro A, Akdis CA, et al. Allergen immunotherapy for insect venom allergy: a systematic review and meta-analysis. Allergy. 2017;72:342–65.

The updated systematic review on venom immunotherapy.

20. Incorvaia C, Mauro M, Gritti BL, Makri E, Ridolo E. Venom immunotherapy in patients with allergic reactions to insect stings. Expert Rev Clin Immunol. 2018;14(1):53–9.
21. Antolín-Amérigo D, Moreno Aguilar C, Vega A, Alvarez-Mon M. Venom immunotherapy: an updated review. Curr Allergy Asthma Rep. 2014l;14(7):449.
22. Schulze J, Rose M, Zielen S. Beekeepers anaphylaxis: successful immunotherapy covered by omalizumab. Allergy. 2007;62:963–4.
23. Wedi B, Wieczorek D, Roap V, Kapp A. Anti IgE treatment overcomes intolerability of honeybee-venom ultrarush immunotherapy in indolent systemic mastocytosis. J World Allergy Org. 2007;(supplement 2):182–3.
24. Kontou-Fili K, Moissidis I. High omalizumab dose controls recurrent reactions to venom immunotherapy in indolent systemic mastocytosis. Allergy. 2008;63:376–8.
25. Averbeck M, Gebhardt C, Renner R, Simon J, Treudler R. Omalizumab helps to induce tolerability in a patient with wasp venom allergy and repeated adverse reactions during specific immunotherapy. Allergy. 2008;P1406
26. Rerinck HC, Rueff F, Przybilla B. Recurrent severe anaphylactic reactions to venom immunotherapy (VIT): omalizumab induces tolerance. J Allergy Clin Immunol. 2008;S29:111.
27. Galera C, Soohun N, Zankar N, Caimmi S, Gallen C, Demoly P. Severe anaphylaxis to bee venom immunotherapy: efficacy of pretreatment and concurrent treatment with omalizumab. J Investig Allergol Clin Immunol. 2009;19:225–9.
28. da Silva EN, Randall KL. Omalizumab mitigates anaphylaxis during ultra-rush honey bee venom immunotherapy in monoclonal mast cell activation syndrome. J Allergy Clin Immunol Pract. 2013;133:687–8.
29. Palgan K, Bartuzi Z, Gotz-Zbikowska M. Treatment with a combination of omalizumab and specific immunotherapy for severe anaphylaxis after a wasp sting. Int J Immunopathol Pharmacol. 2014;27:109–12.
30. Boni E, Incorvaia C, Mauro M. Dose-dependence of protection from systemic reactions to venom immunotherapy by omalizumab. Clin Mol Allergy. 2016 Oct 24;14:14.
31. Stretz E, Oppel EM, Rawer HC, Chatelain R, Mastnik S, Przybilla B, et al. Overcoming severe adverse reactions to venom immunotherapy using anti-IgE antibodies in combination with a high maintenance dose. Clin Exp Allergy. 2017:1–9.
32. Soriano Gomis V, Gonzales Delgado P, Niveiro Hernandez E. Failure of omalizumab treatment after recurrent systemic reactions to bee-venom immunotherapy. J Investig Allergol Clin Immunol. 2008;18(3):223–30.
33. Tartibi HM, Majmundar AR, Khan DA. Successful use of omalizumab for prevention of fire ant anaphylaxis. J Allergy Clin Immunol. 2010;126(3):664–5.
34. Tille KS, Parker AL. Imported fire ant rush desensitization using omalizumab and a premedication regimen. Ann Allergy Asthma Immunol. 2014;113(5):574–6.
35. Rachid R, Keet CA. Current status and unanswered questions for food allergy treatments. J Allergy Clin Immunol Pract 2017. [Epub ahead of print].
36. Wood RA. Oral immunotherapy for food allergy. J Investig Allergol Clin Immunol. 2017;27(3):151–9.
37. Wai CYY, Leung NYH, Leung PSC, Chu KH. Immunotherapy of food allergy: a comprehensive review. Clinic Rev Allerg Immunol 2017 [Epub ahead of print].
38. Wasserman RL, Factor JM, Baker JW, Mansfield LE, Katz Y, Hague AR, et al. Oral immunotherapy for peanut allergy: multipractice experience with epinephrine-treated reactions. J Allergy Clin Immunol Pract. 2014;2(1):91–6.
39.• Leung DY, Sampson HA, Yunginger JW, et al. Effect of anti-IgE therapy in patients with peanut allergy. N Engl J Med. 2003;348:86–993.

The first demonstration on the preventive capacity of omalizumab in patients with severe allergic reactions to peanut.

40. Sampson HA, Leung DY, 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;127:1309–10.
41. Schneider LC, Rachid R, LeBovidge J, Blood E, Mittal M, Umetsu DT. A pilot study of omalizumab to facilitate

rapid oral desensitization in high-risk peanut-allergic patients. J Allergy Clin Immunol. 2013;132:1368–74.
42. 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;139:873–81.
43. Savage JH, Courneya JP, Sterba PM, Macglashan DW, Saini SS, Wood RA. Kinetics of mast cell, basophil, and oral food challenge responses in omalizumab-treated adults with peanut allergy. J Allergy Clin Immunol 2012; 130. 1123-9:e2.
44. Nadeau KC, Schneider LC, Hoyte L, Borras 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):1622–4.
45. 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):1103–10.
46. Martorell-Calatayud C, Michavila-Gomez A, Martorell-Aragones A, Molini-Menchon N, Cerda-Mir JC, Felix-Toledo r, et al. Anti-IgE-assisted desensitization to egg and cow's milk in patients refractory to conventional oral immunotherapy. Pediatr Allergy Immunol. 2016;27:539–53.
47. Takahashi M, Taniuchi S, Soejima K, Yamanouchi S, Kaneko K. Successful desensitization in a boy with severe cow's milk allergy by a combination therapy using omalizumab and rush oral immunotherapy. Allergy Asthma Clin Immunol. 2015;11:18.
48. La Fuente I, Mazon A, Nieto M, Uixera S, Pina R, Nieto A. Possible recurrence of symptoms after discontinuation of omalizumab in anti-IgE-assisted desensitization to egg. Pediatr Allergy Immunol. 2014;25(7):717–9.
49. 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;10:7.
50. Bedoret D, Singh AK, Shaw V, Hoyte EG, Hamilton R, DeKruyff RH, et al. Changes in antigen-specific T cell number and function during oral desensitization in cow's milk allergy enabled with Omalizumab. Mucosal Immunol. 2012;5(3):267–76.
51. Labrosse R, Graham F, Des Roches A, Begin P. The use of omalizumab in food oral immunotherapy. Arch Immunol Ther Exp. 2017;65:189–99.
52.• Golden DB. Long-term outcome after venom immunotherapy. Curr Opin Allergy Clin Immunol. 2010;10(4):337–41.
This review addresses the risk factors for relapse of reactions to insect stings following discontinuation of venom immunotherapy.
53. Lin C, Lee IT, Sampath V, Dinakar C, DeKruyff RH, Schneider LC, et al. Combining anti-IgE with oral immunotherapy. Pediatr Allergy Immunol. 2017;28(7):619–62.