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REVIEW ARTICLE

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Omalizumab and allergen immunotherapy for respiratory allergies: A mini-review from the Allergen-Immunotherapy Committee of the Italian Society of Pediatric Allergy and Immunology (SIAIP)

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Abstract

Although currently approved to treat severe asthma and chronic spontaneous urticaria, omalizumab has also been an effective and safe add-on treatment for other allergic diseases. Namely, omalizumab has been proposed to be used as add-on therapy in patients with allergic rhinitis and asthma and undergoing specific allergen immunotherapy (AIT). AIT is the only treatment that modifies the natural history of IgE-mediated diseases. This brief review summarizes the available evidence and controversies on the efficacy and safety of omalizumab combined with specific AIT.

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Introduction

Allergy is a global health problem, with about 25% of the US population suffering from allergies. Allergen immunotherapy (AIT) can reverse the natural history of IgE-mediated allergy with a disease-modifying effect.¹ Unlike the conventional therapies for IgE-mediated allergy (i.e., antihistamine, corticosteroids, and epinephrine), the immunological effect of AIT persists over time, even after discontinuation. AIT is an effective therapy for allergic rhinitis, asthma, and hymenopter allergy. The first oral immunotherapy for treating peanut allergy was recently approved.² AIT was also proposed in children with atopic dermatitis (AD) as add-on therapy in selected patients characterized by aeroallergen sensitization and severe form of AD.³

AIT can be administered sublingually (SLIT) or subcutaneously (SCIT) to treat allergic respiratory diseases.^{4,5} In children with allergic rhinitis, AIT also showed a preventive role, by reducing the risk of developing asthma and new sensitizations. AIT is a safe treatment, although anecdotal cases of eosinophilic esophagitis have been reported.^{6,7} Possible side effects are primarily associated with SCIT and are described in 0.1-0.2% of injections, with a significant risk during the build-up phase.⁸

Omalizumab was the first anti-IgE monoclonal antibody approved as an add-on treatment for severe allergic asthma. In recent years, several trials tested the combined administration of omalizumab and AIT to evaluate whether this combination can improve the safety of immunotherapy and a rapid dose escalation. The combined use of the two therapies is based on the concept that omalizumab promotes immune tolerance, reducing the risk of side effects during the build-up phase.

This article summarizes the available evidence on combined therapy with specific AIT and omalizumab in respiratory allergies.

Specific immunotherapy for aeroallergens

AIT consists of the administration of increasing doses of the allergen to obtain immunological tolerance.⁹ AIT is the only therapy for IgE-mediated allergy. Indeed, AIT can restore the physiological response to the allergen, inducing the production of specific IgG1-IgG4 and IgA antibodies and polarizing the immune response by activating regulatory T lymphocytes. Therefore, the primary mechanism of action of AIT is the shift from a type 2 (T2) lymphocyte profile to a Th1.

In recent decades, SCIT and SLIT have been demonstrated to reduce respiratory symptoms and rescue therapies in adults and children.¹⁰ In children, SLIT is often preferred to SCIT due to its noninvasive administration and high safety profile. However, the specific route of administration (SCIT or SLIT) should consider several clinical aspects, mainly the risk-benefit ratio.

According to the recent guidelines of the European Academy of Allergy and Clinical Immunology (EAACI), the current indications for AIT are:

1. Allergic rhinitis +/- moderate/severe allergic conjunctivitis or asthma (Step 3 of the GINA guidelines)

2. Inadequate symptom control despite environmental prophylaxis and conventional therapy
3. Confirmed IgE-mediated allergy
4. Age \geq 5 years.¹¹

Omalizumab

Omalizumab was the first humanized monoclonal antibody used in the allergy field.^{12,13} In 2003, omalizumab was approved by the Food and Drug Administration (FDA) to treat moderate to severe allergic asthma in patients > 12 years. Then, in 2009, it received the extension of its indication for children > 6 years of age. This therapy was also approved and registered in 2014 to treat chronic spontaneous urticaria, with or without angioedema, for patients older than 12 years.¹⁴⁻¹⁷ Omalizumab is the most commonly prescribed biological drug worldwide due to its efficacy and good safety profile.¹⁸

Omalizumab neutralizes circulating IgE and reduces the high-affinity IgE receptor (Fc ϵ R) expression on the surface of mast cells, basophils, eosinophils, and neutrophils, thereby inhibiting the release of inflammatory mediators. By binding to the circulating IgE, omalizumab prevents their interaction with the high- and low-affinity receptors, significantly inhibiting the allergic inflammation. Furthermore, some reports have shown that omalizumab reduces cell activation, particularly inhibiting the degranulation of mast cells and basophils. More recent studies have highlighted the possible role of omalizumab in reducing the expression of bronchial tissue remodeling mediators.¹²⁻¹⁷ Finally, long-term studies have shown that omalizumab persistently reduces IgE production, even after discontinuing therapy.¹⁹

AIT and omalizumab: Reports from the literature

Several studies have evaluated the efficacy of omalizumab as an additional treatment to specific immunotherapy for inhalant allergens in patients with respiratory allergies (allergic rhinoconjunctivitis and/or asthma). See [Table 1](#).²⁰

Kuehr et al. conducted the first double-blind placebo-controlled trial (DBPC), enrolling 221 children and adolescents with allergic rhinitis. Omalizumab was administered as an add-on therapy of SCIT for birch and grass pollen for 24 weeks after an induction phase of 12 weeks. The combined administration significantly reduced seasonal symptoms in patients sensitized to birch (-50%) and grass pollen (-57%) compared to the SCIT + placebo group.²¹ In a DBPC trial, 159 adults with allergic rhinitis were treated with omalizumab 9 weeks before beginning the AIT for ragweed. The combined administration was continued for 12 weeks.²² Patients treated with the AIT + omalizumab showed a significant improvement in the allergic rhinitis severity scores compared to those treated with AIT alone.²² Furthermore, a *post hoc* analysis of study patients with anaphylactic reactions revealed a rate of 25.6% for AIT alone versus 5.6% for AIT with omalizumab. In another DBPC trial, 140 adolescents and adults with seasonal allergic rhinitis and asthma were treated with AIT for grass pollen. Subjects received omalizumab 2 weeks before beginning the AIT,

Table 1 Omalizumab and allergen immunotherapy.

Author, year	Study design	Population	Safety	Outcomes
Kuehr et al., 2002 ²¹	DBPC	N = 221 Age: 6-17 years Allergic rhinitis in subjects sensitized to birch or grass pollen.	The placebo group showed local adverse effects (hyperemia and edema) compared to those treated with omalizumab.	Reduction (–48%) of respiratory symptoms in the pollen seasons.
Casale et al., 2006 ²²	DBPC	N = 159 Mean age: 33.3 years Allergic rhinitis in subjects sensitized to ragweed.	Subjects treated with omalizumab showed a reduction in adverse events, including anaphylaxis, during the rapid induction phase of AIT.	Improvement of disease scores during the ragweed season.
Kopp et al., 2009 ²³	DBPC	N = 140 Age: 11-46 years Allergic rhinitis and asthma	Similar rates of adverse reactions in both groups. Local reactions were more frequent in the placebo group compared to the omalizumab arm.	Reduction (–39%) in daily symptoms. Improvement of rhinoconjunctivitis, asthma, and quality of life.
Massarani et al., 2010 ²⁴	DBPC	N = 248 Mean age: 38.2 years Moderate persistent asthma and sensitization to dog, cat, and dust mites.	Subjects treated with omalizumab showed a reduction in systemic allergic reactions and asthma exacerbations.	Reduction in the number of visits required to maintain good disease control.
Kopp et al., 2012 ²⁵	DBPC, extension	N = 128	No significant difference in local reactions.	No clinical difference in both groups after omalizumab discontinuation.
Stelmach et al., 2015 ²⁶	Observational study	N = 17 Age: 7-18 years	No adverse effect has been reported.	Sequential therapy with omalizumab and immunotherapy reduce the frequency of exacerbations and the number of hospitalizations and significantly decrease steroid use.
Lambert et al., 2015 ²⁷	Observational study	N = 6 Age: 11-21 years	One patient discontinued SCIT because of uncontrolled asthma.	Asthma control improved in 5 patients during the combined treatment with SCIT and omalizumab despite a decrease in maintenance treatment.
Valdesoiro-Navarrete et al. 2022 ²⁸	Retrospective study	N = 29 Age: ≤18	Clustering schedule: 3/64 doses have been characterized by systemic adverse reactions. SCIT maintenance schedule: No significant adverse reactions.	After 1 year of treatment, the asthma control score (CAN questionnaire) and FEV1 significantly improved.

AIT: Allergen immunotherapy; DBPC: Double-blind placebo-controlled; FEV1: Forced expiratory volume; SCIT: Subcutaneous immunotherapy.

and then for the other 16 weeks (the last 8 weeks of treatment were in the pollen season). Patients treated with the combined therapy presented a significant reduction in seasonal symptoms (–39%) compared to the placebo group.²³ During the next 2 years of treatment, no differences in symptom control were found in the two arms (AIT + omalizumab vs AIT + placebo).²⁵ However, subjects with moderate to severe asthma showed improved lung function and reduced asthma exacerbations, confirming that omalizumab is effective in patients with a severe asthma phenotype. In a real-life observational study, Stelmach et al.

enrolled 17 children with severe asthma. Five children could not undergo AIT because of frequent asthma exacerbations. Although the route of administration of AIT was not specified (SCIT or SLIT), authors reported an asthma control improvement after starting omalizumab therapy in all patients, and no adverse event was described.²⁶ A more recent trial evaluated the impact of omalizumab and SCIT in 248 adults with uncontrolled asthma.²⁴ After 13 weeks of pretreatment with omalizumab or placebo, patients started SCIT for different aeroallergens (dust mites, cat, and dog). There was a significant improvement in asthma control

scores in the arm of patients treated with omalizumab, and almost 90% of subjects reached the maximum tolerated dose of AIT without adverse reactions. On the other hand, subjects treated with a placebo presented a high frequency of asthma exacerbations, especially during the initial escalation phase. However, severe systemic reactions requiring intramuscular epinephrine have also been reported in the cohort of patients pretreated with omalizumab, despite a lower frequency than that described in the placebo group (9 vs 22 patients). Similarly, in patients treated with omalizumab, systemic reactions were also reported by Kuehr et al.²¹ On the other hand, Kopp et al. did not describe any severe reactions in the arm of patients who received AIT + omalizumab.^{23,25} Several studies also demonstrated a reduction of local reactions in subjects treated with omalizumab.²⁹ In a retrospective study of children with allergic asthma who received SCIT, omalizumab, or combination therapy, the systemic reaction rates were significantly lower in those treated with omalizumab alone or combination therapy ($P = 0.045$ and $P = 0.011$, respectively) compared with children who underwent SCIT alone.³⁰ French authors reported a pediatric female patient affected by severe allergic asthma successfully treated with sequential therapy with omalizumab and AIT to *Alternaria*, who maintained an asthma control for a long time after cessation of omalizumab.³¹

Lambert et al. reported data from six patients (11-21 years) with severe persistent asthma treated with omalizumab who received SCIT to house dust mite (HDM) under a clustering protocol during omalizumab treatment, then SCIT maintenance alone after biological therapy discontinuation. 83% of the population pretreated with omalizumab did not present severe side effects; one patient discontinued SCIT because of uncontrolled asthma. Asthma control improved in five patients during the combined treatment with SCIT and omalizumab (median time duration = 8 months) despite a decrease in maintenance treatment after the omalizumab discontinuation.²⁷ Another recent retrospective, real-life study described the efficacy of combined therapy with omalizumab and AIT in 29 patients with severe asthma, which reported a reduction in hospital admissions per year. The authors reported 10 adverse reactions to SCIT: 7 local reactions and 3 systemic reactions that did not imply AIT discontinuation. This study is limited by the lack of a control group for comparing the duration of omalizumab treatment with or without AIT.²⁸

In summary, available studies suggested a positive effect of combined therapy with omalizumab, especially in patients allergic to pollens and HDM. However, most studies did not clarify whether the omalizumab administration is associated with more rapid and long-lasting development of tolerance because follow-up data are missing.

The immunological effects of omalizumab in AIT

Omalizumab promotes immunotolerance, reducing the specific IgEs and expression of their receptor on the surface of mast cells and basophils.³² The administration of omalizumab before starting the AIT induces a significant downregulation of allergen-induced activation of basophils. Moreover, omalizumab reduces the expression of the high-affinity receptor expressed on the surface of mast cells and thus the ability of these cells to bind to IgEs with the subsequent activation of T lymphocytes. Finally, omalizumab reduces several lymphocyte interleukins (IL), such as IL-13, IL-10, IL-31, and INF- γ produced by lymphocytes.

Practical considerations

There are no standardized protocols for omalizumab therapy in patients undergoing AIT. The most recent evidence suggests that omalizumab may be prescribed considering the therapeutical indications for asthma (serum IgE levels and body weight).³³ The minimum effective dose is 150mg, which corresponds to 100% of the dose administered to a patient with severe asthma (with serum IgE < 100 kU/L and <70kg), or 50% of the dose used for chronic spontaneous urticaria. However, an increase of 300mg or 450mg may be necessary to avoid potential AIT-related side effects depending on the response. Many authors recommend starting with omalizumab before the AIT to reduce the number and reactivity of circulating IgEs. In different studies and case reports, the pretreatment period with omalizumab was arbitrarily chosen and ranged from 1 to 16 weeks, with injections every 2 or 4 weeks. After the beginning of AIT, the administration of omalizumab should be continued for another 3-6 months (Table 2).

Conclusion

The combined administration of omalizumab during the AIT protocols has been tested to treat asthma, allergic rhinitis, hypersensitivity to hymenopter venom, and food allergy. Available studies indicate that omalizumab significantly reduces the time required to reach the maintenance dose of AIT and decreases, but does not eliminate, the risk of adverse events. Moreover, some limitations should be acknowledged. First, most studies concern both the pediatric and the adult population, and the number of enrolled children is limited for generalizing the results. Besides, data on the effects of long-term maintenance therapy are still lacking. However, this protocol was neither standardized nor introduced into the routine clinical practice.

Table 2 Omalizumab: Dosage protocol.

AIT	Dose (mg)	Pretreatment (weeks)	Frequency of administration (weeks)	Entire treatment (weeks)
Aeroallergens	150*	13	2 or 4	12-24

*The dosage is chosen following the recommendations for asthma treatment, considering serum IgE levels and body weight; omalizumab can be increased if necessary.

Therefore, in children, more extensive, randomized, and controlled trials are still needed to confirm:

1. Long-term safety and efficacy of this combination therapy
2. The best candidate cluster of patients
3. Dosage and optimal duration of omalizumab
4. Cost and benefits.

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