EXPERT REVIEWS

The relationship between allergen immunotherapy and omalizumab for treating asthma

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Allergen-specific immunotherapy (AIT) is considered the only treatment capable of modifying the natural history of allergic respiratory disorders. The possible adverse events related to AIT have, until now, limited its use to mild and controlled asthma. The pre-administration or concomitant treatment of AIT and omalizumab (an anti-IgE humanized antibody), recommended for the treatment of severe allergic asthma, could be useful in reducing the adverse events due to AIT and to allow its use in patients with more severe or uncontrolled asthma. AIT/omalizumab combination has been explored in a few trials on asthma patients and also in other allergic disorders, such as rhinitis, hymenoptera systemic reaction and food allergy with significant results. We are at the beginning a new era where phenotype/endotype-based treatment will be associated with drug mass therapy and/or nonpharmacological phenotype/endotype-driven treatment to optimize disease control and/or to make the use of other treatments safer.

Keywords: asthma • IgE • omalizumab • outcomes • specific immunotherapy

Background

Asthma drugs can effectively control disease symptoms in a great percentage of patients, but they do not affect the natural history of the disease. Allergen-specific immunotherapy (AIT), administered subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT), is the only etiology-based treatment capable of disease modification, as demonstrated by prevention of both the onset of new allergic sensitizations and disease progression [1]. Although the Allergic Rhinitis and its Impact on Asthma [2,3] guidelines give a conditional recommendation to AIT due to the moderate and low quality of evidence, a growing body of evidence from double-blind, placebo-controlled studies shows that both SLIT and SCIT are effective in reducing symptom scores and medication use, improving the quality of life and inducing favorable changes in specific immunologic markers. According to the Global Initiative for Asthma document, AIT should be considered only after strict environmental avoidance and pharmacologic intervention including inhaled corticosteroids (ICS) [3]. The evidence for SCIT efficacy has been recently analyzed in a Cochrane review, which reported an overall clinical efficacy in terms of reduction in asthma symptom scores, medication usage and allergen-specific bronchial hyperreactivity, and also limited reduction in non-specific bronchial hyperreactivity [4]. The numbers of patients needed to treat in order to avoid asthma symptom deterioration or increase in medications were estimated as three and five, respectively, while the effects on lung function were not consistent among the trials. Moreover, more recent studies on the long-term efficacy of AIT in asthma showed intriguing treatment effects. Respiratory adverse reactions to SCIT are common, but no deaths were reported in the included studies [5]. For the sublingual route of administration, in a large study including 602 asthmatic patients allergic to house dust mites, a reduced need for ICS for asthma control was demonstrated compared with placebo, only

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after 1 year of treatment [6]. Chelladura and Lin analyzed four trials exploring the effectiveness of SCIT and SLIT in managing allergic asthma [7]. Low-grade evidence supports greater effectiveness of SCIT than SLIT for asthma symptom reduction. All trials reported on adverse events, with an episode of anaphylaxis reported in a child treated with SCIT. Along with general contraindications, severe or uncontrolled asthma is the most important and independent risk factor for both nonfatal and fatal adverse reactions to AIT [1]. In general, the frequency and the duration of therapy and the potential for systemic allergic reactions have limited its use, especially in patients with symptomatic persistent asthma who are at greater risk for severe reactions [8].

Omalizumab is a recombinant, human monoclonal antibody that selectively inhibits the binding of human IgE to high-affinity receptors (FcεRI) on mast cells, basophils and dendritic cells. This prevents mast cell and basophil activation and the subsequent release of proinflammatory mediators and reduces allergen-induced airway reactions. By preventing the release of mast cell–derived mediators, omalizumab may reduce eosinophils' recruitment, tissue remodeling [9,10] and functional changes in the airways. The reduction in IgE binding down-regulates the cell surface expression of IgE and FcεRI in the airway mucosa. Omalizumab is the first biotechnology drug used for treatment of allergy-related asthma [11]. It became available in Europe in 2005 for the treatment of severe persistent allergic asthma, which is insufficiently controlled by conventional treatment. It was registered with restriction to patients with uncontrolled disease in spite of using high doses of ICS and long-acting β2-agonists, with low lung function (forced expiratory volume in the first second <80%) and symptom control (recurrent exacerbations), and having allergy against at least one perennial antigen [12,13]. Omalizumab is currently licensed for adults and children (aged 6 years and older) who may continue to receive treatment into adulthood. It has been successfully adopted into clinical practice, with hundreds of thousands of patients treated worldwide. The overall prevalence of asthma in Europe has been estimated to range from 5 to 18%, with approximately 20–30% of them having severe asthma [14,15]. An estimated 20% of patients with severe asthma have inadequately controlled disease [16] and in Europe, among patients receiving ICS, the prevalence of uncontrolled asthma has been estimated to range from 20 to 67% [17]. About 50% of patients with severe asthma have allergic-atopic asthma [18]; thus, it was estimated that over 9000 patients in Italy and Germany are potentially eligible for omalizumab treatment, in addition to those already receiving treatment with omalizumab [19].

The concomitant treatment with omalizumab and AIT could be potentially useful in reducing the adverse event caused due to AIT and to allow the use of AIT, through the prevention of its potential adverse event, in patients with more severe or incompletely controlled asthma despite using high dose of inhaled steroid and β2-agonists. This approach has been successfully explored in patients with ragweed-sensitive allergic rhinitis where the efficacy of combined therapy was better than that of either therapy alone or placebo and the rate of SCIT allergic reactions during rush immunotherapy was consistently reduced (56.4% in SCIT alone vs 33.3% in SCIT + omalizumab) [20]. A *post hoc* analysis of patients with anaphylactic reactions (defined as reactions involving two or more organ systems concurrently and/or severe enough to require epinephrine) revealed a rate of 25.6% for SCIT alone versus 5.6% for SCIT + omalizumab [21]. However, patients with allergic asthma were excluded from this study. In polysensitized children and adolescents with seasonal allergic rhinitis, omalizumab reduced the symptom load (defined as the sum of daily symptom severity scores plus rescue medication use) over the two pollen seasons by 48% ($p < 0.001$) compared to specific immunotherapy (SIT) alone, regardless of the nature of the allergen, when combined with AIT [22]. When these findings were further analyzed for the grass pollen allergic children, it was noted that omalizumab plus immunotherapy treated groups had significantly diminished rescue medication usage and number of symptomatic days when compared to groups treated with either omalizumab or immunotherapy alone. The combined treatment with both omalizumab and grass immunotherapy was more effective than omalizumab alone [22]. The aim of the present review was to analyze the available evidence concerning the combined use of AIT and omalizumab in patients with allergic asthma.

Clinical research on omalizumab + AIT in allergic asthma

The results of three clinical trials [23–25] exploring the effect of omalizumab before or concomitant to AIT administration have been published in peer-reviewed indexed journals. One hundred and forty rhinitis patients with concomitant asthma (age 11–46 years) were randomized in a double-blind placebo-controlled parallel groups trial, comparing omalizumab in combination with grass pollen specific immunotherapy (Depigoid; Leti pharma GmBH, Witten, Germany) with Depigoid and placebo [25].

The patients were treated with omalizumab for 10 weeks before the expected pollen season, 2 weeks before subcutaneous immunotherapy rash titration protocol and for 8 weeks in the seasonal period. Only patients with total IgE level >30 and <700 IU/ml and suffering from uncontrolled mild to moderate seasonal allergic rhinitis (SAR) with concomitant persistent uncontrolled seasonal allergic asthma (SAA) were included. Allergic rhinitis and asthma drugs were allowed and registered. Combination therapy reduced the symptom load by 39% ($p = 0.0464$) over SCIT monotherapy. While the reduction of symptom severity as well as the improvement in asthma control (asthma control questionnaire; $p = 0.0295$) and health-related quality of life (HRQoL) ($p = 0.0293$) were significant, rescue medication use, forced expiratory volume in the first second and peak expiratory flow measure did not change. No relevant safety problem was reported in both trial arms.

The same authors investigated in a double-blind placebo-controlled multicenter trial the long-lasting effects of an initial combination treatment with SCIT + omalizumab, in a follow-up period with SCIT treatment only in patients with SAR

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and comorbid SAA incompletely controlled by conventional pharmacotherapy [23]. They administered omalizumab 2 weeks before 16 weeks of SCIT, before the first pollen season of observation. SCIT was given for two subsequent years without omalizumab. The combined treatment reduced the symptom load during the treatment period, but showed no prolonged effect during treatment with AIT only, although a slight increase in forced expiratory volume in the first second was registered in patients treated with both drugs. This evidence needs to be further investigated. No systemic reactions were observed at any point, but during the observation period, approximately half of the patients in each treatment group experienced at least one adverse event. Massanari *et al.* performed a 26-week, double-blind placebo-controlled, parallel group study to evaluate the effect of omalizumab on the tolerability of cluster- and maintenance-specific immunotherapy to cat and *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* in patients with symptomatic persistent asthma not adequately controlled by inhaled steroids [22]. In this, 248 patients underwent outcomes analysis, which showed that patients receiving omalizumab experienced significantly fewer systemic allergic reactions to SIT than those receiving placebo ($p = 0.017$) and had fewer respiratory related systemic allergic reactions (6 vs 24). More patients treated with omalizumab were able to reach the target maintenance immunotherapy dose ($p = 0.004$). Anaphylactic reactions were reported in two patients in both arms of the study. According to the authors, 13.5% of patients in the omalizumab group experienced systemic adverse reactions versus 26.2% in the placebo group and had fewer respiratory-related (grade 3) systemic allergic reactions (6 vs 24, respectively). These results of this study showed that although 13 weeks of pretreatment with omalizumab markedly reduced the incidence of severe adverse events, it was not totally protective. This may reflect the incomplete depletion of circulating free IgE or the existence of allergen-specific IgE already bound to effector cells. Other factors such as patients' responsiveness to omalizumab or individual variability in sensitivity to provoking allergen may be also considered.

Expert commentary

Antigen-specific IgE binds to high-affinity receptors (FcεRI) on tissue mast cells, basophils and dendritic cells. On further exposure to the specific allergen, antigen binds to IgE antibodies on mast cells and basophils, leading to cross-linking of two adjacent IgE molecules. This initiates intracellular signaling pathways and degranulation occurs leading to release of preformed and newly generated mediators and cytokines. This type I hypersensitivity is central in the pathogenesis of allergic disorders and followed, several hours later, by the late phase response involving the infiltration of inflammatory cells due to cytokine and chemokine release from the mast cells. The subsequent release of mediators into the nasal or airway mucosa from the basophils and eosinophils manifests as symptoms of early phase, along with significant congestion and inflammation. AIT causes allergen-specific desensitization and has long-lasting immunotolerogenic effects, but can also induce potentially severe adverse events. The binding of omalizumab to free IgE prevents the binding of IgE to FcεRI and the subsequent expression of IgE on the surface of allergic effector cells. The rationale for using the combination of anti-IgE and AIT comes from the above-mentioned pre-existing data about the biologic and immunologic effects of both therapies. Omalizumab-induced decreases in serum IgE and the expression of FcεRI on key immune effector cells, including basophils and dendritic cells, could lead to important immunologic changes that could enhance the immune tolerance to allergens delivered by immunotherapy [26–28]. This phenomenon can lead to a safer administration of AIT. It must also be considered that the risk of adverse events is significantly related to the route of AIT administration since clinical research has shown that SLIT is less associated to unexpected adverse events. Nevertheless, in planning AIT, independent of the route of administration, every effort must be developed to minimize the adverse events and to treat properly and promptly.

Omalizumab is expensive, but the net balance must consider both the costs of omalizumab pretreatment and AIT and the costs avoided, such as those associated with treating systemic allergic reactions and asthma exacerbations, and the benefits of achieving maintenance immunotherapy. Indeed, many studies have evaluated different premedication regimens for various types of immunotherapy using rush, cluster and conventional dosing. Antihistamine pretreatment had no effect on the number of systemic allergic reactions, while omalizumab had a pronounced effect in reducing these events. The potential benefits of montelukast or a short course of prednisone, in terms of both reducing systemic allergic reactions and improving asthma control in this population are yet to be demonstrated in the context of appropriately designed clinical trials. A current limitation to AIT application is represented by severe and or uncontrolled asthma due to the risk that allergen administration can worsen the respiratory symptoms. The pretreatment or concomitant treatment with an anti-IgE monoclonal antibody could broaden the number of patients treated with AIT with an aim to improve asthma control and also to reduce concomitant drug use.

As mentioned before, the immediate [24] and long-lasting [25] effects of 18 weeks of treatment with omalizumab in combination with depigmented SIT have been analyzed. Among them, the impact on HRQoL has been explored. After the pollen season, the combined therapy, compared to SIT alone, was able to produce a significantly higher improvement of asthma HRQoL scores, whereas the same effect was not observed for rhinitis HRQoL scores.

However, in both cases, the difference in scores between the two groups was inferior to the minimal clinical difference. After 1- and 2-year follow-up, no significant differences between treatment groups were shown for HRQoL related to rhinitis and asthma. In other words, the improvement in symptoms and in the other clinical parameters which were evaluated does not correspond to a parallel improvement of HRQoL. The

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concomitant use of effective treatment able to significantly ameliorate HRQoL could mask the effect of omalizumab, since a near-normal HRQoL has been achieved by means of the other ongoing treatments. It is, however, difficult to interpret the data concerning the HRQoL in these studies. As a matter of fact, none of the two studies mention the initial and final scores of HRQoL or the scores for the different subscales of the questionnaires used.

Five-year view

Until the last decade, a mass treatment approach had been used for controlling asthma. In other words, independent of asthma phenotype and endotype, all patients were treated with a β2 short-acting agonists in case of mild intermittent disease or with a controller medication generally represented by inhaled steroid associated or not with a long-acting β2-agonist or methylxanthine or antileukotriene. Data from the GOAL study showed that using this approach, we can achieve the total control of asthma independent of the disease severity in about 40% of patients and a satisfying level of control (good control) can be achieved in about 80% of patients [29]. Montelukast and Zafirlukast represented the first asthma drugs of the so-called phenotype-driven therapy.

Clinical trials showed efficacy of the drugs in specific patterns of asthma such as allergic asthma (with particular benefit in patients with associated allergic rhinitis), aspirin-related asthma and exercise-induced asthma. Indeed, a phenotype-driven non-pharmacological treatment for rhinitis and asthma that is already available is represented by AIT. Omalizumab is the first biotech drug available for IgE-mediated asthma and will be followed by other molecules addressed to inhibit other pathogenic pathways (eosinophils, IL4, IL5, IL13, etc.). While the conventional therapy remains and will be the fundamental treatment of asthma patients, biotech molecules will be reserved to the subgroups of patients who are unable to control the disease with inhaled steroids and β2 long-acting agonists and are characterized by a specific phenotype/endotype. Phenotype-driven therapy is a step toward 'personalized treatment' where through diagnostic tests, we will be able to identify responders and non-responders to a specific treatment among patients with the same phenotype/endotype. Also, in the field of allergy diagnosis and AIT, we are assisting in a revolution with relevant results coming the molecular diagnosis techniques and development of recombinant vaccines. In the above-mentioned context, it is not surprising that in a specific pattern of asthmatic patients where AIT could be an effective treatment in order to optimize the disease control, omalizumab could be used in order to minimize the risk of adverse event related to AIT administration or, on top of other treatments, to further ameliorate the disease control. It is clear that we are at the beginning of a new era in asthma therapy where, through an improvement of the available diagnostic and therapeutic tools, we will be able to improve asthma care. It is relevant to bear in mind that the final outcome in the treatment of chronic disorders is the improvement of HRQoL. By this term, we refer to a scientific parameter that measures the impact of the disease and its treatment from the patients' perspective. Implicit in this definition is the fact that in order to achieve improvement in clinical or biological parameters, if we increase the burden of the treatment, the overall result in terms of quality of life may be not satisfactory. Daily practice needs to be based on solid research evidence exploring not only efficacy and safety but also the patients' perspective and the economical health care sustainability. This last point seems particularly relevant nowadays since the cost of biotech drugs is generally high. In the field of allergic disorders, the use of omalizumab has been shown; also, it is an effective treatment in non-severe asthma and also in rhinitis, atopic dermatitis, chronic idiopathic urticarial and, combined with AIT, also in Hymenoptera and oral food desensitization [30]. This means that its wider use could be seen. A larger use could be related to its reduced cost, but we have to also consider that the expiration date of omalizumab patent is not so far. The case history of other biotech drugs has shown that biosimilars, in other words, biological drugs similar to the originator, have been marketed at a lower price, making their wider use possible.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Key issues

- Asthma drugs can effectively control the disease symptoms in a great percentage of patients, but they do not affect the natural history of the disease.
- Despite the moderate and low quality of evidence, allergen-specific immunotherapy (AIT) is considered the only real curative modality in allergic asthma.
- Omalizumab is the first biotechnological drug used for treating allergy-related asthma.
- The concomitant treatment with AIT and omalizumab has been proved to be useful in reducing the adverse event due to AIT and to allow use of AIT in patients with incompletely controlled asthma.
- Clinical trials exploring the effect of omalizumab before or concomitant with AIT administration reported an improvement as regards reduction of symptom severity and asthma control.
- The impact of combining AIT and omalizumab on health-related quality of life needs to be further explored in order to show a significant improvement from patients' perspective.
- The net balance of omalizumab plus AIT approach must consider both the costs of treatments and the costs avoided such as those associated with treating systemic allergic reactions and asthma exacerbations.
- The evidence for the combination of omalizumab and allergen immunotherapy is low, especially in severe asthma, and it is still not labeled as a pretreatment to improve tolerance of allergen immunotherapy, although it may be valuable in this indication.
- Until now, omalizumab is added to AIT not only in severe asthma but also in venom immunotherapy and food allergy. More studies are necessary to investigate this combination treatment in terms of efficacy, safety and specific pathophysiological mechanisms.

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