

Omalizumab: Anti-IgE Therapy in Allergy

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Published online: 18 January 2011
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Abstract Omalizumab is a humanized, monoclonal anti-IgE antibody that binds specifically to circulating IgE molecules, thus interrupting the allergic cascade. Omalizumab has been shown to be highly effective in treating children and adults with moderate to severe allergic asthma. Beyond this indication, the mode of action itself suggests that omalizumab is not only an antiasthmatic drug but also a promising therapeutic option for various allergic conditions, including allergic rhinitis, food allergy, urticaria, allergic bronchopulmonary aspergillosis, insect hypersensitivity, and atopic dermatitis. However, data from double-blind, placebo-controlled clinical trials are only available for allergic rhinitis and moderate to severe bronchial asthma. The aim of this review is to discuss the current clinical data as well as possible further indications of omalizumab treatment.

Keywords IgE · Allergy · Asthma · Allergic rhinitis · Children · Omalizumab · Therapy

Introduction

The discovery of IgE by Ishizaka, Bennich, and Johansson was a historical milestone in allergology. The recognition of IgE as a key mediator of airway inflammation in allergic respiratory disease led not only to the processing of diagnostic tools but also to new therapeutic options such

as the development of humanized monoclonal anti-IgE antibodies [1]. One such antibody, omalizumab, has been shown to interrupt the allergic cascade and to be effective in treating patients with allergic rhinitis and allergic asthma [2–4]. Omalizumab is currently the only monoclonal anti-IgE antibody approved for the treatment of allergic asthma. It is indicated as add-on therapy in patients 6 years of age or older with severe, persistent allergic asthma and elevated serum IgE levels who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are not adequately controlled with inhaled corticosteroids (ICS) [5]. It is usually administered as a subcutaneous injection every 2 to 4 weeks, depending on the total IgE levels of the patient. Omalizumab decreases the levels of circulating IgE regardless of allergen specificity by binding to the constant region of circulating IgE molecule, which prevents free IgE from interacting with the high- and low-affinity IgE receptors (FcεRI and FcεRII) on mast cells, basophils, macrophages, dendritic cells, B lymphocytes, and other cells.

Consecutively decreased surface binding of IgE on these cells leads to a reduction in the release of the mediators of the allergic response (Fig. 1). Omalizumab also reduces FcεRI expression on basophils and tracheobronchial submucosal gland cells in atopic individuals [6–9]. The mode of action reveals that omalizumab is not only an antiasthmatic drug but also, or even more importantly, a promising therapeutic option in different allergic conditions, including allergic rhinitis, atopic dermatitis (AD), food allergy, urticaria, allergic bronchopulmonary aspergillosis (ABPA), and insect hypersensitivity. However, data from double-blind, placebo-controlled (DBPC) clinical trials are only available for allergic rhinitis and moderate to severe bronchial asthma. The aim of this review is to discuss the current clinical data as well as possible further indications.

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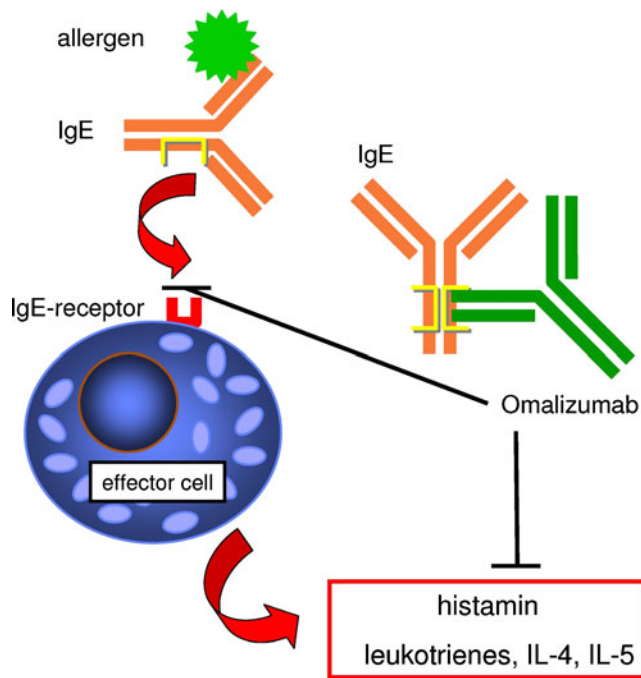


Fig. 1 Mode of action of omalizumab. Omalizumab decreases the levels of circulating IgE regardless of allergen specificity by binding to the constant region of the circulating IgE molecule, which prevents free IgE from interacting with the high- and low-affinity IgE receptors (FcεRI and FcεRII) on effector cells. IL—interleukin

Omalizumab in Patients with Asthma

The clinical efficacy and safety of omalizumab in patients with allergic asthma are documented in many clinical trials including children, adolescents, and adults. Omalizumab is one of the best documented treatment options in severe asthmatic patients. The only limitation regarding the use of omalizumab is that the observation periods in clinical trials are 6 to 12 months, and studies including a long-term follow-up are scarce. This parallels with the restricted expert knowledge of clinicians, which covers a period of about 10 years. Therefore, the question of drug treatment duration and dosage over time is still unacknowledged. The initial dosage and application rate depends on body weight and the total IgE concentration. Theoretically, the reduction of free IgE molecules and the downregulation of the IgE receptor density on effector cells during therapy may lead to disease control managed with less omalizumab administration. Unfortunately, the quantification of free IgE concentrations under ongoing omalizumab therapy requires extraordinary laboratory expenditure. Therefore, analyzable data regarding free IgE concentrations in omalizumab-treated patients are absent. Nevertheless, the data from patients with moderate to severe asthma treated with omalizumab are largely convincing.

In a randomized, DBPC trial involving 419 patients with inadequately controlled, severe, persistent allergic asthma

despite receiving high-dose ICS plus long-acting β_2 -agonists, the addition of omalizumab to high-dose ICS plus a long-acting β_2 -agonist resulted in a 26% reduction in clinically significant asthma exacerbations (defined as asthma worsening requiring treatment with systemic corticosteroids) as compared with add-on placebo during a period of 28 weeks ($P=0.042$) [10]. This was accompanied by significant reductions in severe asthma exacerbations (50%; $P=0.002$) and emergency department visit rates (44%; $P=0.038$). In a pooled analysis of three randomized, DBPC trials of patients with moderate to severe allergic asthma ($N=1405$), add-on omalizumab significantly reduced the rate of emergency department visits (RR, 0.47; 95% CI, 0.24–1.01; $P=0.05$), asthma-related outpatient visits (RR, 0.60; 95% CI, 0.44–0.81; $P<0.01$), and asthma-related hospital admissions (RR, 0.08; 95% CI, 0.00–0.25; $P<0.01$) as compared with placebo [11].

Recently, a total of 627 children 6 to 12 years of age with a history of exacerbations and asthma symptoms despite treatment with at least medium-dose ICS were enrolled in a DBPC trial and received omalizumab or placebo for a period of 52 weeks. Omalizumab reduced the number of clinically significant asthma exacerbations by 31% versus placebo ($P=0.007$) in the first 24 weeks and by 43% versus placebo ($P<0.001$) during the observation period of 52 weeks. Moreover, omalizumab significantly reduced severe exacerbations in these children. The authors concluded that add-on therapy with omalizumab is effective and well-tolerated as maintenance therapy in children with moderate to severe, persistent, IgE-mediated asthma [12•].

Results of various studies also indicate that omalizumab possesses a steroid-sparing effect, causing approximately 25% more reduction in steroid requirement compared with placebo [13–15]. In a 2006 Cochrane review of 14 randomized controlled trials of patients with mild to severe allergic asthma ($N=3143$), treatment with intravenous and subcutaneous omalizumab significantly increased the number of patients who reduced their ICS dose by more than 50% (OR, 2.50; 95% CI, 2.02–3.10) compared with placebo [16]. Furthermore, in several studies, omalizumab yielded significant improvements in the quality of life of patients with severe allergic asthma [14, 17, 18].

In a very recently published systematic review of placebo-controlled studies, 8 trials with a total of 3429 participants were included [19•]. Primary outcomes were reductions in steroid use and asthma exacerbations. During the steroid reduction phase, patients in the omalizumab group completely withdrew from corticosteroid treatment significantly more often compared with those receiving placebo (RR, 1.80; 95% CI, 1.42–2.28; $P=0.00001$).

Moreover, patients treated with omalizumab showed a decreased risk of asthma exacerbations (RR, 0.57; 95% CI, 0.48–0.66; $P=0.0001$). Injection site reactions were more frequent in the omalizumab patients (19.9% vs 13.2%); however, the number of serious adverse events was similar between omalizumab (3.8%) and placebo (5.3%). These data indicate that add-on therapy with omalizumab in patients with moderate to severe allergic asthma is efficacious and has a favorable safety profile [19••].

Omalizumab in Patients with Allergic Rhinitis

In addition to studies on asthmatic patients, the efficacy of omalizumab has been evaluated in patients with seasonal allergic rhinitis. In a large trial of patients with moderate to severe seasonal allergic rhinitis ($N=536$), omalizumab decreased serum-free IgE levels and provided clinical benefit in a dose-dependent manner [2]. In another DBPC trial of adults and adolescents with moderate to severe symptomatic perennial allergic rhinitis ($N=289$), omalizumab decreased the mean daily nasal symptom score ($P<0.001$) and use of rescue antihistamine ($P=0.005$) versus placebo; these effects were accompanied by improved rhinoconjunctivitis-specific quality of life among the patients [20].

In Japan, seasonal allergic rhinitis is often induced by Japanese cedar pollen. A DBPC trial was conducted in 100 Japanese patients who were allergic to Japanese cedar pollen with moderate to severe seasonal allergic rhinitis. Again, the sum of the daily nasal symptom severity score and daily nasal rescue medication score (symptom load) was significantly lower in the omalizumab group than in the placebo group ($P<0.01$). The incidence of local reactions at the injection side was higher in the omalizumab group than in the placebo group; however, adverse events were similarly distributed between the omalizumab and placebo groups [21].

Overall, omalizumab has a favorable safety and tolerability profile. Adverse events reported after subcutaneous administration of omalizumab include injection site pain and bruising, bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue [14]. Omalizumab does not bind to cell-bound IgE, thus avoiding the FcεRI cross-linking that could increase the risk of anaphylaxis during clinical use [9]. Postmarketing reports based on an estimated exposure of about 57,000 patients nevertheless have indicated that anaphylactic reactions occur in about 0.2% of patients, mostly (~60%) within 2 h of the injection. Therefore, it is recommended that omalizumab has to be administered in specialist centers under direct medical supervision.

Omalizumab in Combination with Allergen-Specific Immunotherapy

The combination of a specific immunotherapy (SIT) and omalizumab may be beneficial by improving the short and/or long-term efficacy and safety of the treated patients. Up to now, three clinical trials have been conducted. Additional clinical benefits of a combined therapy using omalizumab and SIT have been shown in all clinical studies.

In a randomized, DBPC trial of children and adolescents with moderate to severe seasonal allergic rhinitis with grass or birch pollen allergy ($N=225$), co-seasonal administration of omalizumab after preseasonal SIT resulted in significantly larger decreases in nasal and ocular symptoms and rescue medication use compared with either treatment alone [22••]. In parallel to the clinical results, in vitro leukotriene release has been shown to decrease in the omalizumab plus SIT group, whereas SIT plus placebo yielded no change in the allergen-specific leukotriene release in these patients [23, 24]. Moreover, rescue medication use, number of days with symptoms, and symptom severity were significantly lower in the SIT plus omalizumab groups compared with SIT alone [22••].

In a randomized, DBPC trial of adult patients ($N=159$), omalizumab pretreatment followed by rush immunotherapy for ragweed-induced seasonal allergic rhinitis significantly decreased daily symptom severity compared with immunotherapy alone ($P=0.04$) [25••]. These results also suggest that omalizumab conferred a protective effect that was independent of the type of allergen. Moreover, patients receiving omalizumab plus immunotherapy had fewer adverse events than those receiving immunotherapy alone. During the rapid increase of allergen dose at the beginning of SIT (rush immunotherapy), the number of adverse events related to SIT therapy was significantly reduced in the group pretreated with omalizumab. Of note, pretreatment with omalizumab resulted in a fivefold decrease in risk of anaphylaxis (OR, 0.17; $P=0.026$). These data suggest that combined treatment with omalizumab and allergen immunotherapy may be an effective option to apply higher doses of allergen immunotherapy more rapidly in a safe way to patients with allergic diseases.

Recently, a randomized, DBPC trial took a step forward involving patients with seasonal allergic rhinoconjunctivitis and comorbid mild to moderate seasonal allergic asthma ($N=140$). In this trial, treatment with omalizumab before and during rush SIT again resulted in more favorable results for the combination therapy as compared with SIT alone [26••]. A significant reduction of 39% in symptom load was observed in favor of SIT plus omalizumab compared with SIT alone ($P=0.0464$). The combination therapy also reduced asthma-related impairments in the activities of daily living and improved lung function to a larger extent

compared with SIT alone. Global evaluations of treatment effectiveness on asthma control by both investigators and patients favored SIT plus omalizumab compared with SIT alone. The clinical implication of these findings is that patients with moderate to severe allergic asthma pretreated with omalizumab may also benefit in the future from SIT as a causal treatment option [26••].

Taken together, these results show that omalizumab and SIT is more effective than SIT alone during the initial treatment phase. Moreover, the combination was well-tolerated in all these studies. There were no serious adverse events related to the administration of the combination therapy. Local reactions (eg, injection site pruritus, pain, and swelling), cough, headaches, and upper respiratory tract infections were the most commonly reported adverse events [22••, 26••, 27•]. It is possible that the effect of SIT plus omalizumab on free IgE levels in the serum may help reduce the risk of SIT-induced systemic, IgE-mediated reactions. In patients with severe asthma, the use of SIT is restricted because of the potential risk of severe asthma exacerbation. In these patients, the combination of omalizumab and SIT may provide improved safety in addition to superior symptom relief compared with SIT alone.

Omalizumab in Patients with Allergic Bronchopulmonary Aspergillosis

Omalizumab is reported to significantly improve symptoms and decrease medication use among patients with inadequately controlled moderate to severe persistent allergic asthma. However, better understanding of the mechanisms of action of omalizumab suggest wider applications in other allergic and allergy-related diseases. Recently, several published case reports noted the use of omalizumab in patients with ABPA, which is responsible for severe worsening of the respiratory symptoms in patients with cystic fibrosis or asthma. A high total serum IgE level is one of the diagnostic criteria seen in all patients. Treatment of ABPA involves administration of corticosteroids and antifungal agents to control airway inflammation and reduce the antigen burden from fungal colonization. Unfortunately, long-term treatment is often required, and the side effects of corticosteroid use are common. Most of the published case reports showed a rapid improvement in clinical symptoms and lung function, as well as steroid-saving effects after administration of omalizumab [28–31], while other reports showed no improvement [32]. A review of the published case reports indicates that early application during the acute phase of ABPA may be more promising than delayed use of omalizumab in these patients. However, properly controlled clinical trials showing

the safety and efficacy of omalizumab in patients with ABPA are awaited.

Omalizumab in Patients with Urticaria

Chronic urticaria has a wide spectrum of clinical symptoms, initial presentations, and etiologies. Unfortunately, disease control is not always satisfying despite a broad range of treatment options (ie, antihistamines, leukotriene receptor antagonists, prednisolone, and other immunosuppressives). Moreover, the cause of the urticaria might be found in a limited number of the patients. Elevated total IgE levels have been noted in several studies, primarily in children. Recently, Kessel et al. [33] demonstrated that patients with chronic urticaria have increased levels of total IgE and that their IgE levels correlate with disease severity.

The link between severity of chronic urticaria and IgE levels may be explained by the effect of IgE on mast cell activation and degranulation. Traditionally, IgE binding to FcεRI was considered a passive sensitization before receptor aggregation was initiated by an antigen or allergen. Recent observations in murine bone marrow-derived mast cells suggest that binding of various monomeric IgE molecules to the FcεRI receptors mediates a spectrum of receptor aggregation and mast cell activation regardless of the specific antigen. This phenomenon led to upregulation of FcεRI expression on cell surface, prolonged mast cell survival, and increased histamine, as well as leukotriene release. Notably, these non-antigen-specific, IgE-mediated events are much stronger than those induced by antigen-dependent activation [34]. Based on these pathophysiologic considerations, it is not surprising that omalizumab, which reduces serum levels of free IgE and FcεRI expression on mast cells and basophils, may also be useful in patients with acute or chronic urticaria. Several published case reports and case series describe a beneficial effect of omalizumab in patients with different forms of chronic urticaria resistant to conventional treatment [35•, 36–40]. Again, the results of the ongoing clinical trials must be examined before final recommendations for the clinical use of omalizumab in patients with chronic urticaria can be given. However, the effects in individual patients that are already published are promising.

Omalizumab in Patients with Atopic Dermatitis

Omalizumab has also been used as a potential new systemic treatment for patients with AD. The effects on patients with AD treated with omalizumab are controversial [41–45]. Some of the published case reports or case series

provide preliminary evidence demonstrating a beneficial effect of omalizumab in AD [41–43]. However, there are also several reports of patients with AD who did not improve with omalizumab [44, 45]. This might be explained by the fact that IgE levels in patients with AD are commonly very high (eg, in the study by Krathen and Hsu [44], IgE levels were between 5440 and 24,400 kU/L). It is possible that in patients with such high IgE levels, omalizumab cannot decrease those levels effectively. However, there are reports on the effects of omalizumab in patients with refractory atopic eczema and IgE levels far exceeding 700 IU/mL. Beloni and colleagues [45] reported that low-dose anti-IgE therapy with omalizumab, 150 mg, administered subcutaneously every 2 weeks resulted in a good to very good clinical response in 6 of 11 patients with IgE levels up to 30,000 IU/mL [45]. Of note, omalizumab was used in a dose range much lower than that required for the complete removal of IgE molecules. The authors discussed their results as an indicator that IgE need not be completely removed in these patients to attain satisfying clinical response, and that the effect of omalizumab seems to be of more regulatory mechanism rather than simple IgE blocking [45]. Further data are awaited that may help identify AD patients with or without response to omalizumab treatment.

Conclusions

Allergic diseases of the airways constitute a significant public health problem with an increasing impact on global health care resources. Evidence from existing studies suggests that omalizumab is highly effective in treating children and adults with moderate to severe allergic asthma and allergic rhinitis. Moreover, DBPC trials demonstrated that the combination of omalizumab and SIT is superior to SIT alone with respect to safety and efficacy. However, up to now, omalizumab is only licensed for the treatment of severe asthma. Beyond this indication, case reports and/or case series suggest that omalizumab is a promising therapeutic option for various allergic conditions, food allergy, urticaria, APBA, and AD. The reported treatment effects of omalizumab are especially promising in patients with chronic urticaria and ABPA. Properly designed clinical trials are awaited to confirm these results.

Disclosure Prof. Dr. Kopp has served as a consultant for Novartis, Bencard Allergie GmbH, and MSD; received honoraria from InfectoPharm, Novartis, and Roche; received payment for development of educational presentations (including service on speakers' bureaus) from Bencard Allergie GmbH, InfectoPharm, and Novartis; had travel/accommodations expenses reimbursed by Novartis, Chiesi, and Roche; and has received grant support from Novartis.

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