



Novel targets of omalizumab in asthma

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Purpose of review

Omalizumab is a recombinant humanized anti-IgE monoclonal antibody approved in the US for moderate to severe persistent allergic asthma (severe persistent asthma in the European Union), uncontrolled despite treatment with inhaled corticosteroids and long-acting beta2 agonists. It reduces asthma exacerbations, symptoms, oral corticosteroid doses, and improves quality of life.

Recent findings

Omalizumab may have an antiviral effect when used as a preventive therapy for fall exacerbations in children and teenagers. Two proof-of-concept studies have evaluated omalizumab in nonatopic asthma and showed that it is safe and possibly efficacious in some patients. Omalizumab has been successfully studied as add-on to specific immunotherapy in moderate allergic asthma. Its safety in pregnancy has been assessed in the EXPECT registry. Case series also report positive effects in cases of allergic bronchopulmonary aspergillosis, and in nasal disorders frequently associated with asthma. Last, omalizumab may have corticosteroid-sparing effect in a subset of patients with eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome).

Summary

Recent studies argue in favor of positive effects of omalizumab beyond its current indications in asthma. Well-designed studies are needed in order to demonstrate the safety and efficacy of omalizumab in these possible novel indications.

Keywords

allergy, asthma, nonatopic asthma, omalizumab

INTRODUCTION

Asthma is one of the most common chronic diseases worldwide, with an estimated 235 million affected individuals [1] and its prevalence consistently increases, becoming a public health problem in many countries. According to the Global Initiative for Asthma (GINA), asthma is a heterogeneous disease, characterized by chronic airway inflammation which manifests as respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, with variable expiratory airflow limitation [2^{••}]. About 70% of asthmatic patients are allergic and their phenotype is characterized by elevated serum levels of allergen-specific immunoglobulin E (IgE) [3]. The GINA experts recommend a stepwise approach for asthma treatment, to achieve good control of symptoms and maintain normal activity levels and to minimize future risk of exacerbations and fixed airflow limitation [2^{••}]. Most of patients have their asthma controlled with standard therapies such as inhaled corticosteroids (ICSs) and long-acting beta2 agonists (LABA). About 10% of asthmatic patients are considered as 'severe'. According to the ERS/ATS

guidelines, when the diagnosis of asthma is confirmed and comorbidities addressed, severe asthma is defined as asthma that requires treatment with high dose ICSs plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy [4].

Omalizumab is a recombinant humanized anti-IgE monoclonal antibody, which competitively binds to free IgE at the same binding site that IgE binds to the high affinity receptor (FcεRI) on mast cells and basophils and the low affinity receptor on

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KEY POINTS

- Omalizumab is approved in the US for moderate to severe persistent allergic asthma (severe persistent asthma in the European Union), uncontrolled despite treatment with inhaled corticosteroids and long-acting beta2 agonists.
- Omalizumab may have an antiviral effect when used as a preventive therapy for fall exacerbations in children and teenagers.
- Omalizumab is safe and possibly efficacious in a subset of patients with nonatopic asthma.
- Positive effects of omalizumab have been reported in cases of allergic bronchopulmonary aspergillosis.
- Omalizumab may have corticosteroid-sparing effect in a subset of patients with eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome).

other immunologic cells. This leads to inhibition of IgE-induced release of inflammatory mediators from mast cells and basophils, down regulation of FCεRI on mast cells, basophils and circulating dendritic cells and contributes to reduced mediator release in response to allergen [5,6]. Use of omalizumab is reported to significantly benefit patients with moderate to severe persistent allergic asthma that is not adequately controlled with high-dose ICS and LABA. This treatment confers improvement in symptoms, decreases exacerbation rates and permits decrease in systemic corticosteroid use. This clinical efficacy has been well documented in several clinical trials [7–12] and in ‘real-life’ effectiveness studies [13–15,16].

Since 2003, omalizumab is approved by the US Food and Drug Administration for treatment of moderate to severe persistent allergic asthma insufficiently controlled with ICS and LABA [6]. In the European Union, omalizumab is approved for the treatment of patients aged 6 years and older with severe persistent allergic asthma inadequately controlled with ICS and LABA [6]. In 2014, it was also approved for the treatment of chronic urticaria unresponsive to H1-antihistamines [17].

In the asthma indication, omalizumab is subcutaneously administered, every 2 or 4 weeks. The dose is calculated with body weight and pretreatment serum total IgE levels. Seventy-five to 600 mg can be administered with each injection; the maximum dose recommended is 375 mg every 2 weeks in the US and 600 mg every 2 weeks in the European Union. Consequently, patients with body weight or baseline IgE levels outside the limits of the dosing table should not receive the treatment. In the EU,

the dosing table was recently revised, expanding the eligible baseline IgE level to 30–1500 IU/ml (instead of 30–700) whereas it was not revised in the US [18]. In all countries, body weight must be no more than 150 kg.

Omalizumab has also been investigated in several clinical conditions other than allergic asthma, which includes nonatopic asthma, or in diseases frequently associated with asthma, such as allergic rhinosinusitis and nasal polyposis. Furthermore, its use in allergic asthma aside from the prescription rules has also been evaluated, such as in pregnancy or for the patients out of the ranging table. In this article, we will review novel targets of omalizumab in asthma.

ALLERGIC ASTHMA

Currently, omalizumab should not be used in patients with IgE levels and/or bodyweight out of the ranging table. However, some studies have evaluated the safety, pharmacodynamics and pharmacokinetics of this molecule on asthmatic patients with baseline IgE/bodyweight combination out of the dosing table [19,20]: in these studies, the safety profile was similar to that of omalizumab at lower doses and omalizumab seemed to block early asthmatic responses over a broad range of IgE/bodyweight combinations. Fewer studies analyzed the clinical efficacy of the treatment when given above the dosing table. A retrospective study compared 26 patients with IgE level greater than 700 IU/ml to patients with an IgE of 30–700 IU/ml [21]: omalizumab was as effective in reducing emergency department visits, controlling asthma symptoms and reducing the need for systemic corticosteroids in both groups. Hew *et al.* [22] also conducted a retrospective analysis, in the Australian Xolair Registry (AXR): 55 of the 176 patients in this registry were above the dosing criteria, mostly because of higher baseline IgE [812 IU/ml (IQR 632 1747) versus 209 (IQR 134 306)] and received higher doses of omalizumab [750 (IQR 650 750) mg] compared with within-range participants [450 (IQR 300 600) mg]. At 6 months, asthma control and FEV1 improved among above-range participants, and there was no difference in response between above-range and within-range participants.

Few studies are available concerning patients under the dosing table. In 2006, two patients with pronounced IgE-mediated asthma but with low serum IgE levels (<30 IU/ml) in Sweden were effectively treated with omalizumab but the dose had to be quadrupled [23].

The administration of omalizumab in pregnancy is not recommended. In 2015, the results of

the Xolair Pregnancy Registry (EXPECT) were published [24[¶]]. This prospective observational study evaluated maternal, pregnancy and infant outcomes after exposure to more than 1 dose of omalizumab within 8 weeks prior to conception or at any time during pregnancy. No apparent increased birth prevalence of major anomalies has been observed.

Omalizumab was developed to be administered every 2 or 4 weeks all year long. However, in children and adolescents, asthma exacerbations are more likely to occur during the fall after school resumes, probably because of rhinovirus infections and underlying allergic sensitization. The PROSE study (Preventive Omalizumab or Step-up Therapy for Fall Exacerbations) is a randomized double-blind placebo controlled trial, designed to determine whether a targeted strategy of preventive therapy with omalizumab beginning 4–6 weeks before the start of school and continuing for 4 months would be more effective than placebo or doubling the ICS dose (ICS ‘boost’) in preventing fall asthma exacerbations among children and adolescents already receiving guidelines-based therapy. The authors found a significant difference in the fall exacerbation rate in the omalizumab group versus the placebo group (11.3 vs. 21% OR 0.48 [0.25–0.92]) but no difference between omalizumab and ICS boost (8.4 vs. 11.1% OR 0.73 [0.33–1.64]). Furthermore, in patients with an exacerbation in the run-in phase, omalizumab was significantly more efficacious than placebo (6.4 vs. 36.3% OR 0.12 [0.02–0.64]) and ICS boost (2 vs. 27.8% OR 0.05 [0.002–0.98]). They explained this efficacy of omalizumab with a possible antiviral role of this treatment: first, omalizumab, by removing free circulating IgE, results in less IgE bound to mast cells and basophils, as well as suppression of allergic reactions and type 2 inflammation; moreover, they showed that interferon-alpha (IFN- α) responses to rhinovirus were significantly increased in the omalizumab-treated group. This raises the possibility that restoration of virus-induced IFN- α responses might be a mechanism for the preventive effect of omalizumab on respiratory virus-associated exacerbations.

Another novel target of omalizumab in allergic asthma is as an add-on to immunotherapy. Because specific immunotherapy (SIT) is contra-indicated in severe uncontrolled asthma, no published study has evaluated the effect of its association with omalizumab in severe asthmatic patients. However, in 2010, Massanari *et al.* [25] conducted a multicenter, double-blind, parallel-group study of 248 patients with an allergic persistent moderate asthma, treated with omalizumab or placebo, after which they received specific immunotherapy to at least 1 of 3 perennial aeroallergens (cat, dog and house dust

mite), according to a 4 week 18 injections cluster regimen, followed by 7 weeks of maintenance therapy. Patients receiving omalizumab experienced fewer systemic allergic reactions and fewer respiratory-related systemic allergic reactions than those receiving placebo and they were more able to reach the target maintenance immunotherapy. This omalizumab pretreatment could ease the use of immunotherapy in asthmatic patients, in terms of tolerance. In terms of effectiveness, Kopp *et al.* [26] conducted a randomized, double-blind, placebo-controlled, multicenter trial to assess the efficacy and safety of omalizumab *versus* placebo in combination with SIT during the grass pollen season in 140 patients with rhinoconjunctivitis and seasonal allergic asthma (severe asthmatic patients were excluded). Omalizumab or placebo was started 2 weeks before SIT; the whole treatment lasted 18 weeks. Combination therapy reduced the symptom load, and also improved asthma control and quality of life, over SIT monotherapy. It was suggested that these beneficial effects of omalizumab are because of its capacity to inhibit the fixation of IgE on B lymphocytes and other allergic response cells (eosinophil cells, mast cells, etc.).

NONATOPIC ASTHMA

Distinction between atopic and nonatopic asthma is not so clear: not finding a specific allergen sensitization does not exclude the participation of IgE in the pathophysiology of asthma, and there are more similarities than differences between these two variants of asthma [27]. IgE may be produced by B lymphocytes in nonatopic patients, may bind to high affinity receptors on mast cells and basophils and produce the same type of inflammation as in allergic patient, including eosinophilic inflammation and increased levels of interleukin (IL)-5, IL-4 and IL-13. Recent studies have attempted to test the safety and efficacy of omalizumab in uncontrolled severe nonatopic asthma. A 16-week proof-of-concept randomized controlled trial compared omalizumab with placebo in 41 nonatopic asthmatic patients who, despite daily treatment with or without maintenance oral corticosteroids, had severe asthma. The primary endpoint was the change in expression of Fc ϵ RI on blood basophils and plasmacytoid dendritic cells (pDC2). The impact of omalizumab on lung function and clinical variables was also examined. The authors found a statistically significant reduction in Fc ϵ RI expression on basophils and pDC2 in the omalizumab group, as compared with placebo, an increase in forced expiratory volume in 1 second (FEV₁), as compared with baseline, and a trend toward

improvement in global evaluation of treatment effectiveness and asthma exacerbation rate in the omalizumab group [28]. This was the first randomized control trial to investigate the biologic and clinical effects of omalizumab in this population. A retrospective analysis from a Spanish multicenter registry of severe asthma also found significant improvement in the clinical status of nonatopic patients treated off label with omalizumab as measured by the ACT (Asthma Control Test). There was also a trend toward reduced exacerbation rates and better lung function [29]. There is little understanding of the mechanisms behind this possible efficacy [30]: first, anti-IgE treatment could reduce a possible local allergic inflammation in the airways (in nonatopic asthma, such an allergic-like inflammation might exclusively occur locally without systemic evidence of IgE-driven pathomechanisms); second, omalizumab could also block the enhancement of mast cells survival; last, omalizumab might modulate innate immunity. In a recent study, 18 symptomatic, nonatopic asthmatics were randomized to receive omalizumab or placebo treatment in addition to existing therapy for 20 weeks [31¹¹]. Bronchial biopsies were collected before and after 12–14 weeks of treatment, then the patients destabilized by supervised reduction of their regular therapy. Primary outcome measures were changes in bronchial mucosal IgE+ cells at 12–14 weeks, prior to regular therapy reduction, and changes in FEV1 after destabilization at 20 weeks. This study showed that omalizumab but not placebo significantly reduced median total bronchial mucosal IgE+ cells but did not significantly alter median total mast cells, plasma cells, B lymphocytes and eosinophils. Omalizumab also improved lung function despite withdrawal of conventional therapy. The authors hypothesize that these results reflect the sequestration by omalizumab of free IgE within the bronchial mucosa, resulting in down-regulation of its receptor on local target cells.

Thus, some nonatopic patients may benefit from omalizumab therapy, but there is a need for further investigation to better assess its clinical efficacy in this setting, as well as to identify predictors of the response to treatment.

Patients with allergic bronchopulmonary aspergillosis (ABPA) [32,33] and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome) [34¹²] frequently suffer from severe asthma. These patients were excluded from the pivotal omalizumab randomized controlled trials. Only case series have studied the effect of omalizumab in these rare conditions. In most published cases of ABPA, anti-IgE therapy has improved

ACT scores, and reduced systemic inflammatory markers and oral corticosteroid doses [35–37].

Some authors have reported the occurrence of EGPA in patients treated with omalizumab [38,39]. It was hypothesized that in these patients, EGPA might be unmasked by the reduction or the withdrawal of systemic corticosteroid therapy, rather than driven by omalizumab itself. By contrast, others have reported cases of patients actually diagnosed for EGPA and successfully treated with omalizumab [40–42]. However, clinical and biological data on the efficacy of anti-IgE therapy are not sufficient to recommend this treatment in EGPA patients. Importantly, a recent report of 17 patients suggests that omalizumab may have corticosteroid-sparing effect in EGPA with asthmatic and/or sinonasal manifestations. However, reducing corticosteroid doses may also increase the risk of severe EGPA flares, raising the question of its safety in this condition [43¹³].

RHINOSINUSITIS AND NASAL POLYPOSIS ASSOCIATED WITH ASTHMA

The incidence of nasal polyposis and chronic rhinosinusitis in asthmatic patients is high, because the pathophysiology of the two diseases has common characteristics: as in asthma, the pathogenesis of these disorders includes local eosinophilic inflammation, with high production of IL-5, local IgE production and a Th2-type cytokine profile [44]. Patients with chronic sinusitis and nasal polyposis are difficult to treat (poor response to therapy and high recurrence rate). The involvement of IgE in the pathogenesis of rhinosinusitis and nasal polyposis associated with asthma suggests that anti-IgE might be relevant in such patients. A pilot study retrospectively collected data from two groups of patients with atopic asthma and nasal polyposis who underwent sinus surgery, half of them treated with omalizumab post-operatively: the nasal polyp scores significantly improved only in the omalizumab group, relative to preoperative values [45]. Since then, case series have suggested efficacy of omalizumab in chronic rhinosinusitis and nasal polyposis in severe asthmatic patients receiving this treatment for their uncontrolled asthma [46–48]. More recently, a randomized, double-blind, placebo-controlled study confirmed these findings, in 24 patients, with beneficial effects on endoscopic polyp score, airway symptoms, and quality of life [49]. In contrast, Pinto *et al.* [50] did not detect any difference in quality of life, symptoms, cellular inflammation, nasal airflow and olfactory testing in another randomized double-blind placebo-controlled study in patients with chronic rhinosinusitis treated with omalizumab.

There is indeed a possible role for IgE in asthmatic patients with nasal polyposis and chronic rhinosinusitis, and thus a need for more robust evidence. A major question in refractory nasal polyposis is whether the use of omalizumab could be useful before and/or after sinus surgery. More data are needed to address this question.

CONCLUSION

In conclusion, since its initial approval in moderate to severe allergic asthma, omalizumab has been successfully tested in other indications, such as chronic urticaria. Recent studies suggest that omalizumab might be efficacious in asthma beyond its current label, including a subset of patients with so-called 'intrinsic' nonatopic asthma. However, well-designed studies are needed in order to demonstrate the safety and efficacy of omalizumab in these possible novel indications.

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