



Targeting IgE in asthma

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Purpose of review

IgE plays a pivotal role in allergic asthma especially in the acute response to antigen and in the propagation of airway inflammation. Therefore, it has become apparent that targeting this antibody and blocking its function may lead to significant clinical effects in some patients with the disease. In this review, we describe the role of IgE in asthma and provide an update on the therapeutic implications of targeting this mediator in patients with severe allergic disease. We also outline future needs of research in this area.

Recent findings

Several randomized clinical trials as well as observational real-world studies have confirmed the long-term efficacy of omalizumab in improving clinical outcomes when added to guideline-recommended maintenance of asthma medications (inhaled corticosteroids and long-acting β_2 -agonists) in patients with moderate-to-severe asthma. Recent pooled data from randomized clinical trials and from a large prospective cohort study provide reassurance about the long-term safety of omalizumab. Future research should explore the long-term effects of omalizumab on the natural history of the disease and identify more accurate predictors of response to this treatment.

Summary

The anti-inflammatory effects of omalizumab at different sites of allergic inflammation and its clinical benefits in patients with allergic asthma emphasize the fundamental importance of IgE in allergic inflammation.

Keywords

asthma, IgE, omalizumab, pathophysiology, therapy

INTRODUCTION

The pathophysiological pathways that lead to airway inflammation, hyperresponsiveness and obstruction in asthma have been well characterized over the last few years, the fact that led to identifying novel targets for the improvement in the therapeutic approach to this disease [1^a,2,3]. Indoor and outdoor allergens are common and important triggers of asthma in the majority of patients. Allergens are presented via various antigen presenting cells such as monocytes, macrophages, B cells, and dendritic cells to Th2 lymphocytes, which are then activated. Activated T cells, under the control of intracellular kinases and downstream transcription factors, produce various cytokines such as interleukin-4, interleukin-5, and interleukin-13, which can further lead to activation and recruitment of several inflammatory cells, antigen-specific IgE production, eosinophilic inflammation, mucus secretion, and airway hyperresponsiveness (AHR). Antigen-specific IgE secreted from B cells interacts with mast cells and basophils via a high-affinity receptor (Fc ϵ RI), thus priming the system. When the same antigen is again encountered, it interacts with the

antigen-specific IgE on the surface of mast cells and basophils resulting in cross-linking and activation of these cells, leading to the degranulation and release of various mediators such as histamine, prostaglandin, leukotrienes, proteases, growth factors, cytokines, and chemokines. These mediators subsequently activate other cells such as B and T lymphocytes, eosinophils, fibroblasts, smooth muscle cells, and endothelial cells, which induce perpetuation of the cycle and further release of chemokine, cytokine, and growth factors. Therefore, IgE is an important mediator in allergic asthma, especially in the acute response to antigen and in the propagation of airway inflammation. In this review, we will describe the role of IgE in asthma

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KEY POINTS

- IgE plays a pivotal role in driving the pathogenesis of allergic asthma.
- Omalizumab is the first and only available recombinant antibody that blocks circulating IgE.
- Omalizumab has several effects on the cellular and clinical markers of airway inflammation.
- Several recent randomized clinical trials as well as observational real-world trials confirmed the long-term efficacy of omalizumab when added to guideline-recommended maintenance of asthma medications (inhaled corticosteroids and long-acting β_2 -agonists).
- Recent pooled clinical trial data and data from a large prospective cohort study provide reassurance about the long-term safety of omalizumab in patients with asthma.
- Future research should explore the long-term effects of omalizumab on the natural history of the disease and identify more accurate predictors of response to this treatment.

and provide an update on the therapeutic implications of targeting this mediator in patients with severe allergic disease, and outline future needs of research in this area.

ROLE OF IgE IN ASTHMA

Since its discovery in 1967, IgE has been shown to be important in many allergic diseases including allergic rhinitis and asthma. IgE can be locally synthesized in airway mucosa [4[•]] and has been recovered in bronchoalveolar lavage fluid from asthmatics. High-affinity receptors for IgE (Fc ϵ RI) are found on basophils, mast cells, and neutrophils, and are expressed in higher levels in allergic asthmatic patients. When IgE binds to Fc ϵ RI, it facilitates antigen presentation to T cells, allowing extremely small doses of the antigen to activate CD4⁺ T lymphocytes further promoting a Th2 response. A novel role for IgE in regulating differentiation of adaptive inflammatory responses through direct interaction with receptors on dendritic cells has been described [5]. Elevated IgE levels correlate with higher Fc ϵ RI expression on the surface of cells; the presence of IgE positively upregulates Fc ϵ RI on mast cells and basophils as well as prevents receptor internalization and degradation. In humans, IgE levels positively correlate with the presence of asthma symptoms, AHR, probability for allergic sensitization, forced expiratory volume in first second (FEV1) decline, eosinophilia, emergency room (ER) visits and severe exacerbations. Despite the strong

association of IgE with asthma, the level of IgE by itself is not a useful tool for diagnosis of asthma, and despite many attempts, a consistent diagnostic cut-off value has not been ascertained.

TARGETING IgE IN ALLERGIC ASTHMA

Because of the crucial and pivotal role of IgE in driving the pathogenesis of allergic asthma, it has become apparent that targeting this antibody and blocking its function may lead to significant clinical effects in some patients with the disease [6–8]. Free IgE in the serum has a very short half-life of approximately 2 days, but IgE is quite stable with a half-life up to several months once it is bound to the Fc ϵ RI. Furthermore, although IgE has the lowest concentrations out of all immunoglobulins, it remains extremely bioactive, requiring only 2000 IgE molecules to trigger a half maximal release of histamines from basophils. Therefore, an ideal potential therapeutic target of this pathway would need to counteract all available circulating IgE but not interfere with other systems or cause unwanted systemic effects.

OMALIZUMAB

Omalizumab is the first and only available recombinant humanized IgG1 monoclonal antibody that specifically targets and binds free IgE, preventing it from interacting with the high and low-affinity receptors, Fc ϵ RI and Fc ϵ RII. This decreases the free IgE available to interact with Fc ϵ RI on mast cells, essentially arresting the downstream cascade of asthma. Omalizumab has several effects on the cellular and clinical markers of airway inflammation as outlined below [9–13,14^{••},15,16[•],17[•],18]:

- (1) Cellular markers
 - (a) Reduces free IgE
 - (b) Downregulates high-affinity Fc ϵ RI receptors on mast cells, basophils, and dendritic cells
 - (c) Reduces IgE positive cells and high-affinity Fc ϵ RI receptors in bronchial submucosa
 - (d) Reduces mast cell-associated interleukin-4 in bronchial submucosa
 - (e) Reduces eosinophils in the blood, sputum, and tissue
 - (f) Decreases IgE production
- (2) Clinical markers and manifestations of disease
 - (a) Reduces exhaled nitric oxide (eNO)
 - (b) Reduces histamine release
 - (c) Reduces skin prick wheal and flare reactions.

In addition to reduction of serum levels of free IgE, it downregulates expression of high-affinity IgE

receptors (FcεRI) on mast cells and basophils. Furthermore, it decreases high-affinity FcεRI receptor expression on circulating dendritic cells, which might lead to a reduction in allergen presentation, and Th2 cell activation and proliferation. In the airways of patients with allergic asthma, it reduces high-affinity FcεRI and causes a profound reduction in tissue eosinophilia, together with reductions in submucosal T-cell and B-cell lymphocyte numbers.

Clinical efficacy

The clinical efficacy of omalizumab as add-on therapy in patients with moderate and severe allergic asthma in improving clinical outcomes has been well documented [19–22,23²²,24²²,25–31]. In the United States, omalizumab is currently recommended as an add-on therapy to inhaled corticosteroids (ICSs) in patients with moderate-to-severe allergic asthma. A minimum of 12–16 weeks is required to assess efficacy of therapy, with recommendations of re-evaluating its efficacy in those patients who have not responded by 6 months of therapy.

Several clinical trials have investigated the efficacy of omalizumab in patients with allergic asthma. A recent systematic review [32²²] of placebo-controlled studies was performed. Eight trials (3429 participants) fulfilled the selection criteria. At the end of the steroid-reduction phase, patients taking omalizumab were more likely to be able to withdraw from corticosteroids completely compared with those taking placebo [relative risk (RR)=1.80; 95% confidence interval (CI) 1.42–2.28; $P=0.00001$]. Omalizumab patients showed a decreased risk of asthma exacerbations at the end of the stable (RR=0.57; 95% CI, 0.48–0.66; $P=0.0001$) and adjustable-steroid phases (RR=0.55; 95% CI, 0.47–0.64; $P=0.0001$); post-hoc analysis suggests this effect was independent of duration of treatment, age, severity of asthma, and risk of bias. Since then, several additional randomized controlled trials and open label prospective real-life studies have been published in both adults and children from different countries that further support the role of omalizumab in asthma [23²²,24²²,26–29,33,34,35²²,36–38,39²²,40]. Early pivotal studies with omalizumab evaluated its efficacy as add-on to ICS in patients with severe allergic asthma; however, current management guidelines recommend its use as add-on to ICSs and long-acting β_2 -agonists (LABA) [41]. Recent studies have assessed the efficacy of omalizumab as an add-on to guideline recommended therapy. In a double-blind, placebo-controlled, parallel-group trial in inner-city children, adolescents and young adults

with persistent asthma, the effectiveness of omalizumab therapy when added to guideline-based therapy over 60 weeks was compared with placebo [23²²]. Omalizumab as compared with placebo significantly reduced the number of days with asthma symptoms, from 1.96 to 1.48 days per 2-week interval, a 24.5% decrease ($P<0.001$). Similarly, omalizumab significantly reduced the proportion of participants who had one or more exacerbations from 48.8 to 30.3% ($P<0.001$). Improvements occurred with omalizumab despite reductions in the use of inhaled glucocorticoids and LABA. In another recent study, Hanania *et al.* [24²²] evaluated the efficacy and safety of omalizumab over 48 weeks in patients with severe asthma not controlled despite treatment with ICS/LABA combination therapy ($n=850$). The rate of protocol-defined asthma exacerbations was significantly reduced for omalizumab compared with placebo (0.66 vs. 0.88 per patient; $P=0.006$), representing a 25% relative reduction. Omalizumab improved mean Asthma Quality of Life Questionnaire scores (0.29 point; CI 0.15–0.43), reduced mean daily albuterol puffs (−0.27 puff/day; CI −0.49 to −0.04 puff/day), and decreased mean asthma symptom score (−0.26; CI −0.42 to −0.10) compared with placebo. Three groups of patients were identified in this study based on baseline treatment; those on LABA and ICS alone (M1); those on LABA, ICS, and other asthma controlling medications (leukotriene modifiers, anticholinergic medications, mast cell therapy, immunotherapy, theophylline) (M2); and those on LABA, ICS, and oral steroids (M3). Although the results of this study demonstrated that all groups had a favorable response with omalizumab when compared with placebo, this response was most pronounced in the M1 subgroup, followed by M2, then M3. Although one explanation for this difference in response may be the smaller sample size of the M3 subgroup, another may be the fact that steroid-dependent asthmatics represent a different phenotype that is relatively poorly responsive to the effects of omalizumab. This issue needs to be addressed in future trials. Other studies have attempted to determine the predictors for response to omalizumab. Bousquet *et al.* [42,43] evaluated pooled data in an attempt to identify patient characteristics as predictors of clinical response. Patients requiring urgent treatment (defined as ER visit, hospital or ICU admission, or urgent doctor visit) in the past year, those with FEV1 less than 65%, and those with high use of ICS (>800 μ g equivalent of beclomethasone dipropionate daily) had a 2.25 times higher chance of responding to omalizumab when compared with placebo. However, there does not appear to be an association between IgE levels or allergen-specific

IgE and increased likelihood of response to omalizumab.

Safety profile

Because of the biologic nature of omalizumab and its systemic administration, its long-term safety has often been questioned. However, data from clinical trials that examined safety of this medication have been reassuring [44,45[¶]]. Anaphylaxis, although rare, has been reported with the use of omalizumab. In one series, 61% of reactions occurred in the first 2 h after one of the first three doses [46], and 14% of those occurring after the fourth or later dose occurred within 30 min. It is, therefore, recommended that this medication should only be administered in a healthcare setting, and patients should be educated about the potential risk for anaphylaxis and be monitored following the administration of the first few doses of the medication [46]. The risk of malignancy has also been a safety concern with omalizumab. Early pooled data from omalizumab pivotal clinical studies showed a numerical imbalance in malignancy arising in omalizumab recipients compared with those receiving placebo. The incidence of malignancy in the omalizumab group (0.5%) was similar to that expected in the general population but higher compared with control (0.2%). However, more recent pooled data from 32 randomized controlled clinical trials including 7432 patients (4254 received omalizumab and 3178 placebo) demonstrated a rate ratio for the incidence of malignancy in the omalizumab compared with placebo of 0.93 (95% CI 0.39, 2.27) [47]. Furthermore, interim results from the Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma (EXCELS) study, a prospective cohort study of 5000 individuals treated with omalizumab and 2500 control patients followed for 5 years [48], did not show any increase risk of malignancy with omalizumab with long-term use [49].

AREAS OF FUTURE RESEARCH

Several areas for future research in this field are needed. Although there are now some data showing continued efficacy of omalizumab in patients with long-term treatment, there is a need to explore predictors for long-term response as well as tools to objectively assess such a response [50–53]. Furthermore, the long-term effects of omalizumab on airway inflammation indices and remodeling have not been fully explored [16[¶],54[¶]]. Important clinical questions need to be answered such as the efficacy of omalizumab in nonallergic asthma

patients and in patients with IgE levels that are below or above the recommended levels. In addition, studies need to address the potential effects of omalizumab on IgE modulation with chronic therapy, on the natural history of the disease and determine an optimal duration, dose and frequency of long-term treatment. Long-term safety of omalizumab in children and the elderly population will need to be evaluated in future trials.

CONCLUSION

The anti-inflammatory effects of omalizumab at different sites of allergic inflammation and its clinical benefits in patients with allergic asthma emphasize the fundamental importance of IgE in allergic inflammation.

Conflicts of interest

K.K. has no conflicts of interest. N.A.H. has received research grant support and honoraria for speaking and serving on advisory boards for Genentech and Novartis.

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