

REVIEW

The role of IgE in allergen-induced inflammation and the potential for intervention with a humanized monoclonal anti-IgE antibody

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Introduction

IgE plays a key role in allergic reactions, particularly the early phase response. A humanized monoclonal anti-IgE antibody (omalizumab) that prevents IgE from binding to receptors on mast cells and basophils is undergoing clinical trials in a number of allergic diseases. Following intravenous or subcutaneous administration in humans, omalizumab has a long plasma elimination half-life (1–4 weeks) and decreases free IgE levels in serum. Omalizumab is well tolerated and shows promise in the treatment of asthma and seasonal allergic rhinitis.

Overview of allergen-induced inflammation

Although asthma, allergic rhinitis, atopic dermatitis, latex allergy and food allergy have very different manifestations, allergen-induced inflammation is a common denominator for all these atopic disorders. When an allergen is introduced into the airways, skin or gastrointestinal tract of a sensitized individual, an early allergic response is observed that peaks 15–30 min after the allergen challenge [1]. Some of these individuals exhibit a late-phase reaction that begins 3–6 h after the challenge and can persist for several hours to days [2]. In the lower airways, this dual reaction is accompanied by bronchial hyper-responsiveness to numerous stimuli, including histamine [3–5]. Chronic allergen exposure in sensitive atopic asthmatics is associated with inflammatory changes in the lung involving T cells, mast cells and eosinophils [6].

Immunoglobulin E (IgE) plays a crucial role in the allergic response [7]. Indeed, the early allergic responses

are mediated primarily by IgE-dependent processes [1]. These immune responses are initiated when IgE binds to high-affinity receptors (FcεRI) located on the surfaces of mast cells and basophils and is subsequently cross-linked by allergen, causing cell activation with the release of inflammatory mediators [8,9]. A number of these mediators, such as histamine as well as the neutral proteases, acid hydrolases and chemotactic factors, are pre-formed in the mast cells and basophils. Other compounds such as eicosanoids and platelet-activating factor are newly generated from precursor molecules once the IgE-triggered process has been established [1]. The relationship of the early- to the late-phase reaction is not well understood [10]. However, current evidence indicates a role for leucocyte-endothelial adhesion molecules in microvasculature, which are up-regulated by mediators and cytokines released during the allergic response [1]. The effects of the mediators depend upon the tissue into which they are released. For example, the predominant effects seen in the complex vascular bed of the nasopharynx include mucosal engorgement and exudation of fluid. Sneezing and nasopharyngeal pruritus result from the stimulation of afferent nerve endings by mediators [11].

The early asthmatic response to allergen is closely associated with the level of specific IgE [12,13]. Indeed, the provocative dose (PD₂₀), i.e. the dose of allergen required to produce a 20% fall in forced expiratory volume in 1 s (FEV₁), can be estimated with a reasonable degree of accuracy from the knowledge of skin sensitivity to allergen and non-specific bronchial hyper-responsiveness [14]. This is not surprising because early response depends upon the cross-linking of IgE by allergen on the surface of mast cells and basophils.

IgE is also postulated to be involved in the late-phase asthmatic response [15]. However, Durham *et al.* were

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unable to find an association between total or specific IgE, and a pattern of asthmatic responses following allergen inhalation [16]. The pathogenesis of late asthmatic response is less well defined and non-IgE (T cell-directed) processes may also be important [17]. The late asthmatic response reflects mucosal inflammation involving neutrophil and eosinophil infiltration and activation, and is linked to enhanced non-specific bronchial responsiveness [3–5,18].

Until recently the role played by the IgE-initiated mechanism has not been clearly understood. Atopy is associated with the development of asthma [19], although a recent meta-analysis suggests that less than 40% of the risk for adult or childhood asthma with an attributable cause can be accounted for by atopy [20]. Evidence supporting the role of IgE in asthma includes the correlation of elevated serum IgE levels with self-reported asthma symptoms [21,22] and airway hyper-responsiveness [23–25]. However, other studies cast doubt on the role of IgE as an important indicator of respiratory allergic diseases [26]. In the African population, serum levels of IgE have been reported to be higher in non-asthmatics than asthmatics [27]. It is likely that the traits of high serum total IgE and bronchial hyper-responsiveness are independently inherited [28].

A high serum total IgE may not always be associated with atopy. The influence of total and specific IgE on the development of asthma phenotype (symptoms and specific and non-specific bronchial hyper-responsiveness) is complex. *In vitro* studies indicate that specific IgE determines allergen responsiveness but does not influence non-specific bronchial responsiveness, which is more closely related to serum total IgE [29]. Beeh *et al.* [30] recently reported that asthma is more common in those with negative skin prick test to common allergens, if their serum total IgE was high. Even non-atopic asthmatics manifest raised serum total IgE in addition to raised blood and airway eosinophilia [31]. The bulk of the evidence suggests that IgE plays an important signalling role in most patients with atopic asthma and perhaps even in some patients with non-atopic asthma.

Currently available anti-inflammatory therapy in allergic disease attempts to suppress inflammation (corticosteroids) or antagonize the receptor-mediated effects of specific inflammatory mediators (leukotriene antagonists). Long-term use of corticosteroids is associated with adverse effects such as suppression of the hypothalamic-pituitary-adrenal axis, osteoporosis, obesity, cataracts, hyperglycaemia and growth retardation in children [32]. Cysteinyl LT₁ receptor antagonists are effective as supplementary therapy but there is considerable inter-individual variability in their efficacy [33]. The anti-inflammatory effects of inhaled drugs with mast cell-stabilizing properties (such as sodium cromoglycate and nedocromil sodium), inhaled long-acting

β_2 adrenoreceptor agonists and H₁ histamine antagonists are limited. There has been relatively little improvement in hospital admissions associated with asthma despite extensive use of inhaled corticosteroids during the past decades [34–36]. Lack of patient education and poor compliance with therapy may have contributed to sub-optimal asthma management. Allergen-specific immunotherapy is useful in the treatment of insect sting sensitivity and in some cases of allergic rhinitis; however, it is not recommended for food allergy and its role in asthma is controversial [37]. In addition, allergen-specific immunotherapy is effective only when one or two allergens are targeted [38]. This makes it unsuitable for the majority of patients with asthma and rhinitis, who exhibit multiple allergen sensitivity. A new approach to circumventing allergen-induced inflammation will soon be available in the form of a blocking, fully humanized, monoclonal antibody that effectively reduces circulating and tissue levels of the sensitizing antibody class, IgE.

Intervention through blocking of IgE binding

The availability of non-anaphylactogenic anti-IgE antibody opens the possibility of preventing the allergic reaction at the outset. It has also helped to clarify the role of IgE in different types of allergic inflammation. In a murine model of asthma, anti-mouse IgE antibody has been shown to suppress both early and late allergen-provoked airway responses, tissue eosinophilia and bronchial hyper-responsiveness, and interleukin (IL)-4, but not IL-5 levels, in bronchoalveolar lavage fluid [39]. A murine anti-human IgE monoclonal antibody was first developed that was directed against an epitope on the F_C fragment of IgE that specifically bound to the α chain of the trimeric high-affinity IgE receptor (Fc ϵ RI) (data on file, Genentech). This antibody was subsequently humanized using genetic engineering procedures [40] and has been designated omalizumab. Omalizumab binds to IgE either free in the serum or expressed on B cells at the high-affinity receptor (Fc ϵ RI) binding site. IgE is thus prevented from binding to the Fc ϵ RI and an IgE-triggered mediator release is inhibited. Importantly, because the epitope is masked when IgE is bound to Fc ϵ RI, omalizumab is not able to bind to mast cell- or basophil-bound IgE and therefore is not able to initiate mediator release. A clear advantage of blocking IgE is that inflammation is prevented at its source rather than relying on suppression of inflammation once it has occurred. The advantages of a humanized over a murine monoclonal antibody are that the former has a prolonged elimination half-life [41], is much less likely to provoke an immune reaction in humans [41,42] and has greater activity in enhancing effector functions such as antibody-dependent

cell-mediated cytotoxicity [43,44]. All these factors contribute to enhanced therapeutic efficacy.

Of considerable interest and importance is the observation that omalizumab, when administered to atopic subjects, also causes a profound down-regulation of FcεRI receptors on circulating basophils in association with a reduction in free IgE levels, thereby enhancing its therapeutic potential [45]. The fact that these effects occur in tandem increases the likelihood that omalizumab will have a measurable clinical effect. The plasma elimination half-life of omalizumab after administration of 0.05–1.0 mg/kg intravenously or 0.005–0.14 mg/kg subcutaneously in adults ranges from 1 to 4 weeks [46] allowing a long dosing interval. The pharmacokinetic and pharmacodynamic properties of omalizumab in children and adolescents are similar to those in adults [47]. When administered directly into the airways in an aerosolized form, omalizumab failed to suppress early- or late-phase allergen responses and was probably more immunogenic than has been observed with the parenteral route [48].

Efficacy and tolerability of omalizumab therapy

Asthma

It is now generally acknowledged that asthma is responsible for a great number of consultations with family doctors and specialists, accident and emergency visits and hospitalizations. The incidence of asthma is rising world-wide [49,50], and the number of asthma deaths has not decreased despite increased use of anti-inflammatory therapy [34]. The pathophysiology of asthma is complex and multifactorial; however, it is recognized that allergic factors and non-allergic triggers interact to cause bronchial inflammation, bronchial hyper-responsiveness and subsequent airway constriction, which in turn leads to the symptoms of wheezing, chest tightness, shortness of breath and cough. Reduced exposure to allergens has been found to improve control of symptoms to some degree, especially if a single allergen is involved (e.g. house dust mite) [51,52].

A number of clinical studies examining the efficacy of omalizumab in patients with asthma have been conducted. In a multicentre, randomized, double-blind, parallel-group study of 20 patients with stable, mild, allergic asthma, 11 received omalizumab 2 mg/kg intravenously on day 0, and 1 mg/kg on days 7, 14, 28, 42, 56 and 70 [53]. Omalizumab blunted early-phase responses to airway challenge with allergen, as measured by the concentration of allergen required to provoke a 15% reduction in FEV₁. In addition, the mean concentration of free IgE in serum decreased by 89% compared with baseline in the omalizumab group, whereas there was no change in the placebo group. Non-specific bronchial responsiveness, as measured by the

concentration of methacholine needed to provoke a 20% drop in FEV₁ (PC₂₀), improved with omalizumab treatment, the change becoming statistically significant on day 76, but not changing in the placebo group. Interestingly, no changes in skin prick tests were noted in either group at the end of the active treatment interval. Omalizumab was generally well tolerated. Four patients in each group reported an adverse effect; one patient in the omalizumab group was withdrawn from treatment because of an urticarial rash thought to be treatment related.

In a similar study in 19 atopic patients with asthma [54], Fahy et al. found that, compared with placebo, omalizumab suppressed both the early- and late-phase responses to inhaled allergens. Mean serum levels of free IgE dropped by approximately 90% in the omalizumab group and remained unchanged in the placebo group. Although the percentage of eosinophils in induced sputum fell significantly after treatment with omalizumab compared with baseline, there was no statistically significant change in the placebo group. There were no changes in the concentrations of eosinophil cationic protein in induced sputum following treatment with omalizumab. Similarly, the decrease in blood eosinophil percentages in the omalizumab group was not statistically different from the change in the placebo group. Treatment with omalizumab resulted in an improvement in the PC₂₀ for methacholine but this change was not statistically significantly different from the change in the corresponding value in the placebo group. The responses to skin-prick tests at the end of treatment compared with baseline were similar in both groups. Omalizumab was well tolerated, with only one patient withdrawing from the study (worsening asthma symptoms.) The moderating effect of omalizumab on the late-phase response to bronchial allergen challenge may be particularly relevant clinically because a reduction in late-phase response has been shown to be a better marker of clinical improvement of asthma symptoms than a reduction in the early-phase response [55].

In these allergen challenge studies the patients had mild disease and consequently there was no effect of omalizumab on asthma symptoms, pulmonary function or medication requirement. However, these studies were not designed to measure the impact of omalizumab on disease symptoms. In contrast, a multicentre, randomized, double-blind study was conducted in patients with moderate to severe allergic asthma who required inhaled and/or oral corticosteroids to compare the effects on asthma symptoms of omalizumab 5.8 (µg/kg/ng IgE/mL, high dose, *n* = 106) and 2.5 (µg/kg/ng IgE/mL, low dose, *n* = 106) intravenously on days 0 (half a dose), 4 (half a dose) and 7 (full dose), and then every 2 weeks for 12 weeks compared with placebo (*n* = 105) [56]. The three treatment groups were well matched with respect to demographic characteristics.

Both the high- and low-dose groups of omalizumab produced a statistically significant improvement in mean symptom scores compared with placebo at 12 weeks ($P = 0.008$ and $P = 0.005$, respectively). Although morning peak expiratory flow rates (PEFR) had increased in both active treatment groups after 12 weeks, the mean change was statistically significant compared with placebo only in the high-dose group ($P = 0.007$). There was no significant change in FEV₁ compared with placebo in either of the treatment groups. After 12 weeks of omalizumab treatment, corticosteroid use was tapered over 8 weeks. This resulted in a reduction in the use of inhaled corticosteroids of at least 50% in 51% of the patients in the high-dose group, 49% of the low-dose group and 38% in the placebo group. The decrease in use of inhaled corticosteroid was significant only in the high-dose group. Over the 20-week treatment period, asthma exacerbations were experienced by 30% of patients in the high-dose group, 28% of the low-dose group and 45% of the placebo group. Serum IgE levels in both omalizumab groups decreased by a mean of $>95\%$ after 20 weeks. After 12 weeks of treatment, patients in the active treatment groups showed statistically significant improvements in quality-of-life compared with placebo, as assessed using the Asthma Quality-of-Life (QoL) Questionnaire ($P < 0.001$ and $P = 0.007$, respectively, for overall QoL score). These improvements were maintained over the entire period of corticosteroid withdrawal.

The adverse events and the numbers of withdrawals from the study were similar in the three groups, with slightly more patients in the omalizumab group experiencing urticaria. No patient in the active treatment group developed antibodies to omalizumab. In this study, considerable improvement was observed in many variables in the placebo group. For example, corticosteroid reduction was possible in 38% of the patients in the placebo group. Therefore, improvements with omalizumab, particularly in the low-dose group, did not always reach statistical significance. It is possible that, at recruitment, patients were not complying fully with the prescribed treatment. In addition, patients often improve under the more regular observation of a specialist during a clinical trial.

The clinical efficacy of omalizumab was corroborated by the results of two randomized, placebo-controlled trials (one in children and one in adults) presented at the 56th Annual Meeting of the American Academy of Allergy, Asthma and Immunology in San Diego [57,58]. Patients who were symptomatic despite taking inhaled corticosteroids were randomized to receive omalizumab or placebo for 28 weeks. After a 16-week stable treatment period, the corticosteroid dose was gradually reduced to determine the minimum dose required for asthma control. In both studies, omalizumab was associated with significantly greater

corticosteroid dose reductions than those in the placebo group. In addition, omalizumab-treated patients also had significantly fewer asthma exacerbations compared with the placebo group.

Allergic rhinitis

Allergic rhinitis affects a large proportion of the population and although often seasonal in nature, it causes considerable distress to the sufferer and cost to society in terms of healthcare resources consumed and lost productivity.

In an open-label study in 47 patients with perennial allergic rhinitis and positive skin prick tests to dust mites, omalizumab 0.015 or 0.030 mg/kg/IU/mL was administered intravenously every 2 weeks for 26 weeks and a reduced dosage was administered every 2 weeks for a further 20 weeks [59]. Both dosage regimens of omalizumab resulted in a $\geq 98\%$ reduction in mean free serum IgE levels compared with baseline and a statistically significant reduction in the mean sums of the wheal areas after skin testing at week 26 compared with baseline ($P \leq 0.001$).

In a double-blind, placebo-controlled multicentre trial, patients with ragweed-induced seasonal allergic rhinitis were randomized to receive omalizumab 300 mg ($n = 129$), 150 mg ($n = 134$), 50 mg ($n = 137$) or placebo ($n = 136$) [60]. Beginning 2 weeks before the pollen season and continuing for 12 weeks, omalizumab was administered subcutaneously every 3 or 4 weeks depending upon serum total IgE levels (151–700 and 30–150 IU/mL, respectively). Daily nasal symptoms, daily ocular symptoms and number of rescue tablets required were recorded. A clear correlation between dose and response was revealed, with the two highest doses providing the greatest relief of symptoms. Urticaria was reported in two patients treated with omalizumab (0.5%) but otherwise the incidence of adverse events was similar in the active treatment and placebo groups. No patients treated with omalizumab developed antibodies directed against the drug. Further analysis of the data suggests that the clinical efficacy of omalizumab, in terms of improvement in symptoms, is related to its ability to decrease serum free IgE levels [61]. Quality-of-life assessments (Juniper Rhinoconjunctivitis QoL Questionnaire, RQLQ), performed in 435 of the patients, indicated statistically significant improvements from baseline to the visit closest to the peak pollen season in the two highest dose groups compared with placebo ($P \leq 0.025$ for RQLQ total scores) [62]. In a recent study [63], 251 adult subjects with birch pollen-induced seasonal allergic rhinitis, received omalizumab 300 mg or placebo subcutaneously two or three times during the season, depending on the baseline IgE levels. There was a statistically significant improvement in

nasal symptom severity scores, rescue medication use and quality-of-life scores.

Other possible indications/future research directions

Because IgE is involved in the inflammatory processes underlying atopic dermatitis, latex allergy, food allergy and anaphylaxis, treatment with omalizumab may also prove to ameliorate these conditions. Latex allergy is not uncommon, with 5–10% of healthcare workers exhibiting sensitization [64]. Once sensitized, very little exposure is needed to initiate a reaction, as indicated by a recent report of an individual who experienced serious reaction after ingesting orange juice stirred with a latex-gloved finger [65]. Food allergies appear to be increasing in incidence [66]. Peanut allergy, in particular, has received attention in the media because of associated deaths, in both children and adults [67]. Individuals with atopic diathesis often suffer from more than one allergic disease. Indeed, it is not uncommon to see children with asthma, allergic rhinitis and atopic eczema as well as allergies to certain foods. The great advantage of anti-IgE therapy is that it is not allergen- or disease-specific and may prove to be efficacious in a number of IgE-mediated disorders.

Allergen-specific immunotherapy is used successfully to treat insect sting allergy, pollen allergy and may have a role in the treatment of other allergic conditions. However, the risk of anaphylactic reactions prohibits its use on a wider scale. IgE mediates the anaphylactic reactions in this situation. As anti-IgE therapy reduces serum IgE to very low levels, another possible use of omalizumab could be to eliminate the risk of anaphylaxis during allergen-specific immunotherapy. However, IgE may play a role in antigen presentation to the T cell, possibly mediated by CD23, the low-affinity IgE receptor [68]. By inhibiting this interaction, omalizumab may reduce the efficacy of allergen-specific immunotherapy.

Implications for clinical use

Asthma

Treatment with anti-IgE is likely to be most effective in patients with allergic asthma. However, recent studies [30,31] suggesting a role of IgE in non-allergic asthma indicate that this therapy may be useful in some patients with non-allergic asthma who have high serum IgE.

The vast majority of asthmatic patients have mild asthma and can be treated adequately with low doses of inhaled corticosteroids. In moderate to severe disease, omalizumab has been effective in reducing symptoms, asthma exacerbations and the need for corticosteroids. For these patients where the asthma is more difficult to treat, including those

with recurrent exacerbations or persistent symptoms despite conventional treatments, and those with poor compliance, or those on high doses of inhaled steroids, omalizumab may be a very useful treatment option. The steroid-sparing effect is particularly important in children because of the concern regarding adverse effects. The infrequent administration schedule of once or twice per month may prove to be very conducive to compliance, particularly if there is an opportunity for patients to self-administer the product. In severe asthma, omalizumab may need to be given in combination with other anti-asthma treatment such as long acting β_2 agonists, leukotriene antagonists or theophylline. This concept has yet to be evaluated.

Other atopic diseases

Patients with other severe atopic diseases may also benefit from anti-IgE therapy. In severe seasonal and perennial allergic rhinitis, inadequately controlled with topical nasal steroids and antihistamines, omalizumab may be useful as a solitary or adjuvant therapy. Omalizumab is effective and well tolerated in allergic rhinitis; however, its usefulness in severe allergic rhinitis and particularly as a steroid-sparing agent has yet to be determined. With the potential of blocking IgE-mediated immune responses, omalizumab may become a standard therapy for other potentially life-threatening IgE-mediated disorders, such as severe peanut and latex allergy. This form of therapy may be particularly attractive for patients who suffer concomitantly with several IgE-mediated disorders.

Conclusions

Allergen-induced inflammation, triggered by IgE binding to high-affinity receptors on mast cells and basophils, is part of the underlying pathophysiology of asthma, allergic rhinitis, atopic dermatitis, latex allergy and food allergy. The consequences of these conditions range from associated discomfort/pain (allergic rhinitis, atopic dermatitis) to increased risk of mortality (asthma, severe food allergy) and have a negative impact on quality of life. Omalizumab is a humanized monoclonal antibody that prevents IgE from binding to the receptors on mast cells and basophils. *In vivo*, it has a long plasma elimination half-life (1–4 weeks) and decreases free IgE levels in serum. Omalizumab has been shown to have a statistically significant beneficial effect on asthma symptoms as well as some objective measures of asthma control. It has also exhibited a dose-related impact on symptom scores for patients with seasonal allergic rhinitis. Positive effects on quality of life measures have been demonstrated with omalizumab for both asthma and seasonal allergic rhinitis. Urticaria has

been reported in association with the use of omalizumab but the incidence is low.

Although atopy is a major risk factor for asthma, not all asthma is atopic. Therefore some patients with asthma may not benefit from anti-IgE therapy. Another disadvantage of omalizumab is the need for parenteral therapy (intravenous or subcutaneous). However, it has a long-term effect and in moderate to severe asthma, where it has been shown to be effective, a dosing regimen of every 2 weeks or once a month may be quite acceptable. Indeed, this will ensure compliance, often a major problem in the treatment of chronic diseases such as asthma.

It seems unlikely, at least at present, that the IgE blocker omalizumab will become a first-line treatment for atopic conditions. However, in refractory asthma and severe allergy, it offers a promising, well-tolerated preventative therapy. Alternative therapeutic options are particularly needed for asthma, which is associated with substantial morbidity and mortality, has no known cure, and is not well controlled in many individuals despite multiple drug treatment. In addition, omalizumab appears to be well tolerated in children, in whom treatment options for atopic diseases are more limited. Finally, because it is administered infrequently, omalizumab may be useful in patients who have difficulty complying with daily treatment.

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