The role of anti-IgE therapies in the treatment of asthma

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The prevalence of asthma, a chronic inflammatory disease often linked to allergy, is on the increase. The introduction of a blocking anti-IgE monoclonal antibody (omalizumab) as a new therapy has not only confirmed the pathogenic role of IgE in asthma but has also provided a novel therapy for a chronic severe disease where there are limited therapeutic options.

Asthma is a disorder in which chronic airway inflammation acting on remodelled airways causes variable airflow obstruction. Atopy is an important risk factor for asthma and it contributes to around 50% of the population risk for asthma (Pearce et al, 1999). Under these conditions of airway inflammation, remodelling and atopy, the consequences of inhaling allergen loads contribute to the severity of disease and allergen avoidance strategies can bring about measurable, albeit limited, improvements in outcome measures (Platts-Mills et al, 2000).

The discovery that reagin, the agent in serum described by Prausnitz and Kustner (1921) that could passively transfer allergy, was an immunoglobulin E (IgE) added a new facet to the understanding of allergic disorders (Ishizaka and Ishizaka, 1967; Johansson and Bennich, 1967). The role of IgE in asthma has been extensively studied. Allergic airway inflammation is the result of a failure to control otherwise harmful IgE-mediated immune responses. This altered immune state is characterized by increased production of IgE in response to environmental antigens and allergens. Epidemiological evidence supporting the role of IgE in asthma includes the correlation of elevated serum IgE with self-reported asthma symptoms and airway hyperresponsiveness. The development of asthma is associated with high levels of serum IgE, which in turn is linked to genetic markers on chromosome 5q 31–33 which includes the interleukin (IL)-4 gene cluster (Postma et al, 1995) containing genes controlling IgE switching (IL-4 and IL-13) as well as cellular events characteristic of allergic inflammation (IL-3, IL-5, IL-9 and granulocyte macrophage-colony stimulating factor (GM-CSF)). Most of the cells implicated in the allergic response bear IgE receptors and can be activated by cross linking of the bound IgE.

ALLERGIC INFLAMMATION IN ASTHMA

An elevated level of serum total and specific IgE circulates in the blood and enters the tissues, including airway mucosa, where it binds to the high affinity receptors (FcεRI) on the surface of mast cells and basophils and low affinity receptors (FcεRII/CD23) on eosinophils, macrophages and platelets. The cross linking of the cell-bound IgE by polyvalent allergens results in activation of mast cells which release a range of preformed (e.g. histamine, heparin, tryptase) and newly generated (prostaglandins and leukotrienes) pro-inflammatory mediators leading to bronchoconstriction. In the case of allergen exposure this is experienced as an early asthmatic response (EAR) which is followed 2–6 hours later by the late asthmatic response (LAR) characterized by the recruitment of inflammatory cells into the airways and accompanied by an acquired increase in bronchial hyperresponsiveness.

The significant role played by IgE in the development and propagation of allergic inflammation creates a possible target for intervening in the allergic cascade. Biotechnological advances have enabled the development of a recombinant humanized IgG_1 monoclonal antibody, omalizumab (rhuMAb-E25, Xolair®, Novartis Pharma AG, Basel, Switzerland), directed specifically to the binding site for high-affinity IgE receptors on the Fc fragment of the IgE molecule (Kolbinger et al, 1993). A therapy interfering with the binding of IgE molecules to

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their receptors should reduce the allergen-induced EAR and LAR by preventing the release of mediators from mast cells. In addition, this should decrease the amplification of the inflammatory responses mediated by helper T-cells (Th) by preventing IgE-dependent allergen presentation (Babu et al, 2001b).

PHARMACOLOGY OF OMALIZUMAB

Omalizumab binds to the same site on IgE as the FcεRI receptors thereby reducing the amount of IgE that is available to bind to the high affinity receptors on effector cells (Presta et al, 1993; Shields et al, 1995). Since the binding site for the FcεRII is located close to the FcεRI binding site, omalizumab probably also prevents the binding of IgE to FcεRII. IgE receptor density is believed to correlate with mast cell excitability, therefore, up-regulation of the number of IgE receptors on the cells activated by specific allergens, such as mast cells and basophils, will enhance immediate hypersensitivity responses. During continued administration, the fall in serum free IgE is accompanied by a reduction in FcεRI expression on effector cells, reduced occupancy of these cellular receptors, and reduced responsiveness of the cells to appropriate antigenic stimuli in sensitive subjects (MacGlashan et al, 1997).

A fundamental aspect in the development of omalizumab as a safe therapy was its inability to bind to IgE bound to cells bearing the FcεRI or the FcεRII (the epitope on IgE against which they are directed is already attached to these receptors and as a consequence masked) thereby avoiding mast cell or basophil activation (*Figure 1*). Omalizumab per se does not have bronchodilator properties but provides significant protection against the bronchoconstriction observed during both the EAR and LAR to allergen challenge in subjects with mild allergic asthma (Boulet et al, 1997; Fahy et al, 1997). As a blocking antibody omalizumab binds to free IgE but not to IgA or IgG, reducing the free IgE levels. Levels of serum free IgE decrease by ≥90% from pretreatment values within approximately 24 hours of subcutaneous administration of omalizumab. However, the total IgE concentration becomes elevated because of the formation of IgE–anti-IgE complexes which have a longer serum half life.

Omalizumab binds to serum free IgE to form complexes made up of trimers or cyclic hexamers that are biologically inert and do not possess antigenicity and lack the ability to fix complement. The mean absolute bioavailability is 53–71% and the terminal half life for the intravenous and the subcutaneous route is approximately 3 weeks (Fox et al, 1996) with no clinically important differences in adults and children. The volume of distribution is similar to the plasma volume, indicating little or no accumulation in peripheral tissue. Omalizumab is slowly cleared from the blood and omalizumab–IgE complexes are cleared more rapidly from the circulation than uncomplexed omalizumab. The major route of elimination is through urine with approximately 50% of the administered dose excreted at 96 hours.

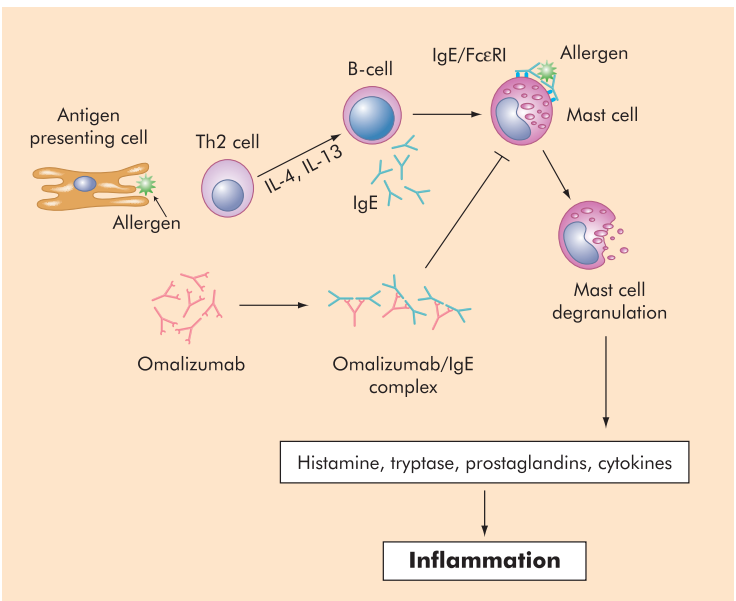

Figure 1. Helper T cells (Th2) provide signals for immunoglobulin (Ig)E production through interleukin (IL)-4 and IL-13. Cross linking of IgE by allergen leads to mast cell degranulation and release of pro-inflammatory mediators, resulting in bronchoconstriction and increased mucus secretion. Omalizumab binds to free IgE thereby reducing its concentration but does not bind to mast cell or basophil bound IgE receptors or stimulate histamine release by itself.

INITIAL STUDIES WITH OMALIZUMAB IN ASTHMA

Early studies on mice sensitized to house dust mites showed that a mouse homologue of omalizumab significantly reduced lung eosinophilia following allergen challenge and a diminished production of IL-5 by airway Th2 cells (Coyle et al, 1996). Intravenous administration of omalizumab attenuated the EAR and significantly increased levels of PC_{15} and PC_{20} after allergen challenge (Boulet et al, 1997). Reductions in circulating eosinophils and eosinophil counts in induced sputum have been reported in patients with allergic asthma during treatment with omalizumab (Fick et al, 2000). These findings suggested a role for omalizumab in the treatment of asthma and encouraged clinical trials. In a phase IIb study on a subgroup of oral corticosteroid-dependent patients (317 subjects) with moderate to severe asthma approximately 50% of patients treated with omalizumab were able to achieve a

50% or greater reduction in their dose of oral corticosteroids (Milgrom et al, 1999).

CLINICAL TRIALS WITH OMALIZUMAB

The phase III trials were randomized, double-blind, parallel group, placebo-controlled multicentre trials conducted on children, adolescents and adult patients with moderate to severe asthma (Busse et al, 2000; Milgrom et al, 2000; Soler et al, 2000). All three studies followed largely the same design. During the run-in period, 4–6 weeks before randomization, patients were switched to beclomethasone dipropionate (BDP). The dose was adjusted to the lowest dose consistent with control of the patients' asthma. Omalizumab was administered every 2–4 weeks for 16 weeks at a dose calculated on the basis of body size and serum total IgE. On completion of the core treatment, patients continued to receive either omalizumab or placebo every 2–4 weeks for a further 24 weeks in either a double-blind (in adolescents and adults) or open-labelled manner in the paediatric study.

In both the adult (n=1071) and the paediatric populations (n=331) in the second phase of the study there was a clinically relevant and significant reduction in the mean number of asthma exacerbations per patient in those treated with omalizumab when compared to placebo. However, the reduction in the exacerbations was not significant in the paediatric population in the active first phase of treatment (P=0.093). The reduction in asthma exacerbations in the omalizumab group occurred despite a significantly greater reduction in BDP dose from baseline to the end of treatment in the omalizumab group compared with placebo. Patients treated with omalizumab also had better symptom control and a reduction in the use of their rescue medications.

In all three studies, the reduction in the dose of corticosteroids was significantly greater in patients treated with omalizumab than in those who received placebo. The median proportion of asthma-controlled days was also significantly greater in the omalizumab group compared to the placebo (0.06 *vs* 0, P<0.001). In addition, more patients treated with omalizumab were able to totally withdraw from use of inhaled steroids than placebo-treated patients. Although the difference was less marked in the paediatric population, it still reached statistical significance (P=0.002). In comparison with placebo, the quality of life was significantly better in patients treated with omalizumab and more patients achieved clinically meaningful improvement in quality of life.

A more recently concluded study conducted on 246 patients with controlled severe asthma requiring high doses of inhaled fluticasone propionate (1000–2000 mg/day) has revealed that two-thirds of the patients in the core treatment group treated with omalizumab were able to reduce their dose of inhaled steroids by approximately 750 mg/day. Furthermore, this control was maintained without worsening frequency of asthma exacerbation, symptom control or rescue β_2-agonist use. The asthma-specific quality of life also showed a significant improvement in favour of omalizumab (Holgate et al, 2001a, b).

SAFETY OF OMALIZUMAB

Results from the phase III studies do not show any difference in the side effect profile of omalizumab and placebo. Subcutaneous administration of omalizumab was well tolerated with the prevalence of local reaction (redness, itching) reported to be 21% and 17% in the omalizumab and placebo groups (Babu et al, 2001a). This was common after the first dose and the incidence reduced with subsequent doses. Treatment appears to be safe and well tolerated in adults, adolescents and in paediatric patients with asthma.

Systemic urticaria reported by 3.4% of children and 1.4% of adults was the only adverse event considered to have a potential relationship to omalizumab administration. The urticaria was mild to moderate in severity and appeared to be highest in children receiving the highest dose. There was no dose relationship in adults, however, the incidence of adverse events was found to be similar to that in the placebo group. All the patients in the key phase III studies were tested for anti-omalizumab antibodies at baseline and at follow-up and none developed measurable titres. There was no evidence of any type II immune complex-mediated disease or similar syndrome or any laboratory abnormalities suggesting impaired organ function resulting from serum sickness. Omalizumab therefore appears to be safe for human use and can be administered with minimal concern for adverse events (Babu et al, 2001a).

CONCLUSIONS

Our understanding of the role of IgE in allergic asthma has relied essentially on indirect evidence. The development of a humanized monoclonal antibody against IgE and its clear clinical efficacy in asthma associated with allergy provides direct evidence for the role of IgE in allergic disorders. Some questions still remain unanswered and further studies are required. IgE

is generally believed to protect against parasitic infections, however, there have been no confirmed reports on the predisposition to parasitic infections after treatment with omalizumab. Careful surveillance will be needed to identify these risks. As to the possibility of precipitating an immune complex disease, omalizumab/IgE complexes are small with the largest complexes detected being approximately 1 million daltons in molecular weight. This size is similar to that of naturally occurring IgM and is unlikely to present any problems for clearance via the reticuloendothelial system. Furthermore, omalizumab–IgE complexes are soluble and easily removed by the reticuloendothelial system.

The treatment of asthma has remained essentially unchanged with inhaled corticosteroids being the backbone of treatment. Since the introduction of leukotriene-modifying drugs in 1995 no new therapies have been introduced for the treatment of asthma. Omalizumab has proven its efficacy in asthma in various clinical trials across the asthma severity spectrum by reducing exacerbations, improving symptoms, lung function and quality of life; however, the most significant outcome of omalizumab treatment is its corticosteroid-sparing effect.

At this stage it is clear that anti-IgE therapy will not be used for mild to moderate asthma, but in those with more severe disease requiring a high dose of inhaled corticosteroids (the subgroup with the greatest health burden) this treatment could represent a real advance. The subcutaneous route of administration might be new to patients but a treatment given only once or twice each month proved popular in a clinical trial (Busse et al, 2000; Milgrom et al, 2000; Soler et al, 2000). Tailoring the dose of omalizumab to patients' individual needs may also be new to the physician but the use of a bio-marker against which dosage is decided is familiar practice in other chronic disorders like diabetes mellitus. Despite these minor drawbacks this new molecule represents an important step forward in the management of asthma and accompanying co-morbidities. **HM**

KEY POINTS

- Asthma prevalence is increasing.
- Immunoglobulin E is important in allergic asthma.
- Omalizumab has proved to be effective in asthma.
- Omalizumab most importantly has a steroid-sparing effect.
- Omalizumab does not have significant side effects.
- Omalizumab could serve as an add-on therapy for patients with severe asthma.

Conflict of interest: Professor Holgate has acted as a consultant for Novartis.

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