

# Treating Moderate-to-Severe Allergic Asthma with a Recombinant Humanized Anti-IgE Monoclonal Antibody (Omalizumab)

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## Abstract

Bronchial asthma is a chronic inflammatory disease of the airways which is recognized as a highly prevalent health problem in both the developed and the developing world, with significant human and economic consequences.

Allergy is acknowledged as a major risk factor for asthma. The pathogenetic aspects of allergic asthma are characterized by airway inflammation with infiltration of mast cells, basophils, eosinophils, monocytes and T helper type 2 lymphocytes, along with the isotype switching of B cells to generate immunoglobulins of the immunoglobulin E (IgE) class. Increased asthma severity is not only associated with recurrent hospitalization and increased mortality but also with higher social costs.

Inhaled corticosteroids are the standard anti-inflammatory medication and are effective for most asthma patients, but there is a substantial number of asthmatics who remain symptomatic even after receiving treatment with inhaled corticosteroids and long-acting  $\beta_2$ -adrenoceptor agonists ( $\beta_2$ -agonists), and sometimes are in need of systemic corticosteroids to control the disease. These patients account for about 50% of the healthcare costs of asthma.

New treatment options more specifically targeting the pathophysiologic events causing development of asthma are therefore required in these patients.

A novel therapeutic approach to asthma and other allergic respiratory diseases involves interference with the action of IgE and prevention of subsequent IgE-mediated responses.

Omalizumab is a humanized recombinant monoclonal anti-IgE antibody developed for the treatment of allergic diseases, with clear efficacy in adolescent and adult patients with moderate-to-severe allergic asthma. This non-anaphylactogenic anti-IgE antibody inhibits IgE functions by blocking free serum IgE and inhibiting their binding to cellular receptors. Omalizumab therapy is well tolerated and significantly improves symptoms and disease control, and reduces asthma exacerbations and the need to use high dosages of inhaled corticosteroids. Moreover, omalizumab improves quality of life of patients with severe persistent allergic asthma that is inadequately controlled by currently available asthma medications. In conclusion, omalizumab may fulfill an important need in patients with moderate-to-severe asthma inadequately controlled with inhaled corticosteroids +  $\beta_2$ -agonists.

Bronchial asthma is a common chronic airways disease characterized by airway inflammation, airway hyperresponsiveness to a variety of specific and nonspecific stimuli, and reversible airway obstruction, with the appearance of respiratory symptoms such as

dyspnea, chest tightness, wheezing and cough. Even though the pathogenesis of bronchial asthma is not completely understood, it is evident that this clinical condition has a multifactorial etiology, and a body of evidence suggests that bronchial asthma has become

more common worldwide in recent years and is recognized as a highly prevalent health problem both in the developed and the developing world.<sup>[1-4]</sup> It is estimated that about two-thirds of asthma patients have an allergic background and about 50% of severe asthma patients have allergic/atopic asthma.<sup>[5]</sup> Airway inflammation plays a central role in the pathogenesis of bronchial asthma and is associated with an increase in airway responsiveness to several trigger factors such as aeroallergens, which induce bronchoconstriction in atopic asthma patients.

## 1. Pathogenesis

Allergic bronchial asthma is a T helper cell type 2 (Th2)-mediated chronic inflammatory disease of the airways, and immunoglobulin E (IgE) antibodies, Th2-derived cytokines and eosinophils play a major role in the development of chronic airway inflammation, which is observed even in individuals with very mild disease.<sup>[6-8]</sup> This inflammation is characterized by airway wall infiltration with T lymphocytes of the Th2 phenotype, eosinophils, macrophages/monocytes, and mast cells. In other words, the development of inflammation in asthma involves a complex array of several inflammatory mediators that promote the recruitment and activation of various immune cells and regulate inflammatory cell trafficking into the lungs.

Activation of chemokine receptors triggers multiple cascades of intracellular signaling events that lead to recruitment and activation of immune effector cells. As the cytokines interleukin (IL)-4, IL-5, and IL-13 seem to be of fundamental importance in the pathophysiology of asthma, anti-cytokine therapy has been postulated as a possible approach in the treatment of allergic asthma.

A number of selective chemokine receptor antagonists are currently at various stages of development for clinical use; the first study using monoclonal antibodies against IL-5 in asthmatic patients demonstrated that the number of eosinophils dramatically decreased, but there was no significant change in airway hyperresponsiveness.<sup>[9]</sup> Recent studies underline the importance of the chemokine receptor CCR3 for the recruitment of eosinophils into the lung tissue and airway hyperresponsiveness in a murine model of allergic asthma.<sup>[10]</sup> Elevated serum levels of specific IgE towards common environmental allergens are a key component in the pathogenesis of allergic asthma. IgE antibody causes chronic airway inflammation through effector cells such as mast cells and basophils, activated via high-affinity (FcεRI) or low-affinity (FcεRII) IgE receptors.

IgE is an immunoglobulin, consisting, like the other four classes of immunoglobulin (IgA, IgD, IgG, and IgM), of a variable antigen-binding fragment (Fab) region and a receptor-binding

constant (Fc) region. The whole molecule consists of two heavy (H) ε chains and two light (L) chains of the κ or λ type. There is also high association between serum IgE levels and FcεRI receptors on precursor dendritic cells, suggesting that IgE participates in the differentiation and activation of allergen-specific Th2 lymphocytes. The expression of these receptors on antigen-presenting cells such as dendritic cells is increased in patients with asthma.<sup>[11]</sup>

Since the discovery of IgE antibody, our knowledge of the mechanisms of allergy has improved to such an extent that now it is possible to modulate the IgE-mediated allergic response. IgE antibody has been viewed as a target for novel immunologic drug development in asthma, and a number of strategies aimed at inhibiting its proinflammatory action have been developed.

## 2. Treatment

Current treatment for asthma recommended by the Global Initiative for Asthma (GINA) program includes several reliever and controller drugs, in particular corticosteroids that reduce recruitment and activation of inflammatory cells in the airways.<sup>[12]</sup> The available anti-asthma treatments are effective for most patients. However, an important subgroup of 5–10% of patients continue to experience severe debilitating disease, since their broncho-obstruction is incompletely controlled by inhaled or systemic corticosteroids alone or in combination with other drugs such as short- and long-acting β<sub>2</sub>-adrenoceptor agonists (β<sub>2</sub>-agonists) and antileukotrienes.<sup>[13,14]</sup>

Severe asthma has been defined as persisting symptoms due to asthma despite high-dose inhaled corticosteroids (2000 μg beclometasone dipropionate or equivalent) plus long-acting β<sub>2</sub>-agonist (LABA), with the requirement for either maintenance systemic corticosteroids or at least two rescue courses of corticosteroids over 12 months, and despite trials of add-ons such as a leukotriene-receptor antagonist or theophylline. The GINA program for patients with severe persistent asthma (step 4 therapy) recommends the use of high-dose inhaled corticosteroids plus a LABA, and, if required, one more additional controller.

Studies have indicated that increased asthma severity is not only associated with enhanced recurrent hospitalization and mortality within 1 year of initial hospitalization but also with higher costs.<sup>[15-17]</sup> Furthermore, several studies showed that severe or refractory asthma remains a frustrating disease for both patients and the clinicians alike.<sup>[18,19]</sup>

The Outcomes and Treatment Regimens (TENOR) study confirmed that patients with moderate-to-severe, suboptimally controlled asthma had the highest rates of healthcare utilization and a high frequency of hospitalization and intubation, despite prescribed regimens of multiple 'standard-of-care' asthma thera-

pies.<sup>[20]</sup> The study indicated the need to target the underlying pathologic processes effectively, to control symptoms, to reduce exacerbations and hospitalizations, to enhance patient quality of life, and to maximize patient adherence to therapy.

### 3. Clinical Efficacy in Allergic Asthma

Since 2005 the first anti-IgE antibody, omalizumab, has been included in GINA recommendations for the treatment of patients with severe allergic asthma not controlled by currently available asthma medications. Omalizumab is able to reduce free IgE levels by avoiding the binding of IgE to FcεRI without subsequent development of allergic reaction (cross-linking, by allergen, of IgE bound to several cell types via high-affinity [FcεRI] or low-affinity [FcεRII] receptors induces cell activation and generation of a wide array of inflammatory mediators that have been strongly associated with mucosal inflammation, bronchial hyperresponsiveness, and symptoms of asthma).<sup>[21-31]</sup> This non-anaphylactogenic anti-IgE monoclonal antibody (omalizumab) binds IgE at the Cε3 domain in the Fc fragment, engendering IgE effector inhibition through blockage of activated mast cells and basophils (table I).<sup>[32-39]</sup> In other words, in allergic individuals, omalizumab prevents the activation of cellular response and the occurrence of asthma symptoms.

Studies in patients with atopic asthma showed that anti-IgE antibodies decrease serum IgE levels and allergen-induced bronchoconstriction during both the early- and late-phase responses to inhaled allergen in a dose-dependent manner.<sup>[24,25]</sup> Serum free IgE levels are rapidly reduced after omalizumab administration, and the expression of high-affinity receptors is significantly reduced after 3 months' treatment of atopic patients.<sup>[40]</sup> Also, skin test reactivity is reduced by omalizumab.<sup>[41]</sup> There is also an improvement in nasal symptoms in patients who experience asthma associated with allergic rhinitis.<sup>[42-46]</sup> The efficacy of

**Table I.** Biologic characteristics of omalizumab

Omalizumab expresses a high degree of isotype specificity and can neutralize serum free IgE without affecting other antibody classes
Omalizumab binds to serum free IgE and reduces IgE serum concentration, but does not bind to high- or low-affinity IgE receptors on inflammatory cells. However, it blocks IgE binding to these receptors and the IgE effector cells of inflammation are 'disarmed'
Long-term treatment with omalizumab down-regulates the high-affinity receptors on basophils and dendritic cells
Omalizumab does not induce extensive immune complex formation
Omalizumab activity does not depend on the allergic sensitization to different types of aeroallergens, but is active in case of sensitization to one or more allergens

omalizumab may be potentiated by combination with specific immunotherapy which operates through different mechanisms.<sup>[29]</sup>

In several controlled clinical trials, omalizumab afforded a reduction of asthma-related symptoms, a decrease in corticosteroid use, and improved quality of life in patients with asthma.<sup>[32-38]</sup> Recent studies showed the benefits of anti-IgE as add-on therapy in patients with moderate and severe persistent asthma who were inadequately controlled by antiasthma pharmacologic therapy. The great advantage of anti-IgE treatment is that it is not allergen or disease specific, and may prove to be efficacious in a number of IgE-mediated disorders such as conjunctivitis and rhinitis, food allergy and atopic dermatitis, although its precise activity and potential clinical benefits in this last condition require further investigation.<sup>[32-38,42-46]</sup> In patients treated subcutaneously, no anti-omalizumab antibody response has been observed. Omalizumab has been shown not only to inhibit mast cell and basophil responses but it also has an inhibitory effect on inflammatory cells, such as eosinophils, T lymphocytes and B lymphocytes, which are fundamental to the chronic inflammatory response in allergic diseases such as asthma.<sup>[39]</sup> This increased understanding places anti-IgE therapy firmly in the domain of anti-inflammatory treatment for chronic allergic disease, with an effect on multiple cell types (table II).

Benefits of omalizumab as add-on therapy in patients with severe persistent asthma was demonstrated in the INNOVATE (INvestigationN of Omalizumab in seVere Asthma TrEatment) study which was specifically designed to evaluate the efficacy and safety of add-on therapy with omalizumab in patients with severe persistent asthma inadequately controlled despite best available therapy (GINA 2002 step 4 treatment).<sup>[47]</sup>

The INNOVATE trial enrolled patients aged 12–75 years with severe persistent allergic asthma (GINA step 3 or 4 clinical features despite step 4 therapy). Enrolled patients had reduced lung function and inadequate symptom control despite therapy with high-dose inhaled corticosteroids (ICS; >1000 µg/day beclomethasone dipropionate equivalent) and LABAs, and with a recent history of clinically significant exacerbation. After a run-in phase, patients were randomized to receive double-blind therapy with omalizumab or placebo for 28 weeks.

The primary efficacy variable was the rate of clinically significant asthma exacerbations (defined as a worsening of asthma symptoms requiring treatment with systemic corticosteroids). Other efficacy variables included the rate of severe exacerbations (PEF or FEV<sub>1</sub> <60% of personal best, requiring treatment with systemic corticosteroids), total emergency visits for asthma, asthma-related quality of life (evaluated using the Juniper Adult Asthma Quality of Life Questionnaire; AQLQ), clinical symptom score, morning PEF, rescue medication use, and patients' and

**Table II.** Beneficial effects of omalizumab in clinical studies in patients with allergic asthma

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Decreased IgE-induced bronchoconstriction during both the early- and late-phase responses to inhaled allergen during bronchial provocation tests
Reduced skin prick test response to allergenic extracts
Reduced asthma exacerbations, regardless of the type of seasonal or perennial allergic sensitization
Showed a corticosteroid-sparing effect
Reduced the use of bronchodilators
Improved the nasal symptoms in individuals with allergic rhinitis associated with asthma
Improved quality of life in patients with asthma, and in those with severe persistent allergic asthma that was inadequately controlled by best available asthma medication
Showed a reassuring safety profile similar to that of placebo; no anaphylactic reactions, nor any immune-complex mediated disease, were observed

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investigators' global evaluation of treatment effectiveness. A total of 419 patients were included in the efficacy analyses (209 omalizumab and 210 placebo). All patients were receiving ICS and LABA, and two-thirds were receiving additional controller medications (including oral corticosteroids in 22% patients). The rate of clinically significant asthma exacerbations, after adjusting for an observed imbalance in asthma exacerbation history prior to randomization, was significantly reduced by 26.2% with omalizumab versus placebo (0.68 vs 0.91,  $p = 0.042$ ).

Compared with placebo, treatment with omalizumab significantly reduced the rate of severe asthma exacerbations (0.24 vs 0.48,  $p = 0.002$ ) and the rate of total emergency visits for asthma (0.24 vs 0.43,  $p = 0.038$ ). Significantly greater improvements were achieved with omalizumab compared with placebo in AQLQ scores (overall and individual domains), with a significantly greater proportion of patients receiving omalizumab achieving a clinically meaningful (>0.5 point) improvement from baseline compared with placebo recipients (61% and 48%, respectively;  $p = 0.008$ ).

The overall changes from baseline in the mean morning PEF ( $p = 0.042$ ) and total asthma symptom score ( $p = 0.039$ ) during the treatment period were also significantly greater with omalizumab. Omalizumab was considered more effective than placebo ( $p < 0.001$ ) by both investigators and patients and proved to be well tolerated, with a safety and tolerability profile similar to placebo. In conclusion, the INNOVATE study results showed that add-on-therapy with omalizumab was a well tolerated and effective therapy for patients with severe persistent allergic asthma who are inadequately controlled by therapy recommended by GINA guidelines.

#### 4. Adverse Effects

The studies of patients with allergic asthma show that anti-IgE treatment has a reassuring safety profile. It is very well tolerated, and its overall incidence of suspected drug-related adverse events is similar to that of placebo. It is worth noting that there have been

no cases of anaphylactic reactions, nor any immune complex diseases or similar syndromes.

Adverse effects following treatment with omalizumab were mild to moderate and did not differ significantly from placebo, with the exception of injection site reactions.<sup>[48]</sup>

#### 5. Role of Omalizumab in Patients with Asthma – Clinical Use and Uncertainties

Currently, experts acknowledge that achieving disease control in patients with severe persistent asthma may not be possible.<sup>[49]</sup>

Patients with uncontrolled asthma, despite the use of high-dose ICS and LABAs, tend to have variable and continuous symptoms, and if their asthma still remains inadequately controlled have a higher risk of exacerbation, hospitalization, and even death. Currently, patients with uncontrolled asthma have very limited therapeutic options, and medications with significant adverse effects (like oral corticosteroids, cyclosporin, and methotrexate) are used to obtain even modest improvements in symptoms that are therefore considered clinically meaningful.<sup>[48]</sup>

Subcutaneous omalizumab reduces asthma exacerbations when used as either an adjunctive or as the corticosteroid-sparing therapy. Omalizumab significantly decreased asthma exacerbation rates in these difficult-to-treat patients and also significantly reduced the severe asthma exacerbation rate and the need for emergency medical interventions.<sup>[47]</sup>

As omalizumab is administered on only a once- or twice-monthly dosage frequency – based on both patient's bodyweight and total serum IgE level measured before treatment – it may be useful in patients who have difficulty in complying with daily treatment.

The role of omalizumab in patients with asthma who have allergies to other aeroallergens, such as molds or pollens, or who have negative allergy skin tests, has not been defined. It is also not clear to what extent omalizumab might be effective in patients with total serum IgE levels outside the trial ranges (30–700 IU/mL for patients 12–75 years of age).

In clinical practice there is considerable variability of response to omalizumab therapy. The reasons for this variability have not been established; specific characteristics of individual patients may help to predict response.<sup>[50]</sup>

In addition, because an hypothesis has been proposed of a positive relationship between FcεRI expression and fatal asthma,<sup>[51,52]</sup> and as omalizumab treatment results in reduced FcεRI expression and IgE+ cell reduction in the airways, it would be interesting to investigate its possible effect in reducing the risk of mortality induced by severe asthma.

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