A review of anti-IgE monoclonal antibody (omalizumab) as add on therapy for severe allergic (IgE-mediated) asthma

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Abstract: Bronchial asthma is recognized as a highly prevalent health problem in the developed and developing world with significant social and economic consequences. Increased asthma severity is not only associated with enhanced recurrent hospitalization and mortality but also with higher social costs. The pathogenetic background of allergic-atopic bronchial asthma is characterized by airway inflammation with infiltration of several cells (mast cells, basophils, eosinophils, monocytes, and T-helper (Th)2 lymphocytes). However, in atopic asthma the trigger factors for acute attacks and chronic worsening of bronchial inflammation are aeroallergens released by pollens, dermatophagoides, and pets, which are able to induce an immune response by interaction with IgE antibodies. Currently anti-inflammatory treatments are effective for most asthma patients, but there are asthmatic subjects whose disease is not completely controlled by inhaled or systemic corticosteroids and who account for a significant portion of the healthcare costs of asthma. A novel therapeutic approach to asthma and other allergic respiratory diseases involves interference in the action of IgE, and this antibody has been viewed as a target for novel immunological drug development in asthma. Omalizumab is a humanized recombinant monoclonal anti-IgE antibody approved for treatment of moderate to severe IgE-mediated (allergic) asthma. This non-anaphylactogenic anti-IgE antibody inhibits IgE functions, blocking free serum IgE and inhibiting their binding to cellular receptors. By reducing serum IgE levels and IgE receptor expression on inflammatory cells in the context of allergic cascade, omalizumab represents a new class of mast cells stabilizing drugs; it is a novel approach to the treatment of atopic asthma. Omalizumab therapy is well tolerated and significantly improves symptoms and disease control, reducing asthma exacerbations and the need to use high dosage of inhaled corticosteroids. Moreover, omalizumab improves quality of life of patients with severe persistent allergic asthma which is inadequately controlled by currently available asthma medications. In conclusion omalizumab may fulfil an important need in patients with moderate to severe asthma.

Keywords: airway hyper-reactivity, asthma, allergic respiratory diseases, atopic respiratory diseases, anti-IgE therapy, hypersensitivity, monoclonal anti-IgE antibody, omalizumab

Introduction

Bronchial asthma is a chronic disease of airways which is recognized as a highly prevalent health problem in the developed and developing world. Asthma is characterized by bronchial inflammation, airway hyper-responsiveness induced by specific and nonspecific stimuli, and reversible bronchial obstruction with the appearance of respiratory symptoms such as dyspnea, chest tightness, wheezing, and cough. 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.

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The pathogenesis of bronchial asthma is not completely understood and it is well known that this clinical condition has a multifactorial etiology (D'Amato and Holgate 2002; Loddenkemper et al 2003; Masoli et al 2004; Rabe et al 2004). Although some asthmatic subjects exhibit a pathogenesis in which immunoglobulin E (IgE)-mediated mechanisms are not evident, asthma is almost always associated with some type of IgE-related reaction and therefore has an allergic basis (Holt et al 1999). Allergic bronchial asthma is a Th2 mediated chronic inflammatory disease of the airways, and IgE antibodies, Th2 derived cytokines, and eosinophils play a major role in the development of chronic airway inflammation, which is observed even in subjects with very mild disease (Wenzel et al 1991; Busse et al 1995; Novak and Bieber 2003). 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 different immune cells (T-lymphocytes of the T-helper type 2 phenotype, eosinophils, macrophages/monocytes, and mast 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. The inhibition of specific chemokines and receptors could prevent the excessive recruitment of inflammatory cells into the airways.

A number of selective chemokine receptor antagonists or anti-inflammatory chemokines are currently at various stages of development, but there are no products yet ready for clinical use.

From IgE antibodies to therapy with monoclonal anti-IgE (omalizumab)

Elevated serum levels of specific IgE in response to common environmental aeroallergens are a key component in the pathogenesis of allergic asthma. IgE antibodies cause chronic airway inflammation through effector cells such as mast cells and basophils activated via high-affinity (FcεRI) or low-affinity (FcεRII) IgE receptors which bind these antibodies.

IgE is an immunoglobulin, consisting, like the other four antibody classes, 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 k or λ type.

There is also high association between serum IgE levels and FcεRI receptors on precursor dendritic cells, and the expression of these receptors on antigen presenting cells such as dendritic cells is increased in asthmatic patients (Hollowaj 2001).

Since the discovery of IgE this antibody has been viewed as a target for novel immunological drug development in asthma, and a number of strategies to inhibit its proinflammatory action have been developed.

Current treatment for asthma suggested by the Global Initiative for Asthma (GINA) guidelines includes several drugs (relievers and controllers), in particular corticosteroids able to reduce recruitment and activation of inflammatory cells, in particular eosinophils, in the airways (NHLBI - GINA 2006).

Previous GINA documents subdivided asthma into four categories by severity based on the level of symptoms, airflow limitation, and lung function variability: Intermittent, Mild Persistent, Moderate Persistent, or Severe Persistent.

The GINA 2006 update recognizes, however, that asthma severity involves both the severity of the underlying disease and its responsiveness to treatment. In addition, severity is not an unvarying feature of an individual patient's asthma, but may change over months or years. Therefore GINA, for this purpose, suggests that a periodic assessment of asthma control is more relevant and useful.

The burden of asthma is greatest in patients with inadequately controlled severe persistent asthma symptoms, limitations in normal daily activities, medical resource utilization, and both direct and indirect costs.

The available treatments are effective for most of these asthma patients, but there are subjects affected by severe asthma who continue to experience debilitating disease, because their control is incomplete by inhaled or systemic corticosteroids associated with other drugs such as beta-2 bronchodilators (short- and long-acting), leukotriene receptor antagonists (Bateman 2004; Partridge 2006).

These patients are at high risk of life-threatening exacerbation, hospitalization, and mortality (Tough 1998; Serra-Batles et al 1998; Guite 1999) and are most affected in terms of quality of life (Turk 2005).

The economic impact of asthma is considerable. Approximately US$13 billion were spent in the United States in 1998 (for indirect and direct cost) (Redd 2002) and €18 billion in Europe in 2003 (European Lung white book 2003).

Several studies have also indicated that asthma severity is associated not only with poor control, such as symptoms, recurrent hospitalization, lower quality of life (QoL), but also with higher social costs (Strunk and Bloomberg 2006), and that the economic burden of asthma increases

with asthma severity and is greatest in this patient group (Antonicelli et al 2004).

Omalizumab in the treatment of IgE-mediated (allergic) asthma

Omalizumab, an anti-IgE monoclonal antibody, can reduce free IgE levels avoiding the binding of IgE to FcεRI without the following development of allergic reaction (Boulet et al 1997; Fahy et al 1997; Chang 2000; Fahy 2000; Holgate et al 2001; Godard et al 2002; Kuehr et al 2002; Mankad et al 2003; D'Amato et al 2004, 2006). Omalizumab acts as a neutralizing antibody by binding IgE at the same site (Cε3 domain of Fc fragment) as the high affinity receptor (FcεRI) binds IgE. Consequently, IgE effector functions (cross linking IgE and triggering degranulation and synthesis of new-generated chemical mediators of IgE-sensitized cells) and the following activation of mast cells and basophils are inhibited (Buhl et al 2002a, b; Ayres et al 2004; Deniz and Gupta 2005; Holgate et al 2005) (Table 1). In other words in allergic subjects, and in the elderly (Milgrom et al 2001), omalizumab prevents the activation of cellular response and reduces occurrence of asthma symptoms (see Table 2).

Studies in patients with atopic asthma showed that anti-IgE antibodies decrease serum IgE levels in a dose-dependent manner and allergen-induced bronchoconstriction during both the early and late-phase responses to inhaled allergen (Chang 2000; Fahy 2000).

Serum free IgE is dramatically reduced after omalizumab administration and the expression of high-affinity receptors is significantly reduced after 3 months' treatment (MacGlashan et al 1997). Also, skin test reactivity is reduced by omalizumab (Togias et al 1998).

In patients who experience asthma associated with allergic rhinitis there is an improvement also in nasal symptoms (Casale et al 1999; Adelroth et al 2000; Kopp et al 2002; Plewako et al 2002; Vignola et al 2004). Omalizumab administered together with specific immunotherapy can help to reduce risk of serious adverse events such as anaphylaxis and the need for epinephrine and corticosteroid use to treat adverse reactions (Casale 2006). However, omalizumab is useful also if used without contemporaneous administration of specific immunotherapy.

In several clinical controlled trials omalizumab reduced asthma-related symptoms, decreased corticosteroid use, and improved quality of life of asthmatic patients (Buhl et al 2002a, b; Ayres et al 2004; Deniz and Gupta 2005; Niebauer et al 2006). Recent studies show the benefits of anti-IgE as add-on therapy in patients with moderate and severe persistent asthma who are inadequately controlled by antiasthma pharmacological therapy. The anti-IgE approach to asthma treatment has several advantages, including concomitant treatment of other IgE-mediated diseases (allergic conjunctivitis and rhinitis, atopic dermatitis, and food allergy) and a favorable side-effect profile regardless of the type of allergic sensitization (seasonal or perennial) (Casale et al 1999; Adelroth et al 2000; Buhl et al 2002b; Plewako et al 2002; Kopp et al 2002; Ayres et al 2004; Vignola et al 2004; Deniz and Gupta 2005). Omalizumab was shown not only to inhibit mast cell and basophil responses but also to have an inhibiting 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. This increased understanding places anti-IgE therapy firmly in the domain of an anti-inflammatory treatment for chronic allergic disease, with effect on multiple cell types (Chang and Shiung 2006; D'Amato 2006).

Severe or refractory asthma remains a frustrating disease for both patients and the clinicians treating them (Busse et al 2000; Humbert et al 2005; Wenzel 2005; Moore et al 2007).

Severe asthma has been defined as persisting symptoms due to asthma despite high-dose inhaled steroids (1000 µg beclometasone dipropionate or equivalent) plus long-acting beta-2 agonist (LABA), with the requirement for either

Table 1 Biological 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 (3 months or more) with omalizumab induced down-regulation of the high-affinity receptors on basophils and dendritic cells.
- Omalizumab does not induce extensive immune complex formation, but only microcomplexes (thrimeric or exameric) which are not able to induce immune-complex pathology.
- Omalizumab activity does not depend on the allergic-atopic sensitization to various types of aeroallergens (seasonal and/or perennial).
- Omalizumab is active in case of IgE-mediated sensitization to one or more aeroallergens.

Table 2 Omalizumab in clinical studies in allergic asthma patients

Omalizumab has been shown to:

- Decrease IgE-induced bronchoconstriction during both the early- and late-phase responses to inhaled allergen during the bronchial provocation tests.
- Reduce skin prick test response to allergenic extracts.
- Reduce asthma exacerbations regardless of the type of seasonal or perennial allergic sensitization.
- Have a corticosteroid sparing effect.
- Reduce the use of bronchodilators.
- Improve also the nasal symptoms in subjects with allergic rhinitis associated with asthma.
- Improve quality of life in patients with asthma, and also in those with severe persistent allergic asthma that is inadequately controlled by currently available asthma medication.
- Have a reassuring safety profile similar to that of placebo. In malignant neoplasms observed in patients treated with omalizumab, blinded and unblended expert oncologist review showed that the neoplasms were most likely pre-existent and there was no evidence that any of neoplasms were linked causally to omalizumab treatment.

maintenance systemic steroids or at least two rescue courses of steroids over 12 months and despite trials of add-ons such as leukotriene-receptor antagonist or theophylline.

The Global Initiative for Asthma (GINA) document for patients with uncontrolled asthma (step 5) recommends the use of high-dose inhaled corticosteroids plus a LABA, and, if required, one more additional controller such as omalizumab.

Response to treatment can take several weeks to appear and it is suggested that patients should be treated for at least 12 weeks before efficacy is assessed (Bousquet et al 2005).

Experimental and controlled clinical studies

During the clinical trial on omalizumab 7 pivotal studies were performed on patients with moderate to severe IgE-mediated allergic asthma. One of these, the INNOVATE (INvestigatioN of Omalizumab in seVere Asthma TrEatment) study, was specifically designed to evaluate the efficacy and safety of add-on therapy with omalizumab in this difficult-to-treat asthma population (Humbert et al 2005).

In the INNOVATE trial were enrolled patients aged 12–75 years with severe persistent allergic asthma (GINA step 3 or 4 clinical features despite step 4 therapy). 108 centers in 14 countries participated in the study. Subjects enrolled had reduced lung function and not adequate symptom control despite therapy with a high dose of inhaled corticosteroids (ICS) (>1000 μg/day beclometasone dipropionate equivalent) and LABA stimulant bronchodilators, 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 (peak expiratory flow (PEF) or forced expiratory volume in 1 second (FEV_1) <60% of personal best, requiring treatment with systemic corticosteroids), total emergency visits for asthma, asthma-related quality of life (Juniper Adult Asthma Quality of Life Questionnaire; AQLQ), clinical symptom score, morning PEF, rescue medication use, and global evaluation of treatment effectiveness by patients and investigators. Safety was evaluated by observing adverse events and by monitoring laboratory parameters and vital signs. A total of 419 patients were included in the efficacy analyses (omalizumab, n = 209; placebo, n = 210). All patients were receiving ICS and LABA and two-thirds were receiving additional controller medications (including 22% oral corticosteroids). Patients had experienced an average of 2.1 exacerbations per year requiring systemic corticosteroids and 67% were considered at high risk of asthma-related death (based on previous history of emergency department or hospital visits or intubations).

After adjusting for an observed imbalance in asthma exacerbation history prior to randomization, the rate of clinically significant asthma exacerbations was significantly reduced by 26.2% with omalizumab versus placebo (0.68 and 0.91, respectively; p = 0.042).

Treatment with omalizumab significantly reduced the rate of severe asthma exacerbations in comparison with placebo (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 obtained with omalizumab compared with placebo in AQLQ scores, with a significantly greater proportion of patients receiving omalizumab achieving a clinically meaningful (>0.5-point) improvement from baseline compared with placebo treated patients (61% and 48%, respectively; p = 0.008).

The overall changes from baseline in mean morning PEF ($p = 0.042$) and total asthma symptom score ($p = 0.039$) during the treatment period were also significantly greater with omalizumab, which was considered more effective than placebo ($p < 0.001$) by both investigators and patients.

The pooled data from all clinical studies in patients with severe persistent asthma show that omalizumab is highly efficacious as add-on treatment to concomitant asthma therapy, as shown by the consistent reduction in asthma exacerbation rates compared with control-treated patients. Overall, exacerbations were significantly reduced ($p < 0.0001$) by 38.3% (annualized rate: 0.910 vs 1.474) with omalizumab compared with the control group (Table 3).

Omalizumab significantly reduced the rate of emergency visits for asthma care by 47% compared with control therapy ($p < 0.0001$). Hospital admissions were reduced by 52%, emergency room visits by 61%, and unscheduled doctor visits by 47% (Bousquet 2005).

The clinical study showed also that side-effects following treatment with omalizumab were mild to moderate and did not differ significantly from placebo with the exception of injection site reactions, and no anti-omalizumab antibody response has been observed (Walker 2006).

A recent exploratory study on allergic subjects living in poor urban areas of Brazil, at high risk of helminthes infections, showed that omalizumab appeared to be effective and safe, but may be associated with a possible slightly increased risk of infections (not statistically significant) (Cruz 2007).

Further studies will need to focus on the utility of long-term treatment with anti-IgE to reduce the risk of life-threating reactions in subjects with food allergy, latex allergy, or stinging insect hypersensitivity.

Preparation for use

Omalizumab is administered by subcutaneous injection. The appropriate dose and dosing frequency of omalizuamb is determined by baseline IgE (IU/mL) measured before start of treatment, and body weight (kg). Based on these measurements, 75–375 mg of omalizumab in 1–3 injections may be needed for each administration.

Omalizumab is supplied as a lyophilized, sterile powder in single-use, 5-mL vials designed to deliver either 150 or 75 mg on reconstitution with sterile water for injection. The powder requires 15–20 minutes or more to dissolve. The solution is viscous and must be carefully drawn up into the syringe before it is administered. Usually the injection needs 5–10 seconds for administration. Once prepared, omalizumab must be injected within 4 hours if at room temperature or 8 hours if refrigerated. It is important to schedule appointment for injection, avoiding preparing injection until the patient arrives. This results in visits that take 1 hour or more, since 30 minutes of observation after the injection are recommended.

Total serum IgE levels are generally increased during treatment, since there are circulating IgE-antiIgE complexes (Hamilton et al 2005).

Conclusions

Studies of patients with allergic asthma show that anti-IgE treatment with omalizumab has a reassuring safety profile. The drug was approved for commercial use in allergic asthma by the Federal Drug Administration in June 2003 and by the European Agency for Evaluation of Medicinal Products in July 2005.

Analysis of data from controlled clinical trials carried with patients affected by severe allergic asthma showed that omalizumab is well-tolerated and safe both in short-term and

Table 3 Reduction in asthma exacerbation rates across studies

	Rate per year			
	Omalizumab	Control	P-Value for rate ratio	Exac. rate treatment difference
INNOVATE study	1.37	1.86	0.042	0.49
ETOPA study[1]	0.98	2.47	<0.001	1.49
SOLAR study[2]	0.49	0.79	0.027	0.29
Busse study[3,4]	0.59	0.99	<0.001	0.40
Solèr study[5,6]	0.51	1.21	<0.001	0.70
Holgate study[7]	1.18	1.60	0.165	0.42
ALTO safety study	1.02	1.20	0.077	0.18
Pooled	0.91	1.47	<0.001	0.56

1) Ayres et al 2004; 2) Vignola et al 2004; 3) Busse et al 2001; 4) Lanier et al 2003; 5) Solèr et al 2001; 6) Buhl et al 2002; 7) Holgate et al 2004.

long-term studies. It is well tolerated, and its overall adverse event profile is similar to that of placebo.

Several clinical studies have shown no evidence that omalizumab enhanced the risk of anaphylactic reactions, infections or parasitic infestations, or bleeding-related or any immune complex diseases or similar syndromes. As for malignant neoplasms observed in patients treated with omalizumab during a pivotal trial, blinded and unblended expert oncologists review showed that the neoplasms were most likely pre-existent and there was no evidence that any of neoplasms were linked causally to omalizumab treatment.

Because omalizumab is administered infrequently, with twice-monthly or monthly dosing, anti-IgE therapy may be useful in patients who have difficulty in complying with daily treatment.

Since omalizumab treatment induces a reduction in FcεRI and IgE+ cells in the airways of asthma patients and because a relationship between FcεRI expression and fatal asthma has been hypothesized (Fregonese et al 2004), the possible effect of omalizumab in reducing the risk of mortality induced by severe asthma should be considered.

A recent study demonstrated that omalizumab add-on in patients with severe allergic asthma results in a cost-per-quality-adjusted life year ratio that compares favorably with other uses of scarce healthcare resources that are recommended by national reimbursement bodies and could be considered cost-effective. In the current climate of scarce healthcare resources, it is important to demonstrate both economic value as well as therapeutic value of a treatment (Brown 2007). Omalizumab offers both therapeutic and economic value and represents a major advance for the treatment of patients with inadequately controlled severe persistent allergic asthma.

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