Review: Omalizumab in the treatment of severe asthma: efficacy and current problems

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***Abstract*:** Omalizumab is a humanized monoclonal anti-IgE antibody recently approved for the treatment of severe allergic asthma. This drug inhibits allergic responses by binding to serum IgE, thus preventing their interactions with cellular IgE receptors. Omalizumab is also capable of downregulating the expression of high-affinity IgE receptors on inflammatory cells, as well as the numbers of eosinophils in both blood and induced sputum. The clinical effects of omalizumab include relevant improvements in respiratory symptoms and quality of life, paralleled by a marked reduction of asthma exacerbations, emergency room visits, and use of systemic corticosteroids and rescue bronchodilators. Omalizumab is relatively well tolerated, and only rarely induces anaphylactic reactions. Therefore, this drug represents a valid option as add-on therapy for patients with severe persistent allergic asthma, inadequately controlled by high doses of standard inhaled treatments.

***Keywords*:** omalizumab, anti-IgE, severe asthma

Introduction

Asthma is a chronic inflammatory airway disorder, originating from complex interactions between genetic factors and environmental agents such as allergens, respiratory viruses and airborne pollutants [Holgate, 2008]. This disease is characterized by recurrent episodes of dyspnoea, wheezing, chest tightness and cough, associated with a reversible airflow limitation and an exaggerated bronchoconstrictive response to a wide variety of stimuli (airway hyperresponsiveness). Airway obstruction and hyperresponsiveness are caused by both inflammatory and structural changes of the bronchial wall. In particular, asthmatic airways can be infiltrated by activated T lymphocytes, mast cells, eosinophils and neutrophils, releasing a multitude of cytokines, chemokines and growth factors. Structural changes are comprehensively defined as airway remodelling, which includes shedding of bronchial epithelium, mucus gland hypertrophy, subepithelial fibrosis, myofibroblast hyperplasia, angiogenesis and increased smooth muscle mass [Pascual and Peters, 2005].

Asthma constitutes a heavy medical, social and economic burden, because its prevalence is continuously increasing worldwide, especially in industrialized countries [Hartert and Peebles, 2000]. Indeed, asthma affects about 300 million people around the world, and some epidemiologic projections estimate that such a number will further increase during the next decades [Masoli *et al.* 2004]. Moreover, despite the recent advances in our understanding of asthma pathophysiology and in the development of new antiasthma therapeutic strategies, mortality due to this disease remains relatively high. For example, in the United States asthma causes approximately, 4000 deaths per year (15 million people) [National Health Interview Survey, 2003–2005]. Although good control of asthma symptoms can be achieved in a large proportion of patients by current standard therapies mainly based on combinations of inhaled corticosteroids and β_2-adrenoceptor agonists [Bateman *et al.* 2004], about 10% of asthmatic subjects who are affected by the most severe forms of the disease, despite receiving the best available inhaled treatments, remain symptomatic and with their symptoms inadequately controlled and thus have a poor quality of life [Wenzel and Busse, 2007; ENFUMOSA, 2003]. Indeed, asthma severity is currently interpreted in terms of treatment intensity required to control the clinical manifestations of the disease

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[Taylor *et al*. 2008]. In particular, severe asthma is defined on the basis of several minor and major criteria, the latter including: (1) treatment with continuous or near continuous ($\leq 50\%$ of year) oral corticosteroids; (2) requirement for treatment with high-dose inhaled corticosteroids [Wenzel *et al*. 2000]. Patients with uncontrolled asthma exhibit a high risk of serious morbidity and mortality, thereby representing within the asthmatic population the group characterized by the greatest unmet medical needs [Dolan *et al*. 2004]. Therefore, even though being a minority (about 10%) of the overall asthmatic population, patients with severe asthma are those who use the largest share of economic resources and health care services, including emergency visits, hospitalizations and additional consumption of drugs utilized for recurrent exacerbations. A further social and economic impact of difficult-to-treat asthma arises from the frequent loss of school and work days, due to such a disabling condition. Moreover, patients with severe asthma often show a tendency to anxiety and depression, which can further impair disease control by reducing their compliance to prescribed medications.

According to various studies, IgE-mediated positive reactions to skin prick tests for common aeroallergens are detectable in a percentage of severe asthmatics ranging from about 50% to 80%, [Haselkorn *et al*. 2006; Dolan *et al*. 2004; ENFUMOSA, 2003]. In these patients, asthma symptoms can be further worsened by concomitant comorbidities, including rhinitis, sinusitis, gastro-oesophageal reflux and obstructive sleep apnoea. For all such reasons, anti-IgE therapy was included in 2006 within step 5 of GINA [Global Initiative for Asthma, 2006] guidelines, as add-on treatment to inhaled or oral glucocorticosteroids, long-acting β_2-adrenergic agonists and other controller medications. After being introduced in Australia (2002) and the United States (2003), utilization of the anti-IgE monoclonal antibody, omalizumab, was also approved in 2005 by the European Union as add-on therapy to improve asthma control in adult and adolescent patients (12 years of age and above) with severe persistent allergic asthma, who have an impaired lung function ($FEV_1 < 80\%$ predicted) and experience frequent daytime symptoms and/or nocturnal awakenings, associated with multiple severe exacerbations despite daily high doses of inhaled corticosteroids and long-acting β_2-adrenoceptor agonists. The latest version of GINA guidelines, released in 2007 and referred to as Expert Panel Report 3 (EPR3), classifies severe persistent asthma in steps 5 and 6, which fulfil criteria for omalizumab use. Furthermore, EPR3 guidelines also suggest that omalizumab may be used as add-on therapy in properly selected asthmatic patients included in step 4, with the aim of avoiding higher doses of inhaled corticosteroids [Lang, 2007]. However, additional clinical trials will be required to better characterize the utility of omalizumab for such patients. Moreover, EPR3 guidelines consider for atopic asthma the use of allergen immunotherapy, which can synergize with omalizumab because these two therapeutic approaches exert their effects at different levels of the allergic cascade. Indeed, it has been shown that the combination of omalizumab and allergen-specific immunotherapy improves the efficacy of either treatment alone, and also enhances the safety of immunotherapy [Parks and Casale, 2006]. On the basis of the above-mentioned considerations, the aim of the present article is to synthetically discuss the rationale for the use of omalizumab in asthma treatment, as well as to focus on both proven benefits and emerging problems related to the recent introduction of this new therapeutic option.

Rationale for the use of omalizumab in asthma treatment

It is well known that the propensity to develop exaggerated IgE responses to common environmental allergens, referred to as atopy, plays a dominant role in the pathologic features and clinical manifestations of allergic asthma. Therefore, given the key importance of IgE in the immunologic mechanisms underlying atopic asthma, such a condition can greatly benefit from IgE-targeted therapies [Gould and Sutton, 2008; Holgate and Polosa, 2008; Hanania, 2008; Tarantini *et al*. 2007; Pelaia *et al*. 2000]. Indeed, IgE are crucially involved at different steps of the allergic cascade. The latter is initiated by intraepithelial dendritic cells, which extend their processes into the airway lumen and capture aeroallergens. This uptake of inhaled antigens is stimulated by IgE bound to high-affinity receptors (FcεRI) located on the surface of dendritic cells. Interaction of IgE with FcεRI receptors expressed by dendritic cells facilitates allergen internalization inside their cytoplasm [Kitamura *et al*. 2007], where antigens are processed by catepsin S, whose action thus results in the generation of allergenic

peptide fragments. The latter are then loaded within the context of HLA molecules belonging to class II of the major histocompatibility complex (MHC class II), and dendritic cells migrate to the T-cell areas of regional thoracic lymph nodes, where antigen presentation to T lymphocytes takes place. Recognition of specific antigenic peptides by T-cell receptors triggers sensitization and the following immune response. Moreover, allergen–IgE complexes interacting in the bronchial mucosa with low-affinity IgE receptors (FcεRII/CD23), expressed by B cells, can enhance antigen presentation to T lymphocytes [Carlsson *et al.* 2007]. As a consequence, Th2 cells synthesize large amounts of cytokines encoded by the gene cluster located on the long arm of chromosome 5, including IL-3, IL-4, IL-5, IL-6, IL-9, IL-13 and granulocyte macrophage colony stimulating factor (GM-CSF). These cytokines and growth factors stimulate the recruitment and maturation of other immune cells involved in the allergic cascade, such as eosinophils and mast cells [Larché *et al.* 2003]. In particular, IL-5 promotes eosinophil differentiation in the bone marrow, IL-9 attracts mast cells and triggers their differentiation, whereas at the level of B lymphocytes IL-4 and IL-13 drive immunoglobulin class switching towards the production of IgE [Barnes, 2008].

Similar to the other antibody classes, the IgE structure consists of two variable antigen-binding fragments (Fab) and a receptor-binding constant portion (Fc). In particular, the IgE molecule (molecular weight: 190 kD) comprises two identical light chains, each made of a variable (V_L) and a constant domain (C_L), as well as two identical heavy chains, each including a single-domain variable region (V_H) and a constant region containing four domains (Cε1, Cε2, Cε3, Cε4). IgE binds to its high-affinity FcεRI receptor, expressed as an $\alpha\beta\gamma_2$ tetramer on mast cells and basophils, and as an $\alpha\gamma_2$ trimer on human antigen-presenting cells (APCs), monocytes, eosinophils, platelets and smooth muscle cells [Gould and Sutton, 2008]. The IgE-binding function of FcεRI is located within the two extracellular domains of its α chain, which interact with the two Cε3 domains of IgE, whereas the intracellular β- and γ-chains are involved in signal transduction. At the level of mast cell surface, adjacent allergenic epitopes induce the cross-linkage of two or more FcεRI-bound IgE molecules, responsible for receptor aggregation and the following cell activation. As a consequence, mast cell degranulation and the subsequent release of preformed granule-associated mediators (histamine, tryptase, chymase and heparin) take place. In addition, eicosanoids (cysteinyl leukotrienes C_4-D_4 and prostaglandin D_2) are secreted, as well as several different cytokines, chemokines and growth factors (IL-3, IL-4, IL-5, IL-6, IL-8, IL-13, RANTES, GM-CSF). These mechanisms are responsible for both early and late responses experienced by atopic asthmatic subjects upon allergen exposure [Holgate, 2008]. The early-phase asthmatic response, which occurs within minutes of antigen binding to FcεRI-bound IgE attached to the cell membrane, is due to airway smooth muscle contraction and mucus secretion induced by inflammatory mediators released from mast cells. The late-phase asthmatic response, usually occurring several hours after allergen inhalation, is characterized by bronchoconstriction and inflammatory changes mainly caused by cytokines and chemokines leading to eosinophil activation and recruitment within the airways.

Currently, the best available option to block at a very upstream step the complex cascade of molecular events responsible for the allergic reactions underlying atopic asthma is provided by omalizumab, an anti-IgE monoclonal antibody (Figure 1). Omalizumab (molecular weight 150 kD) is a recombinant humanized antibody comprising a human IgG framework which embeds the complementarity-determining region obtained from an anti-IgE antibody raised in mice [Presta *et al.* 1993]. Consequently, only about 5% of the humanized monoclonal anti-IgE antibody includes residues of murine origin, and these structural features of course minimize the risk of developing an immune response towards the nonself protein [Spector, 2004]. Omalizumab selectively binds with high affinity to the Cε3 domain of IgE. In particular, one IgE molecule has two antigenic sites for omalizumab, and can thus be bound by two drug molecules at the same time; similarly, one omalizumab molecule has two antigen-binding loci ($V_H - V_L$ domains of IgG), and can thereby interact with two IgE molecules at the same time [Chang *et al.* 2007]. Therefore, binding of omalizumab to free IgE results in the formation of IgE/anti-IgE complexes, which can exist as trimers (molecular weight of about 500 kD) or, less frequently, as examers (molecular weight of about 1000 kD) [Hochhaus *et al.* 2003]. The small dimensions of these biologically inert

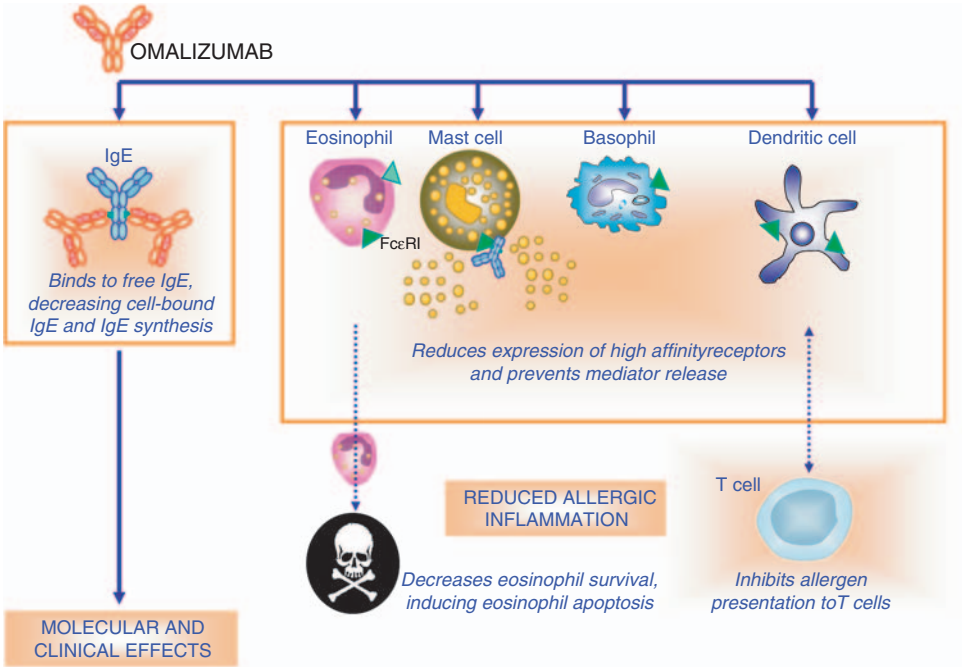

Figure 1. The effects of omalizumab on allergic airway inflammation. Omalizumab binds to and reduces the levels of free IgE, thus inhibiting their binding to cellular receptors expressed by mast cells, basophils, eosinophils and dendritic cells. As a consequence, IgE-dependent antigen presentation to T helper cells and allergic responses are inhibited. Anti-IgE therapy with omalizumab also results in decreased FcεRI expression and increased eosinophil apoptosis. All these effects are responsible for a reduction of immune airway inflammation, as well as of the related respiratory symptoms.

IgE/anti-IgE immune complexes significantly contribute to their safety. Indeed, IgE/omalizumab aggregates are soluble, do not bind complement and do not precipitate in the kidney, thus do not cause immune complex-related diseases [Fox *et al.* 1996]. These IgE/anti-IgE complexes are thus easily cleared from circulation by the reticuloendothelial system, through the interaction of their IgG component with the Fcγ receptors of the hepatic sinusoidal endothelial cells [Hochhaus *et al.* 2003]. IgE, as well as the IgG omalizumab, can freely cross capillaries thereby distributing between the vascular and the extravascular compartments. On the contrary, the IgE/omalizumab aggregates do not diffuse through capillary walls and are also characterized by a marked stability, due to the high affinity of omalizumab for IgE. Because of these features, IgE/omalizumab immune complexes remain and accumulate where they are generated, namely in either blood circulation or local tissues such as airways and nasal mucosa [Chang *et al.* 2007].

The Cε3 domain of IgE is the binding site shared by both FcεRI and FcεRII/CD23 receptors [Presta *et al.* 1994]. The latter, expressed by B lymphocytes, monocytes, eosinophils and epithelial cells, are structurally characterized by an extracellular trimeric α-helical coiled-coil 'stalk', three C-type lectin 'head domains', and the C-terminal tails [Gould and Sutton, 2008]. The head domain interacts with the outer side of an IgE Cε3 domain in a Ca^{2+}-dependent manner [Chang *et al.* 2007]. The main consequences of FcεRII/CD23 activation include upregulation of IgE synthesis and facilitation of B-cell-operated antigen presentation to T lymphocytes. Therefore, the interaction of omalizumab with IgE will prevent the latter from binding to both FcεRI and FcεRII/CD23 [Chang *et al.* 2007]. This implies that omalizumab can interfere with the biological functions mediated by stimulation of both high-affinity and low-affinity IgE receptors. Blocking IgE binding to FcεRI on mast cells and basophils inhibits allergen-induced degranulation (Figure 1), thus preventing histamine and tryptase release, and also affects lipid mediator production and cytokine/chemokine gene expression. Moreover, blocking IgE binding to FcεRI receptors also reduces FcεRI expression on basophils by approximately 97%, which correlates with a decrease in responsiveness of basophils

and mast cells to antigen challenge [Spector, 2004]. It can thus be inferred that IgE is able to upregulate the synthesis of its own high-affinity receptors. Furthermore, binding of omalizumab to circulating IgE reduces their free serum levels by 96–99% [Holgate *et al.* 2005a]. Omalizumab may also be able to suppress new IgE production, probably by inhibiting IgE interactions with the FcεRII/CD23 receptors expressed on IgE-switched B cells. A further mechanism contributing to reduce IgE synthesis may be secondary to an omalizumab-dependent decrease in the production of IgE-switching cytokines such as IL-4 and IL-13. In addition to binding omalizumab, IgE molecules comprised within the immune complexes formed with this drug can still bind allergens (at the $V_L - V_H$ domains), thereby neutralizing some of the antigenic stimuli [Spector, 2004]. In fact, omalizumab-linked IgE antibodies cannot interact with their receptors anymore, thus potentially acting as protective agents against incoming allergens, which in such a way will be trapped and prevented from reaching residual FcεRI-bound IgE on mast cells. Furthermore, by inhibiting IgE binding to FcεRI receptors expressed on dendritic cells, omalizumab can reduce the efficiency of antigen presentation to T lymphocytes. Omalizumab cannot bind to receptor-bound IgE and, consequently, it does not mimic the IgE cross-linking induced by allergens, thus being largely nonanaphylactogenic in clinical use.

The dosage of omalizumab can be determined by taking into consideration serum baseline levels of total IgE and the patient's bodyweight [Marcus, 2006]. Indeed, by matching these two parameters according to the currently available dosing tables it is possible to achieve, with regard to the omalizumab/IgE ratio, a large molar excess (ranging from about 7:1 to approximately 15:1) which is required to optimize the efficacy of anti-IgE therapies. Utilization of omalizumab is currently approved only for allergic asthmatic patients with plasma levels of total IgE ranging from 30 to 700 IU/ml, and dosing tables approximately reflect the use of the following formula: 0.016 mg/kg per IU/ml of IgE per 4 weeks. After subcutaneous administration, omalizumab achieves a bioavailability of 62%, then reaching its peak serum concentration within 7–8 days and maintaining a half-life of 19–22 days [Hendeles and Sorkness, 2007]. Omalizumab binds circulating free IgE regardless of their antigen specificity, thereby being potentially useful for atopic disorders caused by either perennial or seasonal allergens, as well as by multiple sensitizations [D'Amato, 2006]. In contrast to IgE, whose half-life in humans is 1–2 days, omalizumab circulates, similarly to human IgG1 antibodies, with a half-life of about 21 days even when it binds IgE forming trimeric or exameric complexes [Lanier, 2003]. Due to these pharmacokinetic properties, omalizumab is usually administered subcutaneously every 4 weeks. Shorter intervals are chosen only for practical reasons when patients require relatively high drug doses. In fact, because each vial of omalizumab contains 150 mg, in order to avoid multiple subcutaneous injections at the same time, subjects needing more than 300 mg monthly are treated every 2 weeks. After a single subcutaneous injection, omalizumab induces an 84–99% reversible reduction of unbound serum IgE, whose low levels last for 4–6 weeks [Miller *et al.* 2008]. The clinical responses to omalizumab treatment are variable and strictly individual. Currently, an overall physician's evaluation of omalizumab effects is suggested after 16 weeks of therapy [Bousquet *et al.* 2007].

Efficacy of omalizumab as add-on therapy in severe allergic asthma

The first clinical studies showed that, after 9 weeks of treatment, omalizumab was able to inhibit both early and late asthmatic responses triggered by allergen inhalation [Fahy *et al.* 1997]. Since then, several multicentre, randomized, double-blind, placebo-controlled phase III trials (SOLAR, INNOVATE, etc.) have been carried out in adolescents and adults with moderate to severe asthma [Price, 2008; D'Amato *et al.* 2007]. Omalizumab has been given in addition to stable treatment with inhaled corticosteroids (ICS) and other anti-asthma drugs. Taking together the results of these studies, fewer asthma exacerbations, improvements in asthma symptoms and quality of life, and decreased requirements for both ICS and rescue-bronchodilators were observed in patients treated with omalizumab compared with placebo. Moreover, in comparison with placebo-treated asthmatics, omalizumab-treated patients had fewer hospitalizations, unscheduled outpatient visits and emergency room visits. Overall, patients who benefited most from omalizumab treatment were those with the poorest lung function, receiving the highest ICS doses. Therefore, omalizumab exerted its greatest effects in severe asthma, thus being particularly

useful as an add-on treatment option for patients whose disease is not well controlled.

The Busse trial included patients with severe allergic asthma, whose disease exacerbations were significantly decreased by omalizumab during two study phases, including ICS treatments with stable or reduced doses, respectively [Busse *et al*. 2001]. With respect to the placebo group, in addition, a higher percentage of patients receiving omalizumab were able to reduce ICS intake. These findings were also confirmed by Solér *et al*. [2001] and Holgate *et al*. [2004] who enrolled subjects with moderate-to-severe allergic asthma whose symptoms were not well controlled by regular therapy with ICS. The SOLAR (Study of Omalizumab in comorbid Asthma and Rhinitis) study was designed to test the effects of omalizumab in concomitant allergic asthma and rhinitis [Vignola *et al*. 2004], two allergic diseases linked by reciprocal pathogenic connections. During a 28-week treatment with omalizumab, both adolescents and adults with moderate-to-severe asthma and moderate-to-severe persistent rhinitis were investigated. Omalizumab elicited significant improvements in the quality of life related to both asthma and rhinitis, assessed by the respective AQLQ (Asthma Quality-of-Life Questionnaire) and RQLQ (Rhinitis Quality-of-Life Questionnaire) questionnaires. With regard to allergic rhinitic patients, it has also been shown that omalizumab is able, when compared with placebo, to inhibit nasal responses to allergen challenges and to significantly reduce nasal symptom severity scores, rescue use of antihistamine drugs, and tryptase concentration in nasal secretions [Verbruggen *et al*. 2009]. In particular, the allergic rhinitics thought to mostly benefit from omalizumab treatment are polysensitized patients with moderate-to-severe rhinitis and poor compliance to anti-allergic medications, eventually also suffering from concomitant asthma [Casale *et al*. 2001].

One of the most important studies aimed at evaluating the clinical effects of omalizumab has been the INNOVATE (Investigation of Omalizumab in Severe Asthma Treatment) trial [Humbert *et al*. 2005]. This study, referring to 419 allergic patients with severe persistent asthma, whose age ranged from 12 to 75 years, involved 108 centres located in 14 countries. Participating subjects were characterized by a decreased lung function ($FEV_1 \leq 40$–<80% predicted at randomization), associated with a recent history of clinically significant exacerbations. In particular, patients had experienced an average of 2.1 exacerbations per year, and 67% of them were considered to be at risk of asthma-related mortality, assessed on the basis of emergency room visits, hospitalizations or intubations occurring in the past year. Symptom control was not satisfactory, despite a stable inhaled therapy with relatively high doses of corticosteroids and long-acting β_2-adrenoceptor agonists. In addition, an average of 31 school/work days had been missed in the past year. Following an 8-week run-in phase, patients were double-blindly randomized to receive for 28 weeks either omalizumab or placebo as add-on treatment to 2002 GINA step 4 therapy. INNOVATE results show that, when compared with placebo (210 patients), omalizumab (209 patients) induced significant decreases in the total numbers of emergency visits as well as in the rates of both severe and clinically relevant asthma exacerbations, requiring unscheduled systemic corticosteroids. Omalizumab also elicited a clinically meaningful improvement in quality of life, evaluated by the AQLQ questionnaire (>0.5 points). Furthermore, with respect to placebo, omalizumab produced significant improvements in both asthma symptom score and peak expiratory flow (PEF). Treatment with omalizumab was globally considered to be more effective than placebo by both patients and investigating physicians.

Omalizumab efficacy has also been confirmed by the recently published results of a phase IV investigation performed in France [Molimard *et al*. 2008]. These data refer to a historic-prospective study, carried out from July 2003 to January 2006 and completed by 146 patients with severe persistent uncontrolled allergic asthma, who had obtained a nominative temporary use authorization for omalizumab. All such asthmatic subjects were treated with inhaled corticosteroids and long-acting β_2-adrenergic agonists, and among them 54 continuously used oral corticosteroids. During the year before the study period, they had experienced an average of 5.5 exacerbations, 3 emergency visits and 1.5 hospitalizations. The mean monthly dose of omalizumab was 404 mg, which according to currently used dosing tables resulted to be inappropriate in 46 patients (13 received too high and 33 too low doses). Treatment with omalizumab was interrupted by 45 subjects, most often because of therapeutic results thought to be unsatisfactory

by physician's assessment. Among the 28 subjects who stopped omalizumab therapy because of unsatisfactory results, 7 had been however treated for less than 16 weeks. With respect to correctly dosed and overdosed groups, discontinuation resulted to be more frequent within the group of patients receiving underdosed omalizumab treatments. Overall, while taking omalizumab, patients with available follow-up data referring to at least 5 months experienced, in comparison with the previous year, 62% fewer exacerbations requiring oral corticosteroids. Furthermore, a 65% decrease in emergency department visits and a 29% reduction of hospitalizations were also observed in these patients. Another recent study has shown that, when compared with placebo in patients with poorly controlled severe persistent asthma, omalizumab induced a significant increase in the number of symptom-free days, and also improved day-to day symptoms [Humbert *et al.* 2008].

With regard to the effects of omalizumab on lung function, inconsistent data have been reported by various clinical trials [Price, 2008]. However, some increases in FEV_1 (forced expiratory volume in the first second) have been occasionally detected after several weeks of treatment with omalizumab [Lanier *et al.* 2003; Ayres *et al.* 2004]. Furthermore, according to a recent open-label study performed on patients with uncontrolled severe allergic asthma, randomized to receive best standard anti-asthma therapy with or without omalizumab, in comparison with control a significant increase in percentage predicted FEV_1 has been observed throughout a 1-year period of anti-IgE treatment [Niven *et al.* 2008]. Controversial findings have also been reported with regard to the effects of omalizumab on bronchial hyper-responsiveness. In particular, omalizumab does not seem to be able to affect the airway response to methacholine [Prieto *et al.* 2006; Djukanovic *et al.* 2004]. However, bronchoconstrictive effectors that act directly on airway smooth muscle are not the most suitable stimuli in order to test the effects of omalizumab on bronchial hyper-responsiveness. Indeed, after 4 weeks of treatment omalizumab significantly attenuated, in subjects with mild to moderate allergic asthma, the airway response to inhaled adenosine 5′ monophosphate (AMP) [Prieto *et al.* 2006]. AMP-induced bronchoconstriction is due to stimulation of adenosine A_{2B} receptors located on mast cells; therefore, the bronchoprotection against AMP afforded by omalizumab is probably dependent on its capability of inhibiting mast cell activation synergistically triggered by allergens and other degranulating agents like AMP.

Also very interesting are the effects of omalizumab on various markers of airway inflammation. In particular, during the steroid reduction phase of a paediatric study carried out in allergic asthmatic children, when compared with placebo omalizumab was able to maintain at significantly lower levels the fractional concentration of exhaled nitric oxide (FE_{NO}), a reliable noninvasive biomarker of bronchial inflammation [Silkoff *et al.* 2004]. Moreover, omalizumab was also shown to be capable of decreasing eosinophil numbers in peripheral blood [Noga *et al.* 2003], as well as in induced sputum and bronchial biopsies [Djukanovic *et al.* 2004]. This effect of omalizumab is likely due to the induction of eosinophil apoptosis (Figure 1). In fact, omalizumab can increase the numbers of eosinophils stained by the apoptotic marker annexin V, and this effect is paralleled by an omalizumab-dependent decreased synthesis of eosinophil survival factors such as GM-CSF [Noga *et al.* 2006]. The pro-apoptotic action of omalizumab may not be restricted to eosinophils, because this drug could also cause the death of mast cells and B lymphocytes [Kitaura *et al.* 2003; Chang, 2000]; these additional effects can thus further contribute to reduce the numbers of immune and inflammatory cells infiltrating the airways of asthmatic patients.

Our limited clinical experience with omalizumab refers to eight patients affected by severe persistent and oral steroid-dependent, poorly controlled allergic asthma. During omalizumab treatment, all such patients have experienced a marked reduction of asthma symptoms, acute exacerbations and health care utilization (emergency visits and hospitalizations), associated with relevant improvements in quality of life, exercise tolerance and psychological status. Long-lasting improvements in lung function have also been obtained. Moreover, seven subjects have stopped treatment with oral corticosteroids, and one has reduced the daily maintenance dose of these drugs. Despite the interruption of treatment with systemic glucocorticosteroids, known to be strong inducers of eosinophil apoptosis, after some weeks of omalizumab therapy eosinophil counts decreased until normal levels in those subjects who had high blood numbers of these cells

were reached. Therefore, these observations are consistent with the powerful pro-apoptotic effect exerted by omalizumab on eosinophils.

Potential problems related to the use of omalizumab

Overall, omalizumab is well tolerated and the most frequent adverse events are local reactions at the level of injection sites, usually manifesting as warmth, erythema, swelling, bruising and sometimes as urticaria-like eruptions. Other relatively frequent adverse effects include headache, fatigue and nausea. The pivotal phase III clinical trials have shown that the frequencies of adverse events were similar between the omalizumab and control groups; the majority of unwanted side-effects were of short duration and mildly to moderately severe [Holgate *et al*. 2005b]. Such a side-effect pattern has also been confirmed by real-life studies which have made it possible to monitor omalizumab-treated patients for almost three years [Molimard *et al*. 2008].

Although omalizumab is considered to be a non-anaphylactogenic antibody, serious anaphylactic and anaphylactoid reactions have been sporadically reported. Indeed, IgE- or IgG-mediated hypersensitivity reactions against the small murine portion of the omalizumab molecule can occur. Moreover, though the excipients (sucrose, L-histidine hydrochloride monohydrate, L-histidine, polysorbate20) present in omalizumab preparations are generally considered to be safe, reactions to these components can remotely take place [Cox *et al*. 2007]. In particular, both *in vitro* and *in vivo* immunologic evaluations of two patients who experienced anaphylaxis after 1 year of omalizumab treatment, concluded that the likely cause was the excipient polysorbate [Price and Hamilton, 2007]. In order to address all such problems, at the 2007 Annual Meeting of the American Academy of Allergy, Asthma and Immunology (AAAAI), the Omalizumab Joint Task Force (OJTF) was appointed, with the aim of reviewing the data referring to anaphylaxis and anaphylactoid reactions reported by both phase III clinical trials and postmarketing surveillance studies. In particular, OJTF members inferred that, among 39 510 patients receiving omalizumab between 1 June 2003 and 31 December 2005, 35 subjects manifested 41 episodes of anaphylaxis associated with omalizumab administration, corresponding to an anaphylaxis-reporting rate of 0.09% of patients [Cox *et al*. 2007]. These episodes included increased asthma symptoms and urticaria, shortness of breath, tongue swelling, watery/itchy eyes, and subjective sensations of throat closing. All patients responded to anti-anaphylactic treatments, and there were no fatalities or respiratory failures requiring intubation. Among the 41 reported anaphylactic events, timing informations were available only for 36 of such episodes. Considering the latter, 22 (61%) reactions occurred in the first 2 hours after one of the first three doses, whereas five of the episodes occurring after the fourth or later doses took place within 30 minutes. Therefore, an observation period of 2 hours for the first 3 injections, and of 30 minutes for the following administrations would have made it possible to detect 75% of these anaphylactic reactions. Moreover, advising patients to be equipped with an epinephrine autoinjector, will probably allow the management of eventual anaphylactic events occurring outside the recommended observed period [Cox *et al*. 2007].

Given the role played by IgE in the immune defence against parasitic infestations, the risk of developing such infections could be associated with the use of anti-IgE therapies. However, evolutionary theories suggest that although IgE are very important in protecting animals and even humans living in primitive habitats, these antibodies seem to have become nonessential in many regions of the world characterized by relatively clean house- and community-environments [Lanier and Chang, 2004]. According to the results of a recent study carried out in allergic subjects resident in poor urban areas of Brazil, at high risk of helminthic infections, omalizumab appeared to be effective and safe, though its use was associated with a nonstatistically significant, slightly increased risk of parasitic infections [Cruz *et al*. 2007]. However, such findings were not associated with a real risk of increased morbidity. Anyway, caution should be recommended in the utilization of omalizumab by patients at high risk of helminthic infections, particularly when living in or moving for long periods of time to areas where these infections are endemic. In cases of eventual unsatisfactory responses to conventional antihelminth treatments, discontinuation of omalizumab should thus be considered. Overall, the risk of intestinal helminth infections for asthmatic patients living in the United States and European Union is negligible, and is also very low for subjects with short-term

exposures in endemic regions due to tourist travel [Cooper *et al.* 2008]. On the other hand, the role of IgE in protecting against helminth parasites appears to be useful, but not exclusive, in that these antibodies likely act only as one component of a multifaceted, polyfunctional type-2 immune response [Cooper *et al.* 2008].

A major concern arises from the small increase, detected by initial trials in omalizumab-treated patients compared with control groups, in the numbers of malignancies, including tumours of breast, prostate, parotid and a case of lymphoma [Miller *et al.* 2008]. However, no difference in cancer incidence was found between subjects undergoing omalizumab therapy and the general population. Furthermore, most cancers occurred within 1 year from the beginning of omalizumab therapy, thus suggesting that they were likely pre-existing, since drug-induced malignancies usually develop after longer exposures. Therefore, on the basis of these considerations, also including the diversity in the types of neoplasms observed, panels of blinded and independent oncologists concluded that no causal relationship between omalizumab administration and cancer development can be hypothesized.

Attention should be paid to possible haematological changes related to omalizumab treatment. In this regard it is noteworthy to point out that, in preclinical studies performed on monkeys, thrombocytopenia was reported during experimental treatment with omalizumab [No authors listed, 2002]. However, such an untoward effect was observed at very high doses, about 3–27-fold greater than the maximum clinical dosage. Because no thrombocytopenic events occurred in the completed phase III clinical trials, it has been suggested that platelet toxicity might be species-specific [No authors listed, 2002]. Anyway, in order to rule out possible risks associated with omalizumab use, a periodic, cautionary monitoring of blood cell counts could be recommended to patients undergoing treatment with this drug.

Recently, some sporadic cases of Churg–Strauss syndrome possibly related to omalizumab treatment have been reported [Bargagli *et al.* 2008; Puéchal *et al.* 2008; Ruppert *et al.* 2008; Winchester, 2006]. Similarly to previous observations regarding the use of leukotriene receptor antagonists [McDanel and Muller, 2005], it is not yet clear whether these drugs or omalizumab may cause Churg–Strauss syndrome, or simply unmask a pre-existing latent disease because they facilitate corticosteroid tapering and withdrawal. However, at least one report refers to a patient who had only received two short courses of oral corticosteroids in the year before omalizumab administration was initiated [Puéchal *et al.* 2008]. Such a patient experienced a paradoxical increase in blood eosinophil count during treatment with omalizumab, though this drug is a potential inducer of eosinophil apoptosis. Further pharmacovigilance studies are of course needed to ascertain if the development of Churg–Strauss syndrome can be induced by omalizumab. On the other hand, some recent observations suggest that omalizumab can even be useful in treating Churg–Strauss syndrome. In particular, two patients suffering from this systemic vasculitis showed a considerable improvement after a few weeks of add-on therapy with omalizumab, which induced a marked reduction of clinical symptoms associated with normalization of blood eosinophil counts that had previously been very high. Treatment had also included systemic corticosteroids and azathioprine [Pabst *et al.* 2008]. One of these two subjects presented a progressive relapse of airway obstruction, blood eosinophilia and chest x-ray bilateral interstitial infiltrates after voluntarily suspending omalizumab treatment, which was then reintroduced and again elicited clinical, haematologic and radiologic improvements. A second report refers to an asthmatic patient with Churg–Strauss syndrome who has been treated with omalizumab for 1 year thus achieving and maintaining a good asthma control, as well as a low blood eosinophil count, without complaining of any increase in clinical activity of Churg–Strauss syndrome, though systemic corticosteroids have been withdrawn after starting anti-IgE therapy [Giavina-Bianchi *et al.* 2008]. A third publication concerns the case of an asthmatic patient who continued to receive omalizumab in addition to systemic corticosteroids for the concomitant Churg–Strauss syndrome, thereby experiencing a good outcome [Bargagli *et al.* 2008].

In addition to the potential, though not frequent, side-effects of omalizumab, another problem related to the use of this drug refers to its high cost. However, if omalizumab treatment is restricted to selected patients with severe persistent and uncontrolled allergic asthma, who respond within 16 weeks with a marked

improvement in disease control, this therapy can also be cost-effective [Price, 2008]. Such a finding has been confirmed by a recent analysis of the incremental cost-effectiveness ratio (ICER) of adding omalizumab to standard therapy [Brown *et al*. 2007], based on data obtained from the real-life, 1-year randomized open-label ETOPA study [Ayres *et al*. 2004]. To determine the ICER for omalizumab, the cost/QALY (quality-adjusted life years) ratio was calculated. Canada was used as reference country, and only subjects receiving high doses of inhaled corticosteroids plus long-acting β_2-adrenoceptor agonists were considered. Based on such reliable criteria, the authors of this analysis concluded that 'omalizumab add-on therapy in patients with severe persistent asthma results in a cost-per-QALY ratio that compares favourably with other uses of scarce healthcare resources that are recommended by national reimbursement bodies and could be considered cost-effective' [Brown *et al*. 2007]. On the other hand, further comparative economic evaluations of the cost-effectiveness of omalizumab have confirmed that, in patients with severe persistent allergic asthma, add-on therapy is comparable to or more favourable than other biological treatments for chronic disorders such as rheumatoid arthritis, Cohn's disease and multiple sclerosis [Sullivan and Turk, 2008]. This economically advantageous utilization of omalizumab is thus linked to its sparing effect on the heavy burden of resources depleted by the group of patients affected by the most severe forms of asthma.

A final question refers to the duration of omalizumab treatment: in other words, how long should this therapy last? Given the peculiar features of omalizumab mechanism of action, a tentative answer could be: forever! Indeed, after a few months of treatment, discontinuation of omalizumab administration to atopic subjects resulted in a return to pretreatment clinical state, due to a relatively rapid (within months) rise in free serum IgE levels, associated with a repopulation of the basophil surface with both IgE and FceRI receptors [Saini *et al*. 1999]. More recently, it has also been shown that either a dose-reduction of omalizumab therapy or its complete cessation led to increases towards baseline levels of both free serum IgE concentrations and allergen-specific skin prick test reactivity, evaluated as wheal-and-flare reactions [Corren *et al*. 2008]. However, it has been reported that a 6-year omalizumab treatment was capable of inducing a long-lasting improvement in asthma symptoms and lung function, which was maintained in 14 of the 18 patients undergoing this study even for periods of 12 or 14 months after drug withdrawal [Nopp *et al*. 2007]. Such a persistent asthma control was paralleled by a down-regulation of basophil activity, still detectable 1 year after interruption of omalizumab administration. Therefore, this report suggests that an anti-IgE therapy could induce a long-term remission of the allergic state, possibly by inhibiting IgE production and depleting IgE-committed B memory cells [Chang *et al*. 2007]. Of course, further studies are required to verify whether omalizumab should be prescribed for all life, or rather for relatively long-term courses. Although the duration of omalizumab treatment thus remains an open question, there is no doubt that drug injections need to be continued for very long periods of time. Therefore, the short- and especially the long-term safety of omalizumab represents a relevant issue concerning its utilization.

Concluding remarks

Availability of omalizumab in medical practice represents an advance in the management of severe persistent allergic asthma. Indeed, such a drug makes it possible to significantly improve disease control in many of those atopic patients who, though receiving an optimized standard therapy, still experience a persistence of respiratory symptoms and a high frequency of asthma exacerbations. Omalizumab efficacy in reducing allergic airway inflammation and its clinical manifestations has been shown by several phase III trials, and also confirmed by postmarketing studies. With the exception of a few sporadically reported relevant side-effects, the drug appears to be safe overall. However, future investigations are needed in order to further evaluate the long-term actions of omalizumab. Moreover, given the wide expression of IgE receptors on cross-talking immune/inflammatory and airway resident cells, it will be very interesting to explore whether an anti-IgE therapy may eventually prevent and/or attenuate the development of immunologically mediated bronchial structural changes (airway remodelling) and the related progressive functional decline, thus possibly affecting the natural history of severe asthma.

Conflicts of interest statement

None declared.

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