G. D'Amato[1], M. Perticone[2], E. Bucchioni[2], A. Salzillo[1], M. D'Amato[3], G. Liccardi[1]

Treating moderate-to-severe allergic asthma with anti-IgE monoclonal antibody (omalizumab). An Update

[1] Division of Respiratory and Allergic Diseases, Department of Respiratory Diseases, High Speciality Hospital A. Cardarelli, Naples, Italy.
[2] Medical Department Novartis Farma SpA Italy.
[3] Division of PneumoTisiology, Department of Respiratory Diseases, High Speciality Hospital "V. Monaldi" Naples, Italy.

Key words

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Summary

Increased asthma severity is not only associated with enhanced recurrent hospitalisation and mortality but also with higher social costs. Most cases of asthma are atopic in nature, with the trigger for acute asthma attacks and chronic worsening of inflammation being allergens inducing an immune response through immunoglobulins of IgE class. Currently antiinflammatory treatments are effective for most of asthma patients, but there are subjects whose disease is incompletely controlled by inhaled or systemic corticosteroids and these patients account for about 50% of the healthcare costs of asthma. Omalizumab is a humanized recombinant monoclonal anti-IgE antibody developed for the treatment of allergic diseases and with clear efficacy in adolescent and adult patients with moderate-to-severe allergic asthma.. The 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 really new approach to the treatment of atopic asthma . Omalizumab improves quality of life of patients with severe persistent allergic asthma that is inadequately controlled by currently available asthma medications. This therapy is well tolerated and significantly improves symptoms, disease control, reducing asthma exacerbations and the need to use high dosage of inhaled corticosteroids. In other words, omalizumab may fulfil an important need in patients with moderate-to-severe asthma.

Introduction

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 higly prevalent health problem in the developed and developing world (1-4). It is estimated that about two-thirds of asthma has an allergic background and about 50% of patients with severe asthma have allergic-atopic asthma (5), although many previously published data demonstrated that the disease is less frequent in atopic adult-onset asthma (6-8).
Allergic bronchial asthma is a T-helper 2-lymphocites (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 subjects with very mild disease (9-11). Airway inflammation plays a central role in the pathogenesis of bronchial asthma and is associated with an increase in airway responsiveness to a several trigger factors such as aeroallergens which induce bronchoconstriction in atopic asthma patients.

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 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 leukocytes to sites of inflammation.

A number of selective chemokine receptor antagonists are currently at various stages of development for clinical use.

Elevated serum levels of specific IgE towards common environmental allergens are a key component in the pathogenesis of allergic asthma . IgE antibodies cause chronic airway inflammation through effector cells such as mastcells, basophils etc, activated via high-affinity (FcεRI) or low-affinity (FcεRII) IgE receptors.

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 asthmatic patients (12).

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 antibodies have been viewed as a target for novel immunological drug development in asthma, and a number of strategies aimed at inhibiting its proinflammatory action despite an increase in recent years in the availability of drugs used for asthma therapy have been developed.

Current treatment for asthma suggested by Global Initiative for Asthma (GINA) guidelines includes several reliever and controller drugs, in particular corticosteroids which reduce recruitment and activation of inflammatory cells in the airways (13). The available anti-asthma treatments are effective for most of these patients. However, there are asthmatic subjects who continue to experience severe debilitating disease, since their broncoobstruction is incompletely controlled by inhaled or systemic corticosteroids associated with other drugs such as beta2bronchodilators (short and long-acting), antileucotrienes etc.

Several studies have indicated that increased asthma severity is not only associated with enhanced recurrent hospitalisation and mortality within 1 year of initial hospitalisation, but also with higher costs (14-16)

Therapeutic anti-IgE antibodies, omalizumab, able to reduce free IgE levels avoiding the binding of IgE to FcεRI without the following development of allergic reaction (crosslinking IgE and triggering degranulation and syntesis of new-generated chemical mediators of IgE-sensitized cells) have been developed (17-27). This non-anaphylactogenic anti-IgE monoclonal antibody (omalizumab) binds IgE at the same site of Fc fragment defined Cε3 domain as these antibodies bind FcεRI and FcεRII. Consequently, IgE effector functions are inhibited, because the IgE binding to high-affinity receptors on IgE effector cells is blocked, as well as the following activation of mast cells and basophils (28-35) (Table 1). In other words, in allergic subjects omalizumab prevents the acti-

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, while do not binds 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 do not induces extensive immune complex formation.
- Omalizumab acitivity does not depend from the allergic sensitisation to various type of aeroallergens (seasonal, perennial) and is active in case of sensitisation to one or more allergens.

vation of cellular response and the occurrence of asthma symptoms.

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 (20, 21).

Serum free IgE are rapidly reduced after omalizumab administration and the expression of high-affinity receptors is significantly reduced after three months treatment (36). Also skin test reactivity is reduced by omalizumab (37). Nevertheless, when omalizumab was withdrawn after few months of therapy, the serum IgE levels returned to pretreatment values as well as the number of IgE receptors on the basophils surface (38). This structural "involution" reflects the trend of the symptoms related to the ashmatic disease, leading patients to increase the dosage of standard therapy. Nopp et al. investigated the long-term efficacy of 6-year-therapy with omalizumab in 18 patients with moderate-severe IgE-mediated asthma 1 year (39) and 3 years (40) after the withdrawal of omalizumab. In both cases the Authors documented the stabilization of the asthma-related symptoms, similar to that observed during the treatment period with omalizumab, as well as the downregulation of basophil allergen sensitivity.

In patients who experience asthma associated with allergic rhinitis there is an improvement also in nasal symptoms (41-45). The treatment with omalizumab should be potentiated by specific immunotherapy which is active by using other mechanisms (24).

In several clinical controlled trials omalizumab resulted to be able to reduce asthma-related symptoms, to decrease corticosteroid use and to improve quality of life of asthmatic patients (28-34). 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 sensitisation (seasonal or perennial) (28-34, 41-45). No anti-omalizumab antibody response has been observed in patients treated subcutaneously. Omalizumab was shown not only to inhibit mast cell and basophil responses but also to have inhibiting effect on the 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. (Tab. 2).

Severe or refractory asthma remains a frustrating disease for both patients and the clinicians treating them (46, 47). Severe asthma has been defined as persisting symptoms due to asthma despite high-dose inhaled steroids (1000 mcg beclometasone dipropionate or equivalent) plus long-acting beta2agonist, with the requirement for either 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) guidelines for patients with severe persistent asthma (step 5 therapy) recommend the use of high-dose inhaled corticosteroids

Table 1 - Omalizumab in clinical studies in allergic asthma patients showed to be able

- To decrease IgE-induced bronchoconstriction during both the early and late-phase responses to inhaled allergen during the bronchial provocation tests.
- To reduce skin prick test response to allergenic extracts.
- To reduce asthma exacerbations regardless of the type of seasonal or perennial allergic sensitisation.
- To have a corticosteroid sparing effect.
- To reduce the use of bronchodilators.
- To improve also the nasal symptoms in subjects whit allergic rhinitis associated with asthma .
- To improve quality of life in patients with asthma, also in those with severe persistent allergic asthma that is inadequately controlled by currently available asthma medication.
- To have a reassuring safety profile similar to that of placebo. No anaphylactic reactions, nor any immune complex disease has been observed.

plus a long-acting beta2agonist (LABA), and, if required, one more additional controller. Currenlty several studies showed benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy.

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 asthma population (48).

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).

The primary efficacy variable was the rate of clinically significant asthma exacerbations (defined as a worsening of asthma symptoms requiring treatment with systemic corticosteroids). A total of 419 patients were included in the efficacy analyses (omalizumab, n=209;placebo,n=210). 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 and 0.91, respectively; 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).

Recently several "real life" studies confirmed the efficacy and tolerability of omalizumab in severe persistent allergic asthma patients.

The first was an observational study performed in French (49). The second one was a prospective post-marketing surveillance trial that evaluated the efficacy and tolerability of omalizumab in real-life in Germany (50), and the third study was a prospective multicenter real-life study conducted in Belgium, the PERSIST study (51), the fourth a small questionnaire-based observational study in 65 patients in the UK, who had continued with omalizumab therapy beyond 16 weeks, conducted by Niven et al. (52).

In the first study, the authors evaluated 154 patients. The analysis performed during the treatment period and compared to the previous year, showed that patients with a follow-up of at least 5 months experienced 62% fewer exacerbations requiring oral corticosteroids, 65% fewer emergency department visits and 29% fewer hospitalisations per year. Korn and co-workers reported the results of the observation of 280 patients followed-up for 6 months. After 6 months of specific anti-IgE therapy, omalizumab was demonstrated to reduce the daily (–76%) and nocturnal symptoms (–84%), exacerbations (–82%), unscheduled medical assistance (–81%), hospitalizations (–78%) and increase quality of life (Mini-AQLQ: score increase from 2.9 to 4.5). Overall, efficacy of omalizumab was rated as excellent or good by the majority of physicians (82%) and patients (86%).

In the PERSIST Study Brusselle and co-workers evaluated the 15- and 52-week effectiveness of add-on omalizumab treatment in 158 enrolled subjects. After 16 weeks of therapy, a good/excellent GETE was achieved by > 82% (p<0.001), the total AQLQ scores improved in > 82% by > 0.5 points (p<0.001) and > 91% of the subjects were exacerbation -free. At 52 weeks, the same results were achieved by > 72% (p<0.001), > 84% (p<0.001) and > 65% (p<0.001), respectively. In addition, a significant reduction in healthcare utilization compared the year prior to treatment was observed.

Niven and coll. found that out of 33 patients taking oral corticosteroid at baseline, 18 (54.5%) had reduced their oral corticosteroid and 8 (24.2%) had stopped oral corticosteroid altogether. The mean relative reduction in oral corticosteroid dose from baseline was 49% (22.6–11.6 mg, prednisolone equivalent).

All these studies show that anti-IgE treatment has a reassuring safety profile. It is very well tolerated, and its overall adverse event profile is similar to that of placebo .

In a recent review Corren and co-workers evaluated the safety of omalizumab in a pooled analysis of data from 15 randomized multicentric studies involving more than 7500 patients (adults, adolescents and children). All patients suffered from severe persistent allergic asthma and the majority of them received omalizumab for almost 24 weeks at the dose of 150-300 mg every four weeks or 225, 300 or 375 mg every two weeks. In all studies the number of adverse events (AEs) was similar between groups and the majority of AEs were mild or moderate. The most frequent AE observed in both groups was nasopharyngitis; no difference indicative of omalizumab specific tossicity was detected between groups. The only AE with >2% difference between groups was sinusitis, observed in 10.1% of patients treated with omalizumab and in 12.2%

in the placebo groups. The assessment of laboratory parameters did not showed any significant effect of omalizumab on blood cells counts, renal and liver function; however, no previous data exist about patients with previous renal or hepatic impairment treated with omalizumab, thus caution should be used in administering the drug in these sets of patients. This review confirmed that add-on omalizumab is an effective and well tolerated treatment in patients with moderate-to-severe IgE-mediated asthma (53), and its cost-effectiveness is similar to other chronic disease biologics (54). Furthermore, the same Authors highlight that, despite its cost, omalizumab used as an add-on therapy in this setting of patients improves quality-adjusted survival (QALYs) at an increase in direct medical costs, and that this value is directly related to the duration of the therapy.

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