

Treating atopic asthma with the anti-IgE monoclonal antibody

G. D'Amato

ABSTRACT: *Treating atopic asthma with the Anti-IgE monoclonal antibody. G. D'Amato.*

Omalizumab is a nonanaphylactogenic humanized murine monoclonal antibody which binds to circulating immunoglobulin (Ig)E but does not bind to IgE bound to inflammatory cells because in this case the epitope on IgE against which omalizumab is directed is already attached to cell receptors and is masked.

By binding to free circulating IgE omalizumab prevents the allergic and asthmatic responses that are mediated by the interaction of IgE with high affinity and low affinity receptors on a variety of cell types.

To support entry into therapy of human allergic diseases a series of safety and efficacy studies have been conducted with omalizumab in subjects affected by atopic asthma and these trials revealed that omalizumab is well tolerated, resulting in a dose-dependent decrease in serum free IgE levels.

Omalizumab exhibited a prolonged pharmacological effect without inducing anaphylaxis, blunted the early- and late-phase responses to inhaled allergen, reduced the symptoms of asthma improving lung function and quality of life and reduced corticosteroid use.

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Divisione di Malattie Respiratorie e Allergiche, Azienda Ospedaliera ad Alta Specialità di Rilievo Nazionale "A.Cardarelli", Napoli.

Correspondence: Gennaro D'Amato MD; Division of Pneumology and Allergology; Hospital A. Cardarelli; Via Rione Sirignano, 10; 80121 Napoli, Italy; e-mail:gdamato@qubisoft.it

Since the discovery of the function of immunoglobulin (Ig)E and its role such as crucial mediator of allergic airway inflammation, scientists have considered several strategies aiming at the inhibition of this process. The available therapeutic approaches to manage allergic diseases consist of attempts either to desensitize the atopic individual to a given allergen or to diminish the ongoing allergic reaction. Recent research has focused on the mechanism controlling IgE production, including the molecular events of B cell IgE switching, interleukin (IL)-4 and IL-13 receptor signaling, surface receptor interactions between B and T cells, and/or the mechanisms of Th2 differentiation. However, at present, the most promising strategy seems to be the neutralization of IgE by antibodies directed against the region of the IgE molecule that interacts with IgE receptors.

This therapeutic strategy was based on the premise that a therapy interfering with the binding of IgE molecules to both high and low-affinity receptors should reduce the allergen-induced early and late asthmatic responses by preventing the release of mediators from mast cells. In addition, this should decrease the amplification of the inflammatory responses mediated by helper T-cells by preventing IgE-dependent allergen presentation. In other words the inhibition of the allergic component of disease, present in the majority of asthmatic patients, by an anti-IgE monoclonal antibody provides an opportunity to investigate the impor-

ance of IgE as a contributor to disease and to study the clinical effect of this type of treatment.

Omalizumab (rhuMAb-E25) is a monoclonal antibody which has been humanized and contains approximately 5% mouse protein, minimizing the potential for immunogenicity. Omalizumab is able to bind to circulating IgE (regardless of antigen specificity) at the same site as the IgE is able to bind to high affinity receptor of mast cells and basophils. Omalizumab does not bind to IgE bound to cells bearing high and low affinity receptors for IgE, because in this case the epitope on IgE against which omalizumab is directed is already attached to those receptors and is masked. In other words omalizumab does not attach to cell-bound IgE but is able to block the binding of IgE to its receptors, thereby avoiding mast cell or basophil activation. In this way, IgE effector cells are disarmed and IgE dependent allergic reactions can be prevented (table 1).

Serum levels of free IgE fall rapidly after omalizumab administration and the expression of high-affinity IgE receptors over a period of three months biweekly treatment is reduced from a median pretreatment density of 220,000 receptors/cell to approximately 8000 receptors/cell [1].

Early proof-of-concept studies in patients with mild allergic asthma demonstrated that omalizumab prevented both early- and late-phase asthmatic responses induced by allergen inhalation [2, 3]. In one of these studies, induced sputum eosinophilia

Table 1. – Omalizumab has the following characteristics

- Binds to circulating IgE and reduces the free IgE levels.
- Does not bind to high and low-affinity receptors for IgE on inflammatory cells but is able to block the binding of IgE on these receptors (IgE effector cells are “disarmed”).
- Inhibits mast cell degranulation following challenge with sensitizing allergens.
- Reduces the early and late phase responses to inhaled allergens.
- Down-regulates the high-affinity receptors on basophils.

24 hours after allergen challenge was reduced 11-fold [3]. There have also been reports of reduced blood eosinophilia in a subgroup of patients with moderate-to-severe asthma treated in a phase III study [4], and suppression of markers of neutrophilic inflammatory activity [5].

In a phase IIb study by Milgrom and colleagues in patients with moderate-to-severe asthma, significant effects were reported [6]. These included improvements in asthma symptoms, rescue bronchodilator use, requirement for oral corticosteroids, and asthma-specific quality of life (QoL). In this study omalizumab was administered intravenously at doses that were somewhat low compared with the dosing strategy applied in more recent clinical trials.

In the phase III programme, omalizumab was administered subcutaneously at intervals of 4 or 2 weeks, in doses calculated on the basis of the patient's bodyweight and baseline serum free IgE level. It became apparent from early dose-ranging studies that omalizumab needs to be given in molar excess over baseline free IgE in order to bring about 95% or so reduction in free IgE that is necessary for clinical effects to be observed [7].

The phase III asthma programme included 334 children (aged 6-12 years) with asthma of mostly moderate severity, and more than 1000 adolescents and adults (12-75 years) with moderate to severe asthma. All patients had demonstrable sensitivity to a common environmental allergen during initial screening, and required treatment with inhaled corticosteroids (ICS). The studies followed broadly the same design. For the first (add-on) phase, patients were randomized to receive omalizumab or placebo in addition to a fixed dose of ICS for 16 weeks. During the second (steroid-reduction) phase, efforts were made to taper the dose of ICS (by 25% every 2 weeks, when possible) over a 12-week period. The studies focused mainly on the incidence and frequency of asthma exacerbations during these periods (exacerbations were identified by a need for systemic corticosteroids or a doubling of the patient's baseline ICS dose), and on the amount of ICS reduction that could be achieved. Significant effects of omalizumab on these variables in comparison with placebo were

observed in the phase III studies. Furthermore, significant improvement in asthma symptoms, the use of rescue bronchodilator and asthma-specific QoL, as well as a small but significant effect on lung function [forced expiratory volume in 1 second (FEV₁), peak expiratory flow (PEF)], were also observed.

The safety profile of omalizumab has proved reassuring during its use for up to 1 year in phase III study extensions. It appears to be very well tolerated, with an overall adverse event profile similar to placebo. Notably, there have been no cases of anaphylactic reactions to omalizumab, nor any immune complex disease or similar syndrome. The most frequently reported events in both active and placebo groups were headache and infections, mainly of the respiratory system, as would be expected in this patient population. Fewer than 1% of patients in both groups reported injection site reactions (redness, soreness). Events that were suspected as having a possible relationship to treatment included fatigue (omalizumab 0.5%, placebo 0.1%), rash (0.4% and 0) and urticaria (0.4% and 0.1%). No detectably anti-omalizumab antibody response was observed in patients treated by intravenous (i.v.) or subcutaneous (s.c.) administration. Anti-omalizumab antibodies were observed in one patient in a pilot study exploring the effects of aerosolized omalizumab administration [8]. However, this study failed to show efficacy and now this administration route is not used.

Adverse events related to parasitic infections were monitored during the clinical studies in view of the role of IgE in host defence against parasitic infestation. There were four cases of parasitic infestations, but only one of which occurred on omalizumab.

Omalizumab is administered at 4 weekly or 2 weekly visits, the latter schedule for those patients with higher IgE levels and/or bodyweight who require higher doses (multiple injections). However, in phase III studies, more than 60 of patients were treated at 4 weekly visits.

In conclusion in these studies omalizumab exhibited a prolonged pharmacologic effect, blunting the early- and late-phase responses to inhaled allergen, reducing the symptoms of asthma and improving lung function and quality of life (table 2).

Table 2. – Characteristics of omalizumab in subjects with allergic bronchial asthma

- Reduces asthma exacerbations, independently of the type of allergic sensitization (seasonal or perennial).
- Improves asthma symptom scores.
- Improves concomitantly the symptoms of upper airways if allergic rhinitis co-exists.
- Improves the quality of life.
- Has a steroid sparing effect.

On the basis of these studies omalizumab is likely to provide a new strategy for treating allergic asthma.

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