Current and future applications of the anti-IgE antibody omalizumab

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Abstract: IgE antibodies are a pivotal factor in pathophysiology of allergic diseases, and the possibility of reducing their level by anti-IgE has long been envisioned. Following several attempts, an effective biologic agent was obtained with the recombinant humanized monoclonal antibody (rhuMAb)-E25, known as omalizumab. A number of controlled clinical trials demonstrated its efficacy and safety in the treatment of severe allergic asthma uncontrolled by standard drug treatment with maximal recommended doses, and treatment with omalizumab is currently included in international guidelines on asthma management. Other studies reported a clear effectiveness also in allergic rhinitis, but the cost of the anti-IgE treatment suggests its use in patients with rhinitis concomitant with asthma. Other indications to be further investigated are skin disorders such as atopic dermatitis and IgE-mediated urticaria, as well as adverse reactions to foods, with a particularly important role in preventing food-induced anaphylaxis. Finally, there are data indicating the usefulness of omalizumab when used in combination with allergen specific immunotherapy, in terms of reducing the adverse reactions to treatment and increasing the clinical efficacy.

Keywords: IgE, anti-IgE, omalizumab, allergic asthma, allergic rhinitis, atopic dermatitis, food allergy, allergen immunotherapy

Introduction

Immunoglobulin E (IgE) was the last of the immunoglobulin isotypes to be discovered, thanks to the studies of Teruko and Kimishige Ishizaka in US (Ishizaka et al 1966) and of Johansson and Bennich in Europe (Johansson et al 1967). This isotype was thus finally recognized as the antibody responsible for allergic reactions – called "reagine" after the experiments on passive transport in the 1920s (Prausnitz et al 1921) – and designated γE-globulin after the antigen E from ragweed, to which the antibody from allergic patients was directed (Ishizaka et al 1966).

IgE antibody has a pivotal role in type I hypersensitivity reactions, inducing through the binding with its high affinity receptor (FCεRI) the release of inflammatory mediators such as histamine, leukotrienes, prostaglandins, and others, from mast cells and basophils (Siraganian 1993), which in turn induce their typical target organ effects, the most important being vasodilation and bronchoconstriction. IgE appear necessary but not sufficient to cause allergic symptoms, as suggested by the common observation that there are subjects in whom allergen-specific IgE are present but who demonstrate no clinical allergic symptoms. However, it has been possible to demonstrate in an epidemiological study that asthma is associated with serum IgE levels (Burrows et al 1989), and that the quantity of circulating IgE is a critical factor, since symptomatic subjects have specific IgE levels higher than aymptomatic subjects, with variable cutoffs according to different allergens (Pastorello et al 1995).

The concept of treating the IgE-mediated allergies with anti-IgE antibodies was soon apparent and a method for generating monoclonal antibodies was introduced in the

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seventies (Kohler et al 1975), but a number of problems had to be solved to achieve a feasible agent to be used in allergic subjects. The main problems were: i) the humanization, that is, to greatly reduce the murine component and thus the immunogenicity and the potential toxicity of the antibody; ii) the anaphylactogenic capacity, which is a characteristic of anti-IgE antibodies used in vitro to investigate the mediator release by mast cells and basophils; iii) the possible risk of parasitic infections, to which IgE exert a protective role.

After several attempts, the anti-IgE named recombinant humanized monoclonal antibody (rhuMAb)-E25, now known as omalizumab, proved to fulfil such requirements (Presta et al 1993). In fact, omalizumab (MW 150 kDa) contains 95% of a human IgG1 antibody. The specific antibody-binding site, making up $<5\%$ of the total molecule, is of murine origin (variable amino-terminal domains on both heavy and light chains) and represents the portion of omalizumab that binds to IgE. The binding site is the Cε3 domain of IgE, made up of six key amino acids that form a system of three loops; Cε3 is accessible only to free IgEs but not on the IgE bound to mast cells or basophils, where there is no access, as it is occupied by the FCεRI receptor (Schulman 2001). These two characteristics confer to this molecule low immunogenicity (due to an extremely low content of murine components) and non-complement binding properties (due to the human part of the molecule); moreover, it does not bind cell-surface IgE, thus avoiding the FCεRI cross-linking that could potentially lead to anaphylaxis. However, the issue of anaphylactic reactions will be discussed in detail later.

Concerning parasitic infections, in animal studies there are conflicting results: in an experiment IgE deficient mice were significantly more susceptible to infection from *Schistosoma mansoni* (King et al 1997), while in another study the decrease of IgE obtained by anti-IgE abated the burden of infection by the same parasite (Amiri et al 1994). It is of interest that a recent study on omalizumab-treated allergic subjects at high risk of geohelminth infection found a slight increase in the incidence of infections (Cruz et al 2007). This suggests that patients with such risk should undergo accurate surveillance of parasitic infections, though infection severity and response to anti-helminthics appeared to be unaffected by omalizumab therapy.

Considering clinical use, the dosage of omalizumab is established in a range from 150 mg every 4 weeks to 375 mg every 2 weeks; individual dosing depends on the body weight and the target level of total IgE, up to 700 IU/mL. With such doses, a significant reduction of free IgE occurs as early as 24–48 hours from the first administration by subcutaneous route (Jardieu et al 1999; Lin et al 2004), while a significant inhibition of clinical symptoms – by a specific allergen challenge – occurs after 1 week (Lin et al 2004). At present, according to the label indications, some patients might remain excluded from the administration of the drug because of levels of IgE $>$ 700 IU/mL, or because of high weight. In fact the recommended monthly dose is equal to 0.016 mg $\times$ body weight (kg) $\times$ IgE levels (IU/mL), and which may result in greater than 750 mg (maximum monthly dose).

As to safety issues, the possible damage from immune complexes has already been ruled out in phase I studies, which demonstrated that the IgE – anti-IgE complexes were small, did not precipitate, did not activate the complement because of their binding to the Cε3 and were eliminated with urine (Fox et al 1996). Frequency of adverse events, evaluated in more that 5000 patients, was comparable for any kind of event in omalizumab- and placebo-treated subjects (Deniz et al 2005). Some doubt was raised about a report of malignant neoplasms, but the rate of such pathology was below 1% in both omalizumab-treated and control patients, and a panel of oncologists stated the lack of relationship between neoplasms and study treatment.

During the clinical studies of phase II/III on allergic asthmatics, approximately 6700 patients received omalizumab. The most commonly reported reactions have been pain, swelling, itching, and erythema in the injection site, all of these short-lived and self-limited. Anaphylaxis has been reported as a possible adverse event, with a frequency of about 0.1%. In one of these reactions it was possible to achieve tolerance to omalizumab by desensitization, which was, however, followed by a serum sickness-like disease (Dreyfus et al 2006).

More cases have been reported after the launch of the drug in the US market (124 cases of anaphylaxis occurred over 57300 patients treated from June 2003 to December 2006), and consequently the FDA added an additional warning about this risk. The frequency of anaphylaxis attributed to omalizumab use was estimated to be at least 0.2% of treated patients in the wild population. The discrepancy of this datum between clinical trial setting and the wild population could be due to the fact that some clinical trials considered a previous history of anaphylaxis as an exclusion criterion, leading to patients at higher risk not being enrolled in the trials.

Omalizumab should be administered in hospital setting, where this kind of emergency can be dealt with. Patients must be informed about the risk of anaphylaxis, an adverse reaction that is more frequent and life-threatening with other conventional therapies: for instance, specific immunotherapy has

been reported to cause anaphylactic shock with a frequency of 0.6%, and it can even – in 1 out of 2.5 million injections – be fatal (Mellerup et al 2000; Stokes et al 2006).

Moreover, considerating that the frequency and the severity of allergic reactions is higher in the asthma population than in general population (Uguz et al 2005), we do not know which concomitant treatments were prescribed when the reactions happened and, above of all, we do not know the anaphylaxis past-history of these patients. The risk of anaphylaxis must be also compared with the real benefits that patients can obtain from this therapy, which has proved to halve the frequency of severe exacerbations that can possibly threaten the patients' survival.

For clinical application, the first objective of treatment indication for omalizumab was severe allergic asthma, but subsequent research has expanded this to include other IgE-mediated diseases eligible for anti-IgE treatment, such as allergic rhinitis, skin disorders such as atopic dermatitis and urticaria, and adverse reactions to foods. Another emerging indication appears to be the use of omalizumab to improve the safety and efficacy of allergen immunotherapy.

Review objectives

The articles to be considered in the review were researched by using the terms "anti-IgE, omalizumab, allergic asthma, allergic rhinitis, atopic dermatitis, food allergy, anaphylaxis, allergen immunotherapy" in the databases PubMed and Embase.

Omalizumab in allergic asthma

The current indications for the treatment of asthma, according to GINA international guidelines, aim to achieve and maintain clinical control of the disease, using controller and reliever drugs (Global Initiative for Asthma 2007). Controllers drugs are the mainstay for the chronic treatment, as their action has contrasting effects on the chronic inflammation of the bronchi. These drugs include: inhaled and systemic glucocorticosteroids, leukotriene modifiers, long-acting inhaled beta2-agonists in combination with inhaled glucocorticosteroids, sustained-release theophylline, and cromones. Inhaled glucocorticosteroids are the most effective controller medications currently available, but a minority of patients fail to achieve control despite the chronic use of these drugs. This group of patients, suffering from allergic asthma (with a sensitization to at least one perennial aeroallergen) not controlled by drug therapy with maximal recommended dosage of inhaled corticosteroids plus bronchodilators, has the indication to be treated with omalizumab. A number of studies have demonstrated the beneficial effects of reducing the serum levels of IgE, first by the model of allergen challenge (Boulet et al 1997; Fahy et al 1997) and then by clinical trials in adults and children (Milgrom et al 1999; Solèr et al 2001; Busse et al 2001; Buhl et al 2002; Finn et al 2003; Corren et al 2003; Bousquet et al 2005; Holgate et al 2005; Humbert et al 2005) with severe asthma. The results obtained in actively treated compared to placebo-treated patients in these trials can be summarized as follows: a significant reduction of doses of inhaled corticosteroids (ICS), with a greater percentage of actively treated patients able to withdraw from ICS completely; a significant reduction in asthma-related emergency room visits and hospitalizations; and a significant improvement in asthma-related quality of life (Holgate et al 2005). The INNOVATE study has also succeeded in demonstrating that patients with more severe forms of allergic asthma, treated with high dose ICS and long-acting β2-adrenergic agonists, could best take advantage from omalizumab as an add-on therapy. In fact it has been proven that asthma exacerbation rates decrease significantly, as well as the need for rescue medications, and QoL improves (Humbert et al 2005).

Today, the need for scientific evidence for any treatment is fully met by the tool of meta-analysis. The most recent Cochrane meta-analysis included all 14 randomized controlled trials up to February 2006 (Walker et al 2006), with an overall number of 3143 patients with allergic asthma, mostly caused by perennial allergens, high levels of IgE, and at least one positive allergy skin test to aeroallergens. Treatment with omalizumab was associated with a significant decrease in free IgE compared with placebo and with significant changes in clinical parameters, assessed by odds ratio (OR). In particular, there were significant differences in favor of omalizumab concerning the number of patients able to reduce ICS by over 50% (OR 2.50, 95% CI 2.02–3.10), the number of patients completely withdrawing daily ICS intake (OR 2.50, 95% CI 2.00–3.13), and the likelihood of suffering an asthma exacerbation (OR 0.52, 95% CI 0.41–0.65). The reviewers pointed out that the significant effectiveness of omalizumab must be considered in the light of its high cost, and this economic issue has also been considered by Brown et al who demonstrated that add-on omalizumab therapy is cost-effective in patients with severe persistent allergic asthma (Brown et al 2007).

Another important observation in asthma is the ability of omalizumab to act on airway hyper-responsiveness in vitro. A recent study investigated this in human bronchi incubated in normal or asthmatic serum containing different concentrations of omalizumab, and showed that both specific (ie, to *Dermatophagoides pteronyssinus*) and non-specific bronchial

hyper-responsiveness following passive sensitization were significantly inhibited by omalizumab (Berger et al 2007). These properties still have to be demonstrated in vivo, as, though its anti-inflammatory effect, omalizumab did not prove to reduce airways hyper-responsivenss in asthmatic patients (Djukanovic et al 2004).

In the in vitro study by Berger et al omalizumab decreased the number of IgE-bearing cells and mast cell degranulation (Berger et al 2007). The immunologic effects of anti-IgE treatment were also investigated in other studies. Fahy et al found a significant decrease from baseline in eosinophils – which are the leukocytes mainly recruited in IgE-mediated inflammation – measured in blood and in induced sputum (Fahy et al 1997) and the effect of omalizumab on eosinophils was confirmed, with significant difference compared with placebo, along with a significant decrease of IL-13, a cytokine involved in eosinophil activation, and decreases in IL-5 and IL-8 (Noga et al 2006). Another study reported a highly significant difference compared with placebo concerning the reduction in mean percentage of eosinophils in induced sputum achieved by omalizumab, paralleled by a decrease in free IgE to under 50 ng/mL and by a strong reduction in IgE+ cells in the submucosa from bronchial biopsies (Djukanovic et al 2004). Moreover, a significant decrease in cell surface IL-4 associated with the reduction in submucosal eosinophil number was detected (Djukanovic et al 2004). From these data it is reasonable to assume that a major decrease in free IgE induces, through FCεRI+ cells, a change in inflammatory response to the specific allergen(s) and in particular in the eosinophil recruitment and activation mediated by IL-4, IL-5, IL-8, and IL-13.

A point of the utmost interest is the possible prediction of which patients will respond to omalizumab: an analysis on 1070 patients suggested that baseline characteristics do not reliably predict benefit from the treatment with omalizumab. Currently the most meaningful measure of response to therapy is a physician's overall assessment after 16 weeks of treatment (Bousquet et al 2004). Another study evaluated the response to omalizumab in patients not well controlled by treatments including long-acting beta2-agonists, antileukotrienes, and oral corticosteroids, and found better asthma control in subjects who received the anti-IgE compared with drug therapy only (Ayres et al 2004).

Other current and future applications of omalizumab

Allergic rhinitis

Considering the strict relationship between allergic rhinitis and asthma, which often coexist, it is reasonable to expect anti-IgE treatment to be effective for nose symptoms. In a first placebo-controlled trial on subjects with ragweed-induced rhinitis, only patients with a significant decrease in IgE levels, and thus requiring higher doses of omalizumab – up to 375 mg every 2 weeks – showed a clinical efficacy (Casale et al 1997). The same author conducted a dose-response study, randomly assigning patients to receive 50, 150, or 300 mg of omalizumab, or placebo immediately before and during the ragweed pollen season; the dose of 300 mg was significantly more effective than placebo in reducing symptoms scores and consumption of antihistamines and in improving quality of life (Casale et al 2001).

Another controlled trial investigated the effects of omalizumab in birch pollen-induced rhinitis, using the dose of 300 mg at intervals of 4 weeks with IgE levels lower than 150 IU/mL, and 3 weeks with IgE levels higher than 150 IU/mL (Adelroth et al 2000). The results showed a better outcome in patients with free IgE levels decreased to less than 25 IU/mL, who comprised 70% of those actively treated, and significant differences in favor of omalizumab for eye (but not nose) symptoms, use of rescue medication, patient's evaluation of efficacy, and quality of life.

Efficacy of anti-IgE treatment was also evident from studies of perennial allergic rhinitis, which demonstrated significant advantage over placebo for symptom scores, use of rescue medication, and quality of life (Chervinsky et al 2003). Of particular interest is the SOLAR (Study of Omalizumab in comorbid Asthma and Rhinitis) study, a randomized controlled trial dealing with 405 patients with moderate to severe allergic asthma and concomitant moderate to severe allergic rhinitis (Vignola et al 2004). The outcome measures were the number of acute asthma exacerbations and the score obtained from a combined asthma and rhinitis quality of life questionnaire. Significant differences in favor of omalizumab were observed for both parameters ($p = 0.02$ for asthma exacerbations, $p < 0.001$ for quality of life), and the significance was found for quality of life with the rhinitis questionnaire alone. Rhinitis symptoms were taken into account also in the study by Ayres et al; the symptom scores present data showing that the addition of omalizumab to the standard drug treatment significantly ameliorated asthma, rhinitis, and their combination (Ayres et al 2004).

IgE-mediated skin disorders

Atopic dermatitis is a quite common skin disease in childhood, not uncommon also in allergic adults, in which the elevated and persistent production of IgE antibodies plays an important role (Leung et al 2003). This makes such a disorder a possible

target of anti-IgE treatment, but thus far there are scant data on the effects of omalizumab in atopic dermatitis. A first study on 3 adult patients (mean age 39 years) with severe atopic dermatitis (AD) treated for 4 months with a dose of 450 mg every other week – that is, exceeding the currently maximum recommended dose – failed to demonstrate any benefit (Krathen et al 2006). Positive results were instead observed in 3 pediatric patients (mean age 11 years) with severe AD who had not benefited previously from any treatment but showed a clear improvement with anti-IgE (Lane et al 2006), and in a series of 7 patients including 2 children and 5 adults (mean age 31 years) treated with omalizumab for persistent uncontrolled asthma but presenting also AD since early childhood (Vigo et al 2006): 2 patients had a severe, 5 a moderate, and 1 a slight stage of disease. In the two positive studies, doses corresponding to recommended, according to individual weight and IgE level, were used except for a 13-year-old child with a serum IgE level of 6120 IU/mL who was treated with a 450 mg dose. The level of total IgE appeared a critical factor, considering that the three patients in the unsuccessful study had a mean starting level of 17.600 IU/mlL(Krathen et al 2006) compared with a mean level of 3600 IU/mL in the pediatric study (Lane et al 2006), and of 1060 IU/mL in the study on adults and children (Vigo et al 2006).

However, the available data on omalizumab in AD cannot indicate the optimal level of IgE for predicting a positive response to treatment and, as noted by the authors of the studies, well-designed controlled trials are needed to explore such issue, comparing patients with different IgE levels. In any case, levels higher than recommended for asthma deserve to be evaluated, considering that the suggested limit level of 700 IU/mL when applied to AD is likely to be associated with milder stage of disease which, similarly to rhinitis, may hardly warrant an expensive biologic therapy (Beck et al 2006).

Another possible target could be IgE-mediated urticaria: a recent report described a girl with moderate persistent asthma and cold-induced urticaria who had complete resolution of her urticaria following treatment with anti-IgE (Boyce 2006). This led Wanderer to propose in an editorial article a reconsideration of the potential pathogenetic role of IgE in cold-induced as well as in other forms of urticaria (Wanderer 2007).

Adverse reactions to foods

Hypersensitivity to foods affects about 3%–4% of the population, with higher prevalence in children (Kanny et al 2001), but the major concern is for anaphylaxis, which may cause fatal reactions often after inadvertent consumption of the culprit food (Bock et al 2001). In US the most frequently responsible food is peanut, which is estimated to cause 50–100 deaths per year. An important randomized controlled study was conducted on 84 patients with allergic reactions to peanut, randomly assigned to receive anti-IgE in doses of 150, 300, or 450 mg, respectively, or placebo (Leung et al 2003). The results showed a significantly higher effectiveness with the 450 mg dose, which increased the threshold of sensitivity to peanut, assessed by oral challenges, from an average of about half a peanut (178 mg) to almost 9 peanuts (2805 mg), an amount far higher than most inadvertent ingestion. This suggests for anti-IgE treatment the capacity to prevent fatal reactions and warrants for further investigations with other foods involved in anaphylaxis.

Anti-IgE and allergen immunotherapy

Allergen immunotherapy is the practice of administering allergen extracts to induce a tolerance in allergic subjects and is the only treatment able to interfere with the natural history of allergic diseases (Bousquet et al 1998). The conventional form of immunotherapy is administered subcutaneously, but the occurrence of systemic adverse reactions, sometimes even life-threatening (Stokes et al 2006), stimulated the search for non-injective routes, which eventually led to the introduction and validation of sublingual immunotherapy (Canonica et al 2003), in terms of clinical efficacy and safety (Wilson et al 2005). The aims of adding anti-IgE treatment to immunotherapy are to (i) prevent or reduce the adverse effects of subcutaneous route and (ii) improve the efficacy of subcutaneous or sublingual route.

Concerning the first objective, a recent placebo-controlled study (Casale et al 2006) demonstrated that pre-treatment with omalizumab resulted in a 5-fold decrease of risk of anaphylactic reactions in patients with ragweed-induced rhinitis undergoing immunotherapy by a rush schedule, which has the advantage of reaching quickly the maintenance dose but raises the likelihood of adverse reactions. This ability of the anti-IgE treatment has interesting possible applications in immunotherapy with Hymenoptera venom, which warrants rush schedules to achieve rapid protection from stings but must face the problem of adverse reactions, particularly worrying when honeybee venom is used (Muller et al 1992).

The study by Casale et al investigated also the efficacy by an intent-to-treat analysis, and found that the combination of omalizumab and immunotherapy significantly improved symptom scores during the ragweed season compared with

immunotherapy alone (Casale et al 2006). This confirmed the results of two previous studies dealing (Kuehr et al 2002; Rolinck-Werninghaus et al 2004). In a multi-center randomized controlled trial on 221 children and adolescents with seasonal rhinitis caused by birch and grass pollen, the combination therapy of anti-IgE and immunotherapy – started 14 weeks before the pollen season – was significantly more effective than immunotherapy alone for both pollens (Kuehr et al 2002). It is of particular interest that patients receiving combination treatment required almost no additional rhinitis medication. By studying children allergic to grass pollen, the comparison of subjects treated with a combination of omalizumab and immunotherapy with those treated with monotherapies by either anti-IgE or grass immunotherapy showed a higher efficacy of the combined treatment (Rolinck-Werninghaus 2004). An apparent advantage of adding omalizumab to allergen immunotherapy is that anti-IgE treatment is not allergen specific and thus is effective also on symptoms induced by other allergens in polysensitized patients (Hamelman et al 2002).

Concluding remarks

The anti-IgE monoclonal humanized antibody omalizumab is a biologic agent which has demonstrated important clinical effects in patients with severe asthma uncontrolled by conventional drug treatment, and is currently considered a treatment option in international guidelines on asthma therapy. Its ability to reduce circulating IgE antibodies and consequently the IgE-mediated manifestation makes possible its use in a number of clinical conditions, with a particular advantage for hypersensitivity reactions with a favorable cost-benefit ratio.

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