

EXPERT OPINION

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The discovery and development of omalizumab for the treatment of asthma

Amelia Licari, GianLuigi Marseglia, Riccardo Castagnoli, Alessia Marseglia & Giorgio Ciprandi[†]

[†]IRCCS-A.O.U. San Martino di Genova, Department of Medicine, Genoa, Italy

Introduction: The evolution in immunological methods used to assess human allergic diseases has led to the identification of immunoglobulin E (IgE) as a diagnostic biomarker and a potential therapeutic target. Innovative technologies in molecular biology and immunogenetics contributed to the development of a selective blocking agent, disclosing new therapeutic perspectives in the treatment of allergic asthma. Omalizumab is the most advanced humanized anti-IgE monoclonal antibody that specifically binds serum-free IgE. Omalizumab also interrupts the allergic cascade by preventing binding of IgE with FcεRI receptors on mast cells, basophils, antigen-presenting cells and other inflammatory cells.

Areas covered: This review discusses the discovery strategy and preclinical development of omalizumab. Furthermore, it also provides a clinical overview of the key trials leading to its launch and a detailed analysis of safety and post-marketing data.

Expert opinion: The clinical efficacy of omalizumab in allergic asthma has been well documented in clinical trials, involving adults, adolescents and children with moderate-to-severe and severe allergic asthma. To date, omalizumab has also been approved in chronic idiopathic urticaria for patients 12 years and older who remain symptomatic despite high dosages of H₁ antihistamines. Omalizumab has also been investigated in many other different patient populations beyond allergic asthma and may yet have an application to other indications. While omalizumab is the only mAb available for treating allergic asthma, the authors anticipate that new mAbs will emerge in the future that overcome omalizumab's current limitations.

Keywords: allergic asthma, anti-IgE therapy, omalizumab

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1. Introduction

Normally present at very low level in plasma, antibodies of the immunoglobulin E (IgE) isotype were finally discovered through simultaneous studies by the Ishizakas in the USA, Bennich and Johansson in Sweden, and Humphrey and Stanworth in the UK in 1967, decades after the description of the passive transfer of the allergen-specific response in the skin with serum by Prausnitz and Küstner [1,2].

It is now well demonstrated that IgE constitutes a first-line defense against parasites such as helminthes; however, inappropriate IgE-mediated immune responses against normally tolerated environmental antigens represent a crucial pathogenetic process for the development of allergic diseases. IgE levels are usually elevated in patients suffering from atopic conditions such as atopic dermatitis, allergic rhinitis (AR) and asthma, food allergy and anaphylaxis [3].

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Article highlights.

- The evolution in immunological methods used to assess human allergic diseases has led to the identification of IgE as a potential therapeutic target; subsequently, innovative technologies in molecular biology and immunogenetics have led to the development of a selective blocking agent, disclosing new therapeutic perspectives in the treatment of allergic asthma.
- Omalizumab is the first and, at present, the only mAb available in clinical respiratory medicine for the treatment of moderate-to-severe and severe allergic asthma.
- Clinical trials have repeatedly shown that omalizumab is effective in reducing exacerbations and reducing corticosteroid use, as well as baseline control of asthma in adults and children.
- Omalizumab reduced use of health resources, such as hospital admission and ICU, thus decreasing the weight of its economic impact.
- Omalizumab is active on asthma comorbidities, such as AR, as well as other conditions related to allergy and/or IgE.
- Ongoing studies are investigating long-term benefits of omalizumab on airway wall remodelling and potential biomarkers predicting response.

This box summarizes key points contained in the article.

Once produced by plasma cells, the secreted form of allergen-specific IgE exerts its biologic effects binding its third heavy chain constant region domain (Cε3) to receptors FcεRI (the high-affinity receptor) and FcεRII (CD23 or the low-affinity IgE receptor) on the surface of tissue mast cell and circulating basophil. IgE triggers a wide variety of inflammatory responses, including: i) rapid release of preformed mediators such as histamine, proteoglycans and proteases; ii) transcription of pro-inflammatory cytokines (IL-4, TNF, IL-6; iii) *de novo* synthesis of prostaglandins (PGD₂) and leukotrienes (LTD₄), thus resulting in clinical manifestations of type I hypersensitivity; and iv) promotion of adhesion and infiltration of circulating inflammatory cells [4]. In addition to these effects, IgE has a number of immunomodulatory functions, including upregulation of IgE receptors, promotion of mast cell survival, enhancement of allergen uptake by B cells for antigen presentation and induction of T-helper₂ (Th₂) cytokine expression by mast cell and may all collaborate to amplify and perpetuate allergic responses in susceptible individuals [4].

Asthma is one of the most common chronic diseases, affecting more than 300 million people worldwide and represents a significant public health concern [5]. Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. According to the Global Strategy for Asthma Management and Prevention, it is defined by: i) history of respiratory symptoms, such as wheezing, shortness of breath, chest tightness and cough, that vary in duration and in intensity over time; ii) reversible airflow limitation; and

iii) bronchial hyperresponsiveness [5]. Approximately 70% of patients with asthma have an allergic phenotype, such as symptoms are triggered by allergens, which is characterized by elevated serum levels of allergen-specific IgE that give rise to airway inflammation [6]. Although many patients achieve asthma control with standard therapies, a significant proportion continue to experience symptoms and exacerbations despite the use of high dosages of inhaled corticosteroids (ICS) and long-acting β₂-adrenoceptor agonists (LABA), accounting for a significant proportion of the health-care costs and also affecting their quality of life [7]. Therefore, additional therapeutic approaches are required to achieve an adequate asthma control.

The recognition that IgE plays a pivotal role in allergic asthma has stimulated research into the therapeutic potential of targeting this antibody. The interference with the receptor–IgE binding process represented a strategy for the development of a set of humanized neutralizing monoclonal anti-IgE antibodies (chimeric mAb CGP 51901, humanized mAb TNX-901, rhuMAb-E25/omalizumab), which are an interesting example of biotechnology-produced pharmaceuticals, over the past 20 years [8]. Omalizumab is the most advanced humanized anti-IgE monoclonal antibody (mAb) that specifically binds serum-free IgE and interrupts the allergic cascade by preventing binding of IgE with FcεRI receptors on mast cells, antigen-presenting cells and other inflammatory cells [9]. Its clinical efficacy has been well documented in a number of clinical trials involving adults, adolescents and children with moderate-to-severe and severe allergic asthma (Table 1) [10].

2. Discovery strategy and preclinical development

The first description of a mAb to human IgE that did not induce histamine release from basophil concluded that the determinant recognized on IgE was hidden by the FcεRI interaction [11]. Subsequently, it was shown that anti-IgE mAb to murine IgE could efficiently inhibit the binding of IgE to the FcεRI [12]. However, these antibodies induced receptor cross-linking, as they recognized repetitive determinants on IgE. Later, antibodies to murine IgE were obtained that induced neither histamine release nor antibody cross-linking, as they reacted with a single determinant within the ε domain recognized by the FcεRI [13,14]. It has been demonstrated in mice that these antibodies selectively reduced serum IgE, inhibited antigen induced skin reactions, cytokine production by lung Th₂ cells and pulmonary eosinophil infiltration [15].

To avoid the problems of antigenicity in humans that are associated with murine mAbs, humanized murine anti-human IgE antibodies have been developed. The recombinant technique for chimerization of antibodies has been introduced by Morrison *et al.* [16], whereas the humanization technology has been pioneered by Winter *et al.* [17].

Table 1. Discovery and development timeline of IgE and omalizumab.

1919	Following a blood transfusion, it was described a case of transient asthma caused by allergy to horse dander. It is the first indication of a factor in blood capable of mediating an allergic reaction
1921	Prausnitz and Küstner described the passive transfer of the allergen-specific response in the skin with serum
1967	Discovery of antibodies of the immunoglobulin E isotype
1970 – 1975	High-affinity (FcεRI) and low-affinity (FcεRII) IgE receptors were described
1981	First description by Hook <i>et al.</i> of a mAb to human IgE that did not induce histamine release
1984	Baniyash <i>et al.</i> showed that monoclonal anti-IgE antibodies to murine IgE could efficiently inhibit the binding of IgE to the IgE receptors
1987	Chang <i>et al.</i> postulated the concept of using anti-IgE to treat IgE-mediated diseases
1988 – 1991	Antibodies to murine IgE were obtained that did not induce histamine release neither receptor cross-linking
1993	Humanization of a murine anti-IgE antibody by Presta <i>et al.</i>
1996	Phase I clinical trials in USA
1997 – 1999	Phase II clinical trials
2000 – 2001	Phase III asthma programme included three critical large studies in patients with moderate-to-severe asthma, performed in the USA and Europe, that provided the evidence that led to FDA approval of omalizumab
2003	Omalizumab received approval by the U.S. Food and Drug Administration for treating patients 12 years and older with moderate-to-severe allergic asthma
2009	Omalizumab was approved by the European Union for treating patients 6 – 12 years old with severe, persistent allergic asthma
2014	Omalizumab was approved in the European Union and the USA for treating patients 12 years and above with chronic spontaneous urticarial
2003 – present	Post-launch studies

Following this interesting path of research, omalizumab has been 'designed' according to a very detailed knowledge of the structure and antigenic properties of the human IgE. Omalizumab, also referred to as rhuMAB-E25 in the literature, is a humanized IgG₁κ monoclonal anti-IgE antibody that binds with high affinity to IgE at the Cε3 domain with a molecular weight of ~ 149 kD [18]. It is derived from murine mAb, MAE11, which was humanized by incorporating the mouse-derived complementarity-determining region (CDR) into a human IgG1 framework, leaving < 5% of the amino acid residues of nonhuman origin. Advanced genetic engineering procedures in the humanization process minimized its immunogenicity potential [19].

The main breakthrough in its development occurred when it was shown that it was able to effectively block the binding site of IgE for both receptors. Selectively binding circulating free serum (unbound) IgE regardless of its antigen specificity, omalizumab reduces free IgE levels, as demonstrated in pre-clinical studies in murine models [20]. IgE bound to omalizumab cannot interact with FcεRI, thus avoiding receptor cross-linking and inhibiting the IgE-induced release of inflammatory mediators from mast cell and basophil without stimulating degranulation, a property that has been referred to as 'non-anaphylactogenic' [8].

Omalizumab decreases free IgE levels, thus reducing the amount of IgE binding to both high- and low-affinity

receptors [21]. Free IgE levels in serum are reduced in a dose-dependent manner within 1 h following the first dose and maintained between doses. Total IgE levels (bound and unbound) in serum increase after the first dose due to the formation of omalizumab-IgE complexes, which have a slower elimination rate compared with free IgE, and standard clinical lab assays detect IgE in both free and complexed forms. At 16 weeks after the first dose, average serum total IgE levels are fivefold higher compared with pre-treatment levels. After discontinuation of omalizumab, the increase in total IgE and decrease in free IgE are reversible, with no observed rebound in IgE levels after drug washout [22]. Moreover, it has been demonstrated that the removal of free IgE by omalizumab causes downregulation of the expression of high-affinity receptors on mast cell, basophil, eosinophil and dendritic cell [23-25]. In addition, recent studies have shown that IgE facilitates *in vivo* allergen presentation by dendritic cells and are also important in regulating dendritic cell-dependent T-cell cytokines during effector phases of allergic disease [26]. Blockade of IgE inhibits the allergic inflammatory cascade, including eosinophil and basophil recruitment, probably by combined effects influencing allergen presentation by airway dendritic cells and blockade of mediator secreting cells. In particular, these two mechanisms of action are both fundamental to decrease the release of inflammatory mediators, reducing allergic inflammation,

Table 2. Pharmacologic properties of omalizumab.

Binds to serum free IgEs, thus reducing free serum IgE levels
Increases total IgE levels (bound and unbound) in serum due to the formation of omalizumab: IgE complexes, which have a slower elimination rate compared with free IgE
Reduces the amount of IgEs binding to both high-affinity (FcεRI) and low-affinity (FcεRII) IgE receptors
Does not bind to high- or low-affinity IgE receptors on inflammatory cells, but prevents IgEs to bind to these receptors
The removal of free IgEs by omalizumab causes downregulation of the expression of high-affinity receptors (FcεRI) on effector cells
Expresses a high degree of isotype specificity and can neutralize IgE without affecting other antibodies classes
Inhibits mast cell degranulation after challenge with sensitising allergens
Reduces both early- and late-phase responses to inhaled allergens
Does not induce histamine release by basophils
Does not induce receptor cross-linking
Does not induce anti-antibodies formation

thus potentially preventing exacerbation of asthma and reducing symptoms (Table 2).

The pharmacokinetics of omalizumab have been studied in adult and adolescent patients with allergic asthma. After subcutaneous administration, omalizumab is absorbed with an average absolute bioavailability of 62%. Peak serum concentrations are reached after an average of 7 – 8 days, and the half-life is ~ 26 days [18]. Omalizumab dosing is based on important data obtained from a Phase II clinical trial of anti-IgE for the treatment of AR [27]. The study concluded that significant symptomatic benefit was reached only when free IgE levels were completely suppressed and that the magnitude of suppression was associated with both pretreatment serum IgE level and anti-IgE dosing. In particular, early dose-ranging studies have shown 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 [27]. Therefore, omalizumab is administered subcutaneously every 2 – 4 weeks, with the dose and frequency determined based on patient body weight and total serum IgE levels. Due to the requirement of near-total suppression of IgE levels for clinical efficacy, the drug is only FDA approved for pretreatment IgE levels of 30 – 1500 IU/ml [28].

Considering the distribution of the drug, omalizumab forms complexes of limited size with IgE. Depending on the relative concentrations of both free serum IgE and omalizumab, stable and biologically inert omalizumab: IgE complexes are formed, typically trimers of ~ 490 – 530 kD or hexamers of approximately 1.000 kD [29]. Tissue distribution studies in cynomolgus monkeys showed no specific uptake of ¹²⁵I-omalizumab by any organ or tissue [30]. Clearance of omalizumab is based on both IgG clearance processes and clearance via specific complex formation with its target ligand such as the IgE. IgG are eliminated in the liver reticuloendothelial system and endothelial cells. Moreover, intact IgGs are also excreted in bile. In studies with mice and monkeys, complexes of omalizumab with IgE were eliminated by interactions with Fc

receptors within the reticuloendothelial system at rates that were generally faster than IgG clearance [18].

3. Clinical development

Early clinical studies examined the effects of neutralizing IgE on allergic airway responses and demonstrated that IgE blockade resulted in the attenuation of both early and late asthmatic responses to allergen inhalation, reduced eosinophil count in the sputum, decreased airway hyperresponsiveness, and improved symptom control in patients with mild allergic asthma [31–33]. The validity of this approach was supported by the results of studies in patients with seasonal AR, where the clinical efficacy of the anti-IgE antibody was related to the reduction in serum-free IgE concentrations [34,35].

These results confirmed the importance of IgE antibodies both in immediate hypersensitivity and in cellular recruitment and the initiation of inflammation, and provided a rationale for further evaluation of IgE blockade in patients with asthma. A first Phase II multicenter, double-blind placebo-controlled study demonstrated the efficacy of anti-IgE treatment, administered by intravenous injection, in 317 patients with moderate-to-severe allergic asthma (adolescents and adults, aged 11 – 50 years) in reducing free serum IgE and improving asthma symptoms as evidenced by reduced use of rescue β₂-agonist inhalers, decreased oral and ICS requirement, and improved pulmonary function testing [33]. In addition, anti-IgE therapy was safe and well tolerated [33].

The subsequent Phase III asthma programme included three critical large studies in patients with moderate-to-severe asthma, performed in the USA and Europe; it provided the evidence that led to FDA approval of omalizumab [36–38]. Two of them included a population of 1071 ICS-dependent symptomatic adolescents and adults [35,36]; the third study involved 334 pediatric patients (aged 6 – 12 years), who were asymptomatic upon study entry [38]. These trials focused on the incidence and the frequency of asthma exacerbations during the steroid-stable and the steroid-reduction periods and the amount of the reduction in ICS as primary end

points [36,37]. In the pediatric study, the primary objectives were safety and tolerability [38]. The secondary end points were the improvement in lung function and asthma symptoms, rescue bronchodilator use, oral corticosteroid requirement and asthma-related quality of life (AQoL) [36-38].

These trials shared a common study design. After a run-in period during which the ICS beclomethasone dipropionate (BDP) dose was adjusted to the optimal level to maintain symptom control, the patients were randomized to receive omalizumab or placebo in addition to BDP at stable doses for 16 weeks. A subsequent 12-week steroid-reduction phase completed the core treatment periods. Omalizumab was administered subcutaneously every 2 or 4 weeks at doses calculated on the basis of baseline-free serum IgE levels and body weight.

In the two studies of adults and adolescents, omalizumab patients suffered from fewer asthma exacerbations during both study phases: the results showed mean values of 0.28 and 0.60 (respectively) exacerbations per patient in the omalizumab and placebo group during the steroid-stable phase, and 0.38 and 0.71 during the steroid-reduction phase [36,37]. Significant improvement in asthma symptoms, use of rescue bronchodilator and AQoL were observed, as well as a small, but significant, effect on lung function. Omalizumab treatment also determined a decreased need for both oral corticosteroid and ICS. In both studies, the overall incidence of adverse events was comparable between the treatment groups [36,37].

Results of the first pediatric study were encouraging in the treatment group: omalizumab was well tolerated, with no serious adverse effects. Moreover, the mean reduction in BDP use was 100% in the omalizumab-treated patients and 40% in the placebo group; during the steroid-reduction phase in the treatment group, use of rescue bronchodilator was reduced, and asthma exacerbations requiring additional treatment declined in both frequency and severity. No significant change between the groups was seen in asthma symptom scores or pulmonary function parameters [38]. Following completion of the above trial, further information regarding quality-of-life evaluations was published [39]. No change in AQoL was found during the steroid-stable phase of the trial, but at the end of the study changes from baseline in overall AQoL were significantly higher for omalizumab than placebo ($p < 0.05$). This was likely affected by the reduction in exacerbations, decrease in ICS use, and lack of hospitalizations in the treatment group [39].

A considerable number of trials followed on the heels of these initial studies. In a recent Cochrane review, the pooled analysis of data was evaluated from 25 anti-IgE trials involving a total of 6,382 patients with moderate-to-severe allergic asthma [10]. Most of the included studies evaluated subcutaneous administration of omalizumab as adjunctive therapy to ICS and/or LABA. Overall, the pooled data indicated that omalizumab was effective in reducing asthma exacerbations and hospitalizations as an adjunctive therapy to ICS and

during steroid tapering phases of clinical trials. Participants in 7 of 11 studies also noted modest but significant improvements in asthma symptom scores and quality-of-life assessments. Furthermore, omalizumab was generally well tolerated, with the only exception being transient injection site reactions [10]. Only three of these studies focused exclusively on a pediatric or adolescent population, and, in adult studies, the adolescent population was represented by a small percentage (6 – 8%) [40]. However, the results of clinical trials with omalizumab in children (6 to < 12 years) were consistent with those in the adult and the adolescent populations [41-43].

To date, several multicenter, observational studies support results of randomized trials, demonstrating that omalizumab is effective as add-on therapy in adults, adolescents and children with severe persistent allergic asthma in the real-world setting [44-47].

4. Post-launch

The increasing interest in omalizumab is due to its evidence of both efficacy and safety. In particular, in terms of safety, data obtained from patient populations including adults, adolescents, and children, within the context of clinical studies and post-marketing surveillance, showed that omalizumab was generally well tolerated [10,42,48,49]. A systematic review (adults, adolescents and children, $n = 3429$) [48] and a pooled safety analysis from completed clinical studies (adults and adolescents, $n > 7500$) [49] indicated an overall incidence of adverse events with omalizumab similar to that in the placebo or control groups. The most common reported adverse events were nasopharyngitis, headache, upper respiratory tract infections and sinusitis, both in adults and children [42,49]. The known safety profile has been confirmed in omalizumab-treated patients of all ages from the real-world setting studies [46,47], and it is currently under further investigation in two observational ongoing studies of Phase IV, EXPECT (NCT00373061) and X-PAND (NCT00813748).

About adverse events of special interest, hypersensitivity reactions (including anaphylaxis, urticaria and serum sickness) occurred rarely in omalizumab clinical trials and at frequencies that were lower than those of other mAbs in other indications [48,49]. In the analysis from completed clinical studies, urticaria was reported in 1.3% of patients who received omalizumab and 1.3% in the control groups, whereas anaphylaxis occurred in 0.14 and 0.07%, respectively [49]. Post-marketing data, based on an estimated exposure of 57300 patients between 2003 and 2006, showed that the frequency of anaphylaxis attributed to omalizumab use was estimated to be at least 0.2 % of patients, comparable to the incidence of anaphylactic reactions for other drugs, such as oral penicillin, aspirin and nonsteroidal anti-inflammatory drugs, as well as to the incidence of anaphylaxis reported in the general population (about 0.05 – 2%) [49]. Post-marketing data have also highlighted that anaphylaxis may occur not only after first administration of omalizumab, but also after subsequent

administrations and sometimes with a delayed time of onset [49]. This rare, but potentially life-threatening, occurrence of anaphylaxis implies practical recommendations regarding patient education, monitoring and treatment. All patients who are candidates for omalizumab therapy should be informed of both the potential benefits of the medication and also of the possibility of rare adverse events. In particular, patients should receive counselling about the potential symptoms and signs of anaphylaxis and an explanation that the potential for such events is the motivation behind post-dose monitoring. Health-care providers administering omalizumab should observe patients closely for an appropriate period of time after omalizumab administration (2 h after the first three injections and for 30 min after all other injections) and should also be prepared to manage anaphylaxis.

No case of serum sickness developed in any patient, and none of the omalizumab recipients developed measurable anti-omalizumab antibodies [49].

Reasonable concerns emerged for the possible association between omalizumab and malignancy risk, due to previous analysis from Phase I to III studies of omalizumab showing a numeric imbalance in malignancies arising in omalizumab recipients (0.5%) compared with control subjects (0.2%) [49]. Although numerically higher than in the placebo group, the observed incidence rate of malignancy in the omalizumab group was comparable with that in the general population [49]. No cases of malignancy have been reported in clinical trials of omalizumab in children 6 to < 12 years of age [40]. No observed association between omalizumab treatment and risk of malignancy was found in a more recent analysis of pooled data, including 7,789 omalizumab-treated patients in a considerable number of Phase I – IV clinical trials [50]. The incidence of primary malignancy per 1000 patient years was 4.14 in the omalizumab group compared with 4.45 in the placebo group (rate ratio 0.93 [95% CI, 0.39 – 2.27]) [50]. Additional omalizumab long-term safety data come from the 5-year EXCELS study, which specifically evaluated the incidence of all malignant tumors and other serious AEs reported from greater than 7000 patients with moderate-to-severe persistent allergic asthma in a real-world clinical practice setting [51]. Initiated at the request of the FDA, this observational cohort study did not show any increase in the risk of primary malignancy with long-term omalizumab therapy [51]. However, because of some limitations in the study design, a definitive conclusion regarding the risk of malignancy with omalizumab treatment cannot be made merely on the basis of EXCELS study results [52], so this information was added to the Warnings and Precautions section of the drug label [53].

Omalizumab is clearly more expensive than any other controller medication patients with allergic asthma and there has been some controversy on whether the benefits of its use are outweighed by its costs. Among the first analysis to support its use, cost-effectiveness was improved in a very restricted group of patients with severe asthma [54].

The costs associated with severe asthma place a substantial economic burden on health-care providers and among patients, when the work productivity is also taken into account [55]. Improved control of the disease results in cost savings. Several recent studies have recorded that the use of omalizumab in clinical practice reduces health-care resource use [56–59]. In particular, add-on omalizumab was cost-effective compared with standard therapy in cost-utility analyses modelled on randomized trials and on real-world data over a lifetime horizon with incremental cost-effectiveness ratio falling within generally accepted willingness-to-pay thresholds [56–60]. Even though the main driver of costs was the purchase price of the drug, the beneficial effects of its administration (lower incidence of clinically significant or severe asthma exacerbations, reduction in the use of oral corticosteroids, and improvement in AQoL) were important factors in reducing costs. Evidence also suggests that cost utility increases as the duration of treatment increases [56–59]. In this context, clinicians should be aware of these considerations in deciding the best treatment options for asthmatic patients to ensure an efficient use of the available health-care resources.

The optimal duration of omalizumab treatment has yet to be determined. Although omalizumab should be administered over the long-term, recent evidence demonstrates that IgE production tends to decrease over time during therapy, suggesting that indefinite treatment may not be required [61]. A small trial, conducted in patients who had received omalizumab for six years, reported that asthma symptoms remained relatively well controlled three years after therapy completion [62]. The ongoing trial XPORT (NCT01125748) is investigating the clinical effects of omalizumab withdrawal after successful long-term therapy.

Few studies have examined the potential anti-inflammatory effects of omalizumab on airway inflammation and its potential role in bronchial structural changes, especially occurring in severe asthma and globally defined as airway remodeling. Given the IgE-dependent increased airway smooth muscle cell proliferation and deposition of pro-inflammatory collagens and fibronectin [63], blocking IgE action may also exert disease-modifying effects on remodelling components. Thus, a reduction of airway wall thickness in severe asthma patients treated with omalizumab has been recently demonstrated [64].

The identification of predictors of response to omalizumab therapy is another open issue of debate. To date, the most meaningful measurement of response is represented by the physician's overall assessment after 16 weeks of treatment [65]. Recent findings suggest that baseline levels of biomarkers of Th₂ inflammation, as well as protein profiles from bronchial biopsies, may potentially have a role in identifying patients most likely to benefit from omalizumab treatment. In particular, high eosinophil blood counts are likely going to be an important biomarker for assessing successful omalizumab treatment effects, as has been consistently shown in two recent omalizumab clinical trials, which included blood eosinophils in their baseline analyses [66–68]. However, further studies are required to

investigate the role of biomarkers as predictor of omalizumab treatment response in patients with allergic severe asthma.

5. Conclusions

IgE is central to the pathophysiology of allergic asthma. The evolution in immunological methods used to assess human allergic diseases has led to the identification of IgE as a potential therapeutic target. Subsequently, the innovative development of a selective blocking agent has disclosed new therapeutic perspectives in the treatment of allergic asthma. Omalizumab, the first biologic agent to treat allergic diseases, represents an important treatment option for patients with moderate-to-severe or severe allergic asthma who remain uncontrolled despite current standard therapies. Its clinical efficacy has been well documented in clinical trials and observational studies, involving adults, adolescents and children. Additional studies are still required to characterize the potential benefit of anti-IgE therapy in airway wall remodelling in asthma and to identify potential biomarkers of response.

6. Expert opinion

Innovative technologies in molecular biology and immunogenetics have made it possible to synthesize specific mAb interacting with any target antigen and have opened the way for the development of tailored therapeutic options in severe asthma.

Omalizumab is the first and, at present, the only mAb available in clinical respiratory medicine for the treatment of moderate-to-severe and severe allergic asthma.

For many years, pathogenetic concepts and the results of clinical trials supported the view that anti-IgE treatment is specifically effective in allergic asthma. As mentioned before, several early studies demonstrated the clinical effectiveness of omalizumab in patients with asthma comorbidities, first AR. Recent studies highlighted its role in improving the safety of subcutaneous immunotherapy, especially with rush therapy.

Recent molecular and clinical evidence suggests that anti-IgE treatment might be effective in many different patient populations other than those with allergic asthma. Humbert *et al.* have interestingly demonstrated the effectiveness of omalizumab in nonallergic asthma patients on long-term treatment, supporting both the hypothesis of a local production of IgE without systemic sensitization and of an inhibitory effect on dendritic cells in the context of viral infection. The first hypothesis assumes that patients with intrinsic asthma have a localised allergy with elevated concentrations of allergen-specific IgE antibodies in the airways. Thus, anti-IgE treatment would reduce local allergic inflammation in the airways, leading to a reduction in disease severity and exacerbation rates. The other hypothesis assumes that plasmacytoid dendritic cells (pDCs) of patients with nonallergic asthma are characterised by an immunological imbalance: enhanced

cross-linking of the high-affinity IgE receptor on pDCs suppresses anti-viral activity of these cells. In this case, viral infections could trigger nonallergic asthma. Anti-IgE treatment would reduce serum IgE concentrations and IgE receptors on pDCs, and restore the anti-viral activity of pDCs—resulting in reduced disease severity and reduced exacerbation rates.

Most notably, evidence from Phase III clinical trials led FDA to approve the use of omalizumab in patients 12 years and older for chronic spontaneous urticaria (CSU) who are unresponsive to modern, second-generation H₁-antihistamines. Omalizumab is effective already in doses from 150 to 300 mg per month with no need to use a nomogram for the doses, as occurs in asthma. Omalizumab shows an excellent positive response rate in all chronic urticaria subtypes and unlike in asthma, a complete response is often observed after as little as 24 h after first injection. Interestingly, its mechanism of action seems to be not dependent on IgE levels and patient's weight and needs to be better clarified. Based on a growing understanding of the heterogeneous effects of IgE, a number of potential pharmacological mechanisms of omalizumab in CSU have been postulated. Omalizumab is mainly thought to reduce mast cell degranulation by: i) desensitizing and reaching the thresholds for mast cell and basophil degranulation; ii) reducing the amount of free IgE that can cause degranulation; iii) reducing the secretion of pro-inflammatory mediators, which indirectly reduces recruitment of pro-inflammatory cells; and iv) reducing local inflammation and subsequently impairing the upregulation of H₁ receptors by histamine itself.

Based on these findings, the identification of an extended phenotype of responders discloses new potential clinical indications in a number of IgE- and non-IgE-mediated diseases beyond allergic asthma but need to be further investigated.

To overcome limitations of omalizumab, first represented by dosing restrictions based on IgE levels, an expected progress has been the production of a new set of mAbs with greater avidity for IgE: RG7449, a new humanized mAb that binds to the M1 segment of membrane IgE and has as a target the B-lymphocytes before they are activated to produce IgE; QGE031/ligelizumab, an highly potent inhibitor of the high-affinity IgE receptor, that is currently under investigation in patients with allergic asthma, (4/5 clinical severity stage according to GINA guidelines), in a Phase IIa clinical trial, with omalizumab as active comparator.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Affiliation

Amelia Licari¹, GianLuigi Marseglia¹,

Riccardo Castagnoli¹,

Alessia Marseglia¹ & Giorgio Ciprandi^{†2} MD

[†]Author for correspondence

¹University of Pavia, Foundation IRCCS

Policlinico San Matteo, Department of Pediatrics,
Pavia, Italy

²IRCCS-A.O.U. San Martino di Genova,

Departemnt of Medicine, Largo R. Benzi 10,

16132 Genoa, Italy

E-mail: gio.cip@libero.it