

## Anti-Immunoglobulin E, a Monoclonal Antibody to Treat Respiratory Disorders

P. Cabrera-Navarro

Servicio de Neumología, Hospital Universitario Dr. Negrín, Las Palmas de Gran Canaria, Las Palmas, Spain.

**Omalizumab is a monoclonal antibody that interrupts allergic reaction—irrespective of the nature of the allergen—by blocking free immunoglobulin E (IgE). The IgE is thus prevented from attaching to cell receptors and setting in motion an allergic cascade of inflammatory mediators. Other interesting biological effects of omalizumab are that it downregulates IgE receptor expression on cell membranes and reduces bronchial eosinophilic infiltration. Clinical trials have demonstrated omalizumab's efficacy and safety in treating most allergic disorders. However, given its high cost, omalizumab is generally reserved for more severe cases of asthma and for asthma that responds poorly to conventional treatments.**

**Key words:** *Asthma. Anti-immunoglobulin E. Omalizumab. Monoclonal antibodies.*

Antiimmunoglobulina E, un anticuerpo monoclonal, en el tratamiento de las enfermedades respiratorias

El omalizumab es un anticuerpo monoclonal que interrumpe la reacción alérgica, independientemente de cuál sea el alérgeno, bloqueando la inmunoglobulina E (IgE) libre, de forma que le impide unirse a sus receptores celulares y poner en marcha la cascada de mediadores de la inflamación alérgica. Además, presenta otros efectos biológicos de especial interés, como disminuir la expresión de los receptores de membrana para la IgE y la infiltración eosinófila bronquial. Los ensayos clínicos han demostrado su utilidad clínica en la mayoría de las enfermedades alérgicas, junto con una gran seguridad terapéutica. No obstante, su alto precio hace que se reserve para los casos de asma de mayor gravedad y mala respuesta al tratamiento convencional.

**Palabras clave:** *Asma. Anti-IgE. Omalizumab. Anticuerpos monoclonales.*

### Introduction

The immune response of the T-helper 2 (T<sub>H</sub>2) cells is characterized by the way in which these cells—acting through interleukins (IL)—induce a humoral reaction in the form of overproduction of immunoglobulin E (IgE) and a cell reaction that is predominantly eosinophilic. This is, essentially, the basic immunological defense mechanism against parasites. The same IgE/eosinophilia-based T<sub>H</sub>2 response is responsible for the pathological development of atopic respiratory disorders such as rhinitis, asthma, and allergic bronchopulmonary aspergillosis.<sup>1-3</sup> This type of reaction has also been reported in a number of animal models.<sup>4</sup>

Research into allergy therapies has thus been largely aimed at either neutralizing the signals that prevent eosinophil production or neutralizing circulating IgE. In

the first of these research lines, anti-IL-5 monoclonal antibodies were investigated, given that these represent the main signal for eosinophil production, chemotaxis, and apoptosis inhibition.<sup>5</sup> Unfortunately, however, although IL-5 inhibition controlled the eosinophil population, it did not affect bronchial hyperresponsiveness in asthma patients, and so its therapeutic benefits were limited.

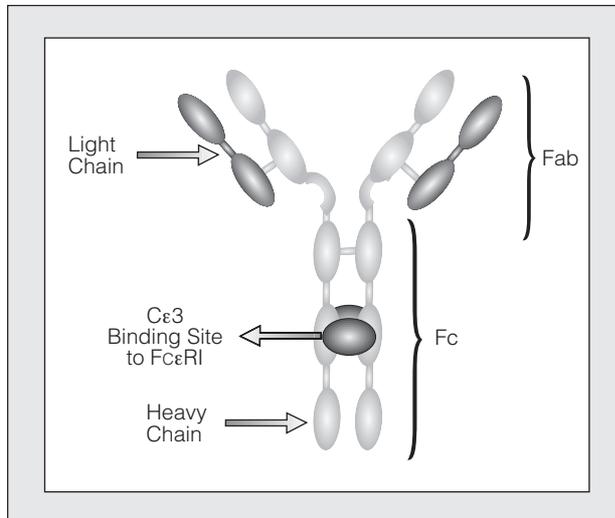
The other target for asthma control from a molecular biology perspective has been IgE. Omalizumab (rhuMAB-E25), an anti-IgE humanized monoclonal antibody which has been marketed in a number of countries as an anti-asthma drug, is the first monoclonal antibody which has been made commercially available for the treatment of asthma.<sup>6</sup>

### Monoclonal Antibody Therapy

The fact that monoclonal antibodies act in a very precise manner to target serum proteins, cell markers, and pathogens is the reason why they have come to play a highly relevant role as reactive antibodies in molecular research. Acting so precisely that they are referred to as “magic bullets,” they have proven highly effective vehicles for anti-cancer agents. Typical

Correspondence: Dr. P. Cabrera-Navarro.  
Servicio de Neumología.  
Hospital Universitario Dr. Negrín.  
Barranco de la Ballena, s/n.  
35020 Las Palmas de Gran Canaria. Las Palmas. España.  
E-mail: pcbnav@gobiernodecanarias.org

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**Figure.** Diagram depicting the structure of human immunoglobulin E (IgE). The Fab region is the variable part of the molecule, capable of recognizing a specific allergen. The Fc region is the constant region of the IgE. The cell membrane receptor binding site is located in the Cε3 domain. Note that this domain is expressed on both sides of the molecule.

antibody formation is polyclonal, which means that a number of antibodies are formed against a foreign body. Each of these antibodies recognizes different portions of the molecular structure (antigenic determinants, or epitopes) and each comes from a specific B-cell clone. When faced with a foreign body, numerous B-lymphocyte clones participate in the normal immune response, with each clone recognizing a specific part of the foreign body. Monoclonal antibodies, on the other hand, are obtained from B-cell clones which produce a specific antibody that only reacts to a specific foreign body epitope. This degree of specificity reduces reactions to common epitopes expressed on different molecules, which would lead to cross-reactivity.<sup>7</sup>

Monoclonal antibodies are produced by isolating B-lymphocyte clones. However, because B-cell cultures can only be kept for a few days in laboratory conditions, techniques have been developed to sustain "immortal" cell cultures, by means either of viral transformation of the isolated B-cells and/or fusion of the B-cells with a proliferation of monoclonal neoplastic cells forming multiple myeloma. The resulting cell culture, known as a "hybridoma," is an inexhaustible source of monoclonal antibodies.<sup>8</sup>

Although a raised serum IgE level has always been linked to asthma associated with atopy, to a lesser but still significant extent, IgE levels are also elevated in nonallergic asthmatics.<sup>9</sup> IgE production by the B-lymphocytes is induced by IL-4 and IL-13 action originating in activated T<sub>H</sub>2 cells.

The IgE structure is made up of 2 heavy chains and 2 light chains. The light chains are located in an area known as the Fab region, which is both the immunoglobulin variable domain and the allergen recognition site. The constant Fc region is composed

exclusively of heavy chains. This is the location of the Cε3 domain, which is where IgE binds with the specific receptors of the various cell line membranes (Figure). Mast cells and basophiles have surface receptors with a high affinity to IgE (FcεRI); eosinophils and B-lymphocytes, on the other hand, are equipped with low-affinity receptors (FcεRII, also known as CD23).

Circulating IgE has a very short half-life, largely because it binds rapidly to cell receptors, which is why it is very active biologically, even at low concentrations.

Allergenic activation of IgE bound to cell receptors by means of the FcεRI receptor releases both preformed and newly synthesized inflammatory mediators. This is why inhalation of allergens by sensitized asthmatics causes both early-phase and late-phase obstruction of the airways, as well as a fall in forced expiratory volume in 1 second (FEV<sub>1</sub>). Furthermore, IgE regulates the production of its own cell receptors.<sup>10,11</sup>

Omalizumab is a monoclonal antibody which specifically attaches to the IgE Cε3 domain and prevents IgE from binding to the cell receptors.<sup>11,12</sup> Monoclonal antibodies are produced by injecting purified human IgE into mice, which then produce antibodies against the immunoglobulin. Once production reaches a maximum, the mouse spleen is removed and the clone that produces the anti-Cε3 antibodies is selected for fusion with myeloma cells in order to create the hybridoma that will produce the anti-IgE. However, monoclonal antibodies have to be "humanized," as the mouse anti-IgE obtained from the hybridoma is a foreign protein that would give rise to an anaphylactic reaction if administered directly to humans. Humanization consists of grafting the final segments of the Fab portion of the monoclonal antibody (ie, the part that recognizes the human IgE Cε3 domain) onto a human IgG1 framework. This ensures that the mouse residue in the final product is minimal and so incapable of causing an immunological reaction in the host.

As the Cε3 domain is expressed on both sides of the IgE, omalizumab blockage on one side will still permit the IgE to cleave to cell receptors on the other side of the molecule. Each circulating molecule of IgE, therefore, has to be blocked by 2 molecules of omalizumab.

Moreover, once bound to the cell receptors, IgE undergoes a spatial transformation that facilitates recognition of the allergen. The spatial transformation also affects the Cε3 domain, rendering it unrecognizable to omalizumab. This represents an advantage from the therapeutic viewpoint, as the binding of omalizumab to the free Cε3 domain on the other side of IgE would consume large quantities of the drug while failing to prevent cellular release of the inflammatory mediators. Omalizumab, therefore, can only bind to IgE that is not bound to cell receptors.<sup>13,14</sup>

### In Vitro Effects of Omalizumab

The first study of omalizumab in humans demonstrated that the serum concentration of circulating IgE fell rapidly following administration.<sup>15</sup>

Previous evidence showed that both circulating IgE and exposure to allergens regulated overexpression of the IgE cell receptors.<sup>10,11,16</sup> These findings have been corroborated by studies of individuals that have demonstrated that treatment with omalizumab causes a 93% reduction in basophil FcεRI receptors.<sup>17</sup>

Similar results were obtained in a study of bronchial biopsies of asthmatic patients treated with omalizumab. In these asthmatic patients, moreover, reductions were also evident in the other IgE-mediated inflammation markers, namely IL-4, eosinophil cationic protein, and IgE bound to its cell receptors.<sup>18</sup>

### Clinical Effects of Omalizumab

Administration of omalizumab reduces the skin's response to allergens. In a study of 47 mite-sensitized patients with allergic rhinitis, it was observed that, following 6 months' treatment with omalizumab,<sup>19</sup> the mean (SD) skin reaction area decreased significantly from 181 (42) to 61 (15) mm<sup>2</sup>.

As for the impact of omalizumab treatment on bronchial hyperresponsiveness, results have been contradictory. In a study of 46 asthmatics treated with omalizumab for 16 weeks, the methacholine challenge test showed no evidence of a change in bronchoconstrictor concentrations capable of causing a fall of 20% in FEV<sub>1</sub>.<sup>18</sup>

In another study evaluating 20 adult patients for early-phase response to allergen inhalation challenge,<sup>20</sup> omalizumab-treated patients required a larger allergen concentration to produce a fall of 15% in FEV<sub>1</sub>.

Other researchers have measured early-phase and late-phase falls in FEV<sub>1</sub> following allergen inhalation. In patients treated with omalizumab, the fall in FEV<sub>1</sub> for both responses was significantly reduced.<sup>21</sup>

As for allergic rhinitis, studies have generally demonstrated a good response to omalizumab. The study involving the largest number of cases—536 patients with seasonal rhinitis—reported an improvement in symptoms in the treated patients.<sup>22</sup> A clinical trial of patients allergic to birch pollen demonstrated that during the pollen production season, patients treated with omalizumab had fewer symptoms and a better quality of life than patients treated with a placebo.<sup>23</sup> The same researchers demonstrated in another trial that, unlike placebo-treated patients, patients treated with omalizumab did not show an increase in eosinophil population in the nasal mucosa during the pollen season.<sup>24</sup>

In another trial enrolling 405 patients with concomitant asthma and allergic rhinitis, treatment with omalizumab improved quality of life in regard to both illnesses.<sup>25</sup>

In another study, nasal response to allergens was inhibited in patients in the treatment group compared to those in the placebo group, whether measured in terms of symptoms or by means of inflammatory markers in the nasal lavage fluid.<sup>26</sup> Although most studies have been conducted in patients with seasonal rhinitis, similar findings have been made in relation to perennial rhinitis.<sup>27</sup>

Omalizumab's main indication is asthma associated with atopy and elevated serum IgE. One of the first studies of asthmatic patients treated with omalizumab demonstrated that serum IgE in treated patients fell by 95% while holding steady in patients who had received a placebo. Furthermore, daily symptom scores were lower for patients treated with omalizumab. Patients in that study had moderate or severe persistent asthma and the treatment group patients were receiving inhaled or oral glucocorticoids; although the difference was not significant, more patients in the treatment group compared to the placebo group were able to leave off using glucocorticoids.<sup>28</sup> In another published study involving a larger number of patients (546) with equally severe asthma, however, omalizumab was demonstrated to be useful (with a high degree of significance) in reducing inhaled glucocorticoid doses.<sup>29</sup>

In a pediatric study of children aged 6 to 12, an improvement in quality of life parameters was observed; there were, moreover, no significant complications.<sup>30</sup>

That said, it seems that the best results for omalizumab are obtained in patients with severe asthma of a persistent nature associated with atopy, a fact which is attested to by many publications. Thus, omalizumab has demonstrated its efficacy in reducing the number of severe attacks in high-risk asthma patients who have recently received emergency treatment and or who have a history of tracheal intubation.<sup>31</sup> Moreover, omalizumab reduces the annual hospitalization rate for this type of patient.<sup>32</sup> These observations were recently confirmed in an analysis of the factors that predict a good response to omalizumab treatment: the drug was more effective in patients with high inhaled glucocorticoid consumption, who made frequent visits to the emergency services, and who had a poor respiratory function.<sup>33</sup>

A study that pooled data from several clinical trials applying a similar methodology included 4308 patients, 93% of whom had severe persistent asthma. For the 2511 patients treated with omalizumab, the asthma exacerbation rate and the number of visits to emergency services were significantly lower. An analysis of subgroups, moreover, revealed a nonsignificant trend toward fewer exacerbations among patients with higher IgE, patients with poorer FEV<sub>1</sub>, and younger patients.<sup>34</sup>

There are as yet no published studies on the usefulness of omalizumab for treating occupational asthma, although it appears to be useful in other occupation-related atopic manifestations.<sup>35</sup>

The drug is presented in the form of injectables for subcutaneous administration on a fortnightly or monthly basis. Dosage is calculated on the basis of weight and serum IgE concentrations. Although some studies have been performed on administration of omalizumab as an aerosol, this route is not as yet recognized.<sup>36</sup>

As for the safety of omalizumab, clinical trials performed to date describe the same adverse effects for both treatment and placebo groups. In a study to evaluate the safety of omalizumab in children, of 225

patients aged 6 to 12 analyzed over the long term, only 11 experienced urticaria episodes (brought under control using antihistamines), and in only 1 case was it necessary to suspend treatment with the drug.<sup>37</sup>

An analysis of adverse effects in another clinical trial, based on 3 groups of around 100 patients each, showed no significant differences between the high-dose group, the low-dose group, and the placebo group; there were, however, 14 cases of urticaria among patients receiving treatment compared to 3 cases in the placebo group.<sup>28</sup>

The immune complex composed of circulating IgE and the 2 omalizumab molecules is non-complement-fixing and lacks potency as an immunological pathogen; this complex is eliminated by the leukocytes and the reticuloendothelial system.<sup>38,39</sup> Among the thousands of treated patients that are represented in medical publications, no case of illness arising from immune complexes or damage to renal function have been reported.

Humanization of the drug means that the murine residue is less than 5%; the rest of the framework is human IgG1. This minimal percentage of omalizumab that is of murine origin is incapable of provoking hypersensitivity reactions. Thus, in a study of 212 patients who completed 20 weeks of treatment, none developed antibodies against omalizumab.<sup>28</sup>

One of the drawbacks to omalizumab is its price; this is a problem common to all drugs developed using the monoclonal antibody technique, which is costly in production terms. In the United States of America it is estimated that annual treatment costs vary between \$5000 and \$10 000 per patient, depending on the dose. This elevated cost has led national healthcare authorities to restrict indication to severe cases of asthma. A cost-benefit study for omalizumab recommends the drug for cases where the disease is poorly controlled after all other possible therapies have been tried. The cost of the drug can be offset against the costs associated with prolonged hospitalization (in the USA, for example, over 20 days annually).<sup>40,41</sup>

To sum up, omalizumab is a monoclonal antibody that interferes with allergic reactions, irrespective of the nature of the allergen. It does this by blocking free IgE, preventing it from binding to cell receptors and setting in motion an allergic cascade of inflammatory mediators. Omalizumab also has the important advantage that it does not bind to IgE that is already attached to cell receptors; if omalizumab did this, there would be an unnecessarily high consumption of the drug with no corresponding increase in therapeutic usefulness. Omalizumab also has other interesting biological effects, primarily that it downregulates IgE receptor expression on cell membranes and reduces bronchial eosinophilic infiltration. Clinical trials have demonstrated the efficacy and therapeutic safety of omalizumab in treating most allergic disorders. However, given the high cost of omalizumab, it is generally reserved for more severe cases of asthma and for asthma that responds poorly to conventional treatments. The factors that define such

cases are the same factors that predict an improved response to therapy, namely a high consumption of inhaled glucocorticoids, elevated serum IgE levels, repeated emergency visits, and poor respiratory function.

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