

Omalizumab for Severe Asthma: Efficacy Beyond the Atopic Patient?

Christian Domingo

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Abstract Several years ago, omalizumab became commercially available for the treatment of severe asthma. It remains the only monoclonal antibody to be marketed for this purpose. Since then, many studies have been published endorsing its efficacy and effectiveness. Concomitantly, evidence of an overlap between atopic and non-atopic severe asthma has emerged. However, there also appears to be some disagreement regarding the value of omalizumab in the management of non-atopic disease, as some studies have failed to show any benefit in these patients. The recent literature has also sought to identify appropriate prognostic biomarkers for the use of omalizumab, other than immunoglobulin (IgE) levels. This article briefly summarizes the evolution of asthma treatment, the pathophysiology of the condition, and the method of action of omalizumab. The author describes the controlled and uncontrolled studies (also named “real-life studies”) published in adult and pediatric populations in different countries and expresses his view on the current place of the drug in the management of severe allergic asthma. He offers a personal perspective on the recent evidence for the use of omalizumab in non-atopic patients, highlighting the implications for current clinical practice and the gaps in our knowledge. The author justifies his belief that omalizumab is not only an IgE-blocking drug and should be considered as a disease-modifying therapy because of its multiple effects on

different biologic pathways. Finally, some areas for future research are indicated.

1 Brief History of Asthma Treatment

Asthma is a common, chronic, inflammatory disorder of the airways. It is clinically characterized by bronchial hyper-responsiveness, reversible airflow limitation, and recurrent episodes of wheezing, shortness of breath, chest tightness, and cough. Asthma is in fact a complex syndrome with many clinical and inflammatory phenotypes [1–6]. However, it took a long time to reach this conclusion, and the lack of definition regarding the disease has slowed the development of appropriate therapeutic approaches. Two major breakthroughs have significantly improved the clinical management of asthma. The first one dates from 1992, when the first international guidelines for asthma treatment recommended the systematic prescription of inhaled corticosteroids as standard therapy for patients with persistent disease [7]. During the next 20 years, repeated attempts were made to find the most appropriate dose of inhaled corticosteroids for use at the different asthma severity steps. Some other drugs that are helpful in the management of inflammation such as leukotriene modifiers and for persistent bronchial smooth cell fiber constriction such as long-acting β -agonists were marketed, but none made an essential contribution to conceptually improving asthma treatment, which seemed to have advanced as far as it could [8]. These drugs attempt to treat the last step of the pathophysiologic pathway of asthma, that is, inflammation. At the same time, conventional, subcutaneous, allergen-specific immunotherapy continued to market new products and tried to find alternative administration routes [9–14].

C. Domingo (✉)
Pulmonary Service, Hospital de Sabadell (Corporació Sanitària i Universitària Parc Taulí), Parc Taulí 1, 08208 Sabadell
(Barcelona), Spain
e-mail: cdomingo@tauli.cat

C. Domingo
Departament de Medicina, Universitat Autònoma de Barcelona
(UAB), Barcelona, Spain

The second breakthrough dates from the early 2000s, with the advent of what were known as “biologic treatments,” that is, treatments that try to block the proteins or molecules originating in cells, which in turn trigger or modulate the asthma cascade. When the aim is to block the production of intracellular proteins we call it anti-sense therapy, because the procedure comprises the administration of molecules that are short, single-stranded, nucleic acids complementary to target messenger RNA (mRNA), which bind to receptor mRNA with levels of affinity and avidity that can far surpass those shown by traditional drugs targeting protein receptors [15]. These molecules are thus a chain of oligonucleotides arranged in the opposite sense (anti-sense) of the RNA strand to be blocked. This approach is still at a very early stage of development.

Monoclonal antibodies (mAbs) represent a form of immunotherapy using passive immunity in which pre-formed antibodies against a target antigen are injected into the body. Because of their specificity, mAbs can efficiently target an antigen on a cell of interest or in the serum and block the binding of cytokines, immunoglobulins (Igs), hormones, or proteins that promote certain unwanted functions including inflammatory and immune responses. Ultimately, both methods can attenuate the expression of disease-associated genes [16].

2 Physiopathology of Allergic Asthma

The induction, maintenance, and progression of the inflammatory and remodeling responses of asthma are driven by complex interactions of adaptive (i.e., dendritic cells, B cells, and activated T cells) and innate immune responses (i.e., macrophages and neutrophils) with structural cells of the airways (i.e., epithelial cells, airway smooth muscle cells, and myofibroblasts). These interactions lead to the secretion of preformed and/or newly synthesized mediators, IgE, cytokines, growth factors, and chemokines, which results in distinct asthma phenotypes [17]. Classically, allergic diseases are generally defined as significant pathologic changes caused by excessive reactions of the immune system to innocuous substances. When an atopic individual is exposed to an antigen, the dendritic cells (specialized macrophages located in the organism’s epithelium) internalize it, process it, and present it to a T lymphocyte, via the major histocompatibility complex. In this process, the T lymphocyte develops a T-helper 2 (Th2) or a T-helper 1 (Th1) profile. The relative amount of each is both antigen and host dependent (Fig. 1) [18]. When the antigen is an allergen, the lymphocyte differentiates into a Th2 cell able to produce interleukin (IL)-4, which in turn promotes the synthesis of IgE by the B lymphocytes (Table 1). As well as regulating IgE, IL-4 stimulates the

migration and activation of the mast cells. Mast cells contain in their membrane the high-affinity receptor for IgE (FcεRI). When this receptor binds to IgE, the molecule is able to recognize the antigen. When two or more IgE molecules bound to their receptor recognize the same antigen molecule, they cause cross linking of the receptors, a phenomenon that triggers a series of biochemical signaling reactions that culminate in mast cell degranulation [18] and the release of the immediate mediators of the inflammation—histamine, leukotrienes, prostaglandins, ILs, and cell growth factors. This phase lasts approximately an hour. Later, a second phase may occur after 4–8 h of exposure to the allergen. The chemotactic factors, IL-5, IL-3, IL-13, and the cell growth factors released in the immediate inflammation phase enhance eosinophil recruitment. The eosinophils release IL-5, which in turn enhances the recruitment of new eosinophils and perpetuates the inflammation. This may lead to chronic allergic inflammation in the case of continued exposure to the allergen. On occasion, if the number of eosinophils and mediators is very high, this process may persist without the need for an allergenic stimulus [18, 19].

IgE plays a key role in the physiopathology of asthma [20]. IgE binds to its high-affinity receptors, FcεRI, on the surface of mast cells and basophils via the Cε3 domain of its Fc fragment. The correlation between the expression of FcεRI on the basophils and serum levels of IgE is well established [21]. IgE itself [22] seems to up-regulate the expression of FcεRI on human basophils probably by interacting with FcεRI (Fig. 2).

Recent data have suggested that IgE has some additional immunobiologic effects. This molecule may promote mast cell survival through autocrine production of IL-6 [23]. Survival assays performed on cultures of human lung mast cells provided further evidence that IgE and IL-6 contribute to the pathogenesis of asthma, and it is speculated that anti-IgE therapy may achieve its therapeutic effect through this mechanism. IgE binds to dendritic cells and enhances allergen uptake and presentation to T cells [24]. It has been reported that dendritic cells in patients with mild atopic asthma bind significantly more IgE than cells taken from healthy individuals [25], and FcεRI receptors are known to be up-regulated on dendritic cells (as well as eosinophils, mast cells, and macrophages) in patients with seasonal allergic rhinitis [26].

3 Omalizumab: The First Monoclonal Antibodies Marketed for Asthma Treatment

3.1 Mechanism of Action

The monoclonal antibody omalizumab is an IgG of clonal origin and is therefore specific for a single antigen. The

Fig. 1 T-helper 1 (Th1) and T-helper 2 (Th2) differentiation and the allergic cascade (from Domingo et al. [18] with permission). Interleukin (IL)-4 and IL-12 promote, respectively, the differentiation into a Th2 and Th1 profile. APC antigen-presenting cell

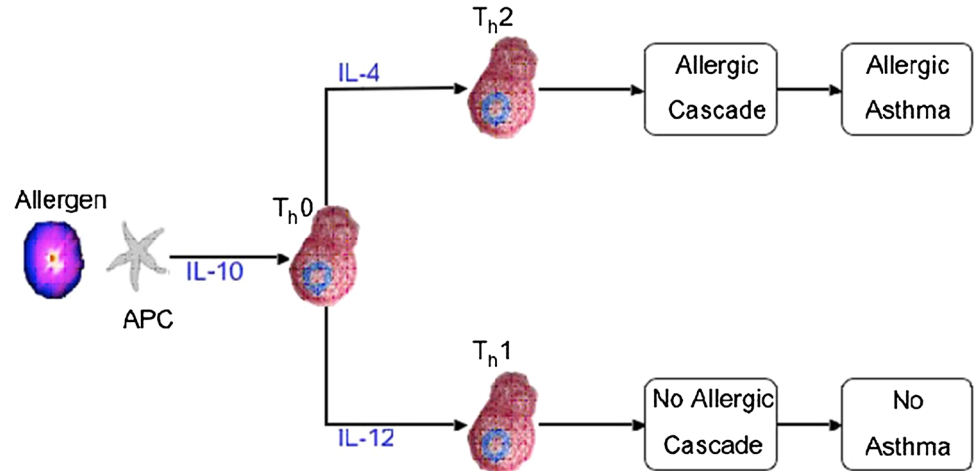


Table 1 Differences between T-helper 1 (Th) and T-helper 2 (Th2) profiles

Th1 cells	Th2 cells
Interleukin-12 induces differentiation	Interleukin-4 induces differentiation
Cytokine production:	Cytokine production:
•Interferon- γ	•Interleukin-4
•Interleukin-2	•Interleukin-5
	•Interleukin-13
Intracellular pathogens	Extracellular pathogens
Macrophage activation	B-cell activation and immunoglobulin E eosinophil responses

most important step in the production of a monoclonal antibody is the selection of the target. In the case of anti-IgE therapy, the aim is to achieve a specific monoclonal antibody to a key epitope of the IgE molecule. Omalizumab, known in its first trials as rhu MAb-E25, is a humanized murine monoclonal antibody that recognizes the C ϵ 3 domain of human IgE, the portion of the IgE molecule that binds to the receptors of the mast cells and basophils. Once bound to the cell receptors, the IgE undergoes a spatial transformation that favors recognition of the allergen. This spatial transformation also affects the C ϵ 3 domain and makes it unrecognizable to omalizumab; as a result, omalizumab binds to free IgE but not to IgE bound to the cell receptors [27].

The administration of omalizumab results in a rapid and substantial decrease in free serum IgE, which falls by 99 % within 2 h of its administration. It also induces down-regulation of Fc ϵ RI on basophils, dendritic cells, and monocytes within 7 days (Fig. 2). At 3 months, the quantity of Fc ϵ RI receptors on basophils falls by up to 93 % [28, 29]. Therefore, the effect of omalizumab on serum IgE is to reduce both the amount of surface-expressed IgE and the expression of Fc ϵ RI on mast cells and basophils. In addition, the fall in the expression of Fc ϵ RI on dendritic cells may reduce the processing and presentation of allergens [30], and consequently this may lead to a decrease in the

activation of the lymphocytes and the generation of cytokines from Th2 lymphocytes (Fig. 2). Finally, omalizumab has been shown to decrease serum, tissue, and sputum eosinophilia (Fig. 2).

Briefly, the concept of anti-IgE treatment in asthma is closely linked to the pathogenesis of type I hypersensitivity: allergen-induced cross-linking of IgE antibodies on the surface of mast cells causes mast cell degranulation, inflammation and, subsequently, obstruction of the airways. Removal of IgE antibodies appears to be a logical strategy to treat allergic asthma.

3.2 Efficacy in Allergic Asthma

Administered by subcutaneous injection, the efficacy and safety of omalizumab in allergic GINA step IV and V asthma patients have been established in a number of studies that can already be considered as reference points even though they were published only recently [31–38]. In three, large, prospective studies of up to 28 weeks [31–33], omalizumab produced statistically significant reductions in the rate of clinically significant asthma exacerbations compared with placebo, along with improvements in asthma symptom scores. A decrease in the use of rescue medication such as short-acting β -agonists and bursts of oral corticosteroids was also observed. The long-term

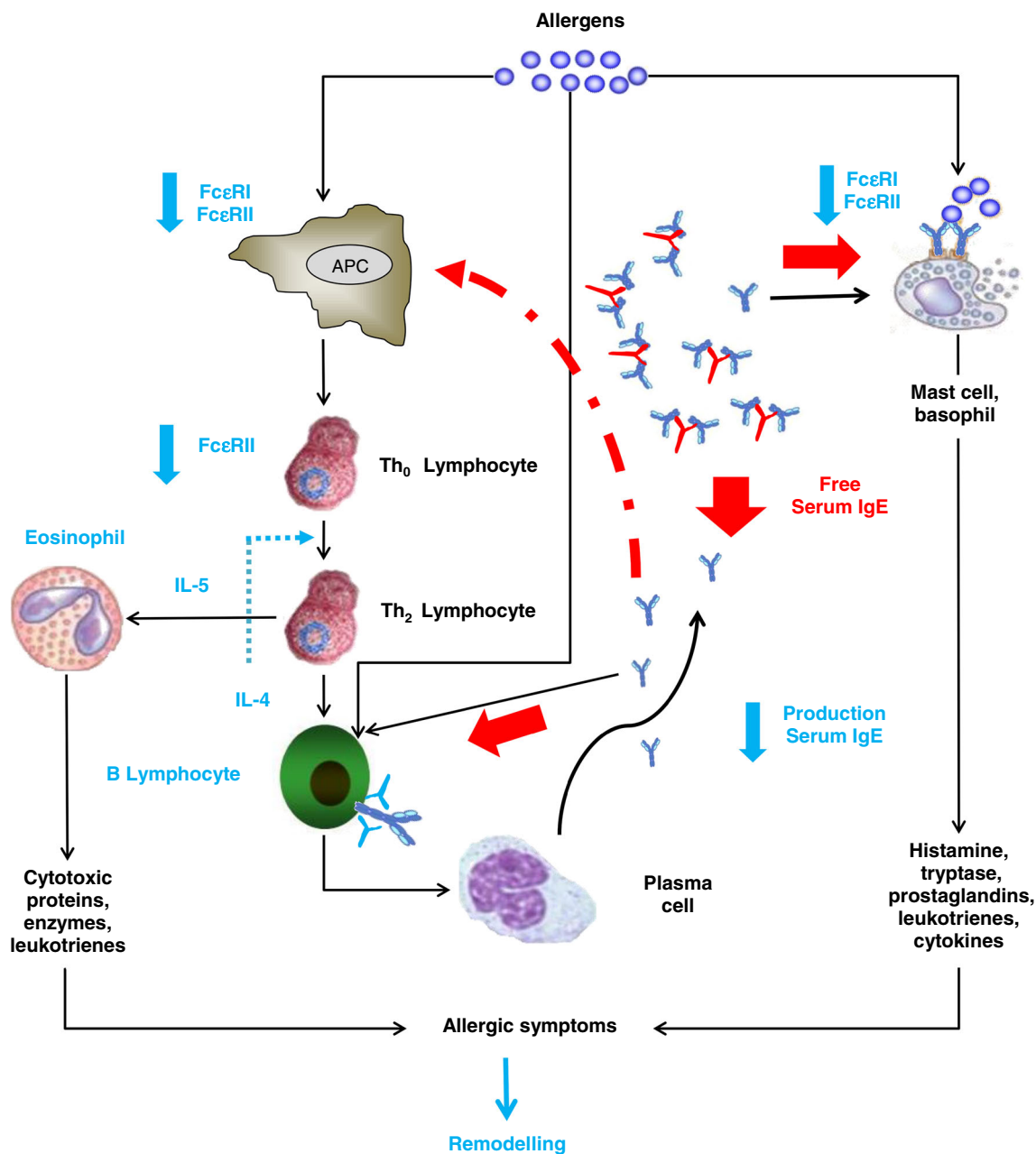


Fig. 2 Effects of omalizumab. In *black*, steps of the allergic process. In *red*, the steps blocked by the direct immunoglobulin E (IgE)-blocking effect of omalizumab. In *blue*, the indirect immunomodulation mediated by the action of omalizumab that causes a down-

benefits of continuing treatment with omalizumab were shown in extensions of the trials for up to 24 weeks [34–36]. Although many of these studies were performed in adults, some papers have also endorsed the efficacy of this treatment in the pediatric population [39]. In a recent multicenter study, Deschildre et al. [40] evaluated the efficacy and safety of omalizumab in a real-life setting in 104 severe asthmatic children (aged 6–18 years) treated in pediatric, pulmonary, tertiary care centers in France. They observed that omalizumab improved asthma control in

regulation of the FcεRI, FcεRII cell expression at different levels, interleukin (IL)-4 and IL-5 secretion, eosinophil and B-lymphocyte levels as well as IgE production. *APC* antigen-presenting cell

children with severe allergic asthma and that the drug was generally well tolerated. As is generally the case, the observed benefit was greater than that reported in clinical trials.

The next step was to test the effectiveness of the drug in real clinical practice. The intrinsic goal in the literature was to determine whether the clinical experience was the same in every country or whether, on the contrary, differences would appear. In France, Molimard et al. [41] observed that after excluding patients treated for less than the 16 weeks

recommended to evaluate efficacy and also the nine patients who were under-dosed, omalizumab was effective in controlling asthma. In Italy, Cazzola et al. [42] observed that following treatment with omalizumab, the annual rate of exacerbations, emergency visits, and hospitalization notably decreased. Later, Pelai et al. [43] also noted that in uncontrolled asthma patients, omalizumab decreased exacerbation frequency and the oral intake of corticosteroids. In the USA, in an observational retrospective assessment limited to patient data at their clinic, Storms et al. [44] also supported the results of earlier controlled studies. Similar results were observed in other locations [45–47].

In a pediatric population in a 16-week, uncontrolled, therapeutic trial of omalizumab in 34 consecutive children with severe asthma, Brodlić et al. [48] noted the oral corticosteroid-sparing effect of omalizumab. The authors made great efforts to distinguish between children with asthma that is difficult to treat because of poor treatment compliance or environmental, social, and/or psychological issues and those with genuinely severe disease despite carefully administered, maximal standard treatment.

The vast majority of studies included patients with moderate or severe asthma, but omalizumab was instituted after the best standard care to quantify the drug's capacity to spare inhaled corticosteroids rather than oral corticosteroids [31–33]. Hardly any of the studies included oral corticosteroid-dependent asthma patients [31–33]. Chronic allergic inflammation is believed to result in airway remodeling because of a repetitive cycle of injury and repair in the airway wall. Features of this remodeling process include epithelial shedding (which results in the release of additional cytokines, growth factors, and other inflammatory mediators), goblet cell hyperplasia, myofibroblast proliferation, smooth muscle hyperplasia and hypertrophy, subepithelial fibrosis, and inflammatory cell infiltration. Several studies indicate that this remodeling process continues after the removal of the original antigen challenge. One murine model of chronic asthma using low antigen levels for 3 days per week over 8 weeks found that inflammation reversed on cessation of the antigen challenge, while remodeling (subepithelial fibrosis and epithelial hypertrophy) persisted throughout the 4-week follow-up period [49].

Severe asthma patients constitute a very special population because remodeling systematically occurs. In pediatric patients, Brodlić et al. [48] observed that despite the marked decrease in oral corticosteroid dose, patients' forced expiratory volume in 1 second (FEV₁) increased. In adults with a long history of oral corticosteroid-dependent asthma and fixed airway obstruction, we observed [47] that after implementation of omalizumab, patients' oral corticosteroid requirements progressively decreased although

FEV₁ did not change substantially. Thus, the drug also showed a controller effect in the presence of remodeling, which helped to preserve the lung function despite the non-use of oral corticosteroids.

The interaction between anti-IgE therapy and free IgE interrupts a key step in the allergic inflammatory cascade. Given the central role of IgE in airway inflammation and the likely inflammatory component involved in the development and maintenance of airway remodeling, it is plausible that therapies that target IgE may influence the remodeling process, either by attenuating its progress or by reversing long-term changes [50]. Our study [47] was an observational, prospective, uncontrolled study in a real-life setting. This is why we decided not to compare the exacerbations during treatment with the patient's history because these data are frequently considered unreliable; instead, we carefully recorded the monthly dose of oral corticosteroids. According to many trials, an exacerbation occurs when patients require oral corticosteroids or, if they are taking them, when the dose is doubled for at least 3 days. Thus, our monthly control of oral corticosteroid therapy reflects to some extent the exacerbations that occurred. In contrast, although the follow-up was quite long (24 months) and airway inflammation measured by exhaled nitric oxide concentration improved slightly, this does not preclude the possibility that remodeling might have progressed because histologic data are lacking. In a randomized, open-label, parallel-group study in Poland, Siergiejko et al. [51] observed after 32 weeks of follow-up that omalizumab allowed a reduction in the oral corticosteroid use.

3.3 Present Indications, Treatment Duration, and Biomarkers

The indication of omalizumab has not changed significantly in recent years; it continues to be prescribed as an add-on therapy for patients with moderate and severe allergic asthma (Table 2). Although the vast majority of studies have been performed in patients receiving moderate/high doses of inhaled corticosteroids, the drug was approved mainly as add-on-therapy to oral corticosteroids.

The first point to stress here is the new dosing table recently introduced. Omalizumab was first marketed for patients with an IgE level range of 30–700 IU/mL [18]. At present, the dosing table has been extended to a maximum IgE level of 1,500 IU/mL. Assessing the length of the treatment period needed to achieve clinical response and thus continue or terminate therapy is also a challenge. Our experience with methotrexate [52, 53] showed that in asthma patients receiving oral corticosteroids, the clinical response may be delayed up to several months. Thus, although the guidelines (based upon the recommendations

Table 2 Past and present indications for omalizumab treatment

	At marketing	At present
Age (years)	≥12	≥6
Allergy sensitization	Positive skin prick test or in vitro reactivity to at least one perennial aeroallergen	Positive skin prick test or in vitro reactivity to at least one perennial aeroallergen
Baseline immunoglobulin E level	≥30–700 kU/L	≥30–1,500 kU/L
Monthly calculated omalizumab dose	≤750 mg	≤1,200 mg
Asthma severity	Severe or inadequately controlled asthma	Severe or inadequately controlled asthma
Re-evaluation	After 16 weeks of treatment	After 16 weeks of treatment
Long-term treatment withdrawn	Not specified	Not specified

Please note that points 1, 3, and 4 have now been modified (see the body of the text)

of the manufacturer) advise considering whether to continue or discontinue treatment after 16 weeks, our policy [47] is to perform this evaluation (in oral corticosteroid-dependent patients) after 6 months of therapy to avoid missing patients who could potentially benefit from this treatment.

The second aspect that requires further study is the duration of the treatment after considering that the patient has responded, or, in other words, when treatment should be stopped. This point has not been conclusively established and in fact there is no clear evidence about patients' clinical and immunologic response, although some significant details have been elucidated.

Slavin et al. [54] were the first to report that asthma symptoms re-emerged after omalizumab withdrawal. The information available in the literature is quite limited. One small study has highlighted the possible role of anti-IgE therapy in improving the course of asthma, with clinical improvements still seen 3 years after treatment withdrawal. The studies by Nopp et al. [55, 56] evaluated a particular population of allergic patients (15 of the 18 were cat allergic and other three mite allergic) with an age range of 37–71 years who had received omalizumab for 6 years as part of a prospective clinical trial of severe asthma. In summary, most of the patients in this study had surprisingly mild and stable asthma 3 years after completing 6 years of omalizumab treatment.

Some researchers have noted that after a period of time on the labeled regimen, the efficacy of omalizumab in allergic diseases such as asthma and urticaria can be maintained, even when the dosing interval is extended beyond the original 2- or 4-weekly administrations [57]. This suggests that a fixed dosing rate may not be obligatory in the long term. Lowe and Renard [58] assessed whether excessive IgE production by patients with atopic allergic asthma decreases with omalizumab therapy. The impact of long-term treatment with omalizumab on the IgE system remains an important key unanswered question. To ascertain whether excessive production of IgE by patients with allergic asthma remains constant over time or decreases

with omalizumab therapy, Lowe and Renard [58] used a model-based pharmacokinetic-pharmacodynamic analysis of omalizumab and free and total IgE, contrasting a published model in which IgE production was assumed to be constant with a model in which IgE production could change over time. To evaluate the long-term implications of treatment with omalizumab, the final model was used to predict total IgE levels after 1-, 3-, or 5-year treatment periods. The resulting simulation suggested that treated patients would be expected to approach new equilibriums in IgE levels approximately 5 years after initiating treatment. The authors concluded that with this down-regulation, treatment with omalizumab may not have to be maintained for long periods. Based on these results, it has been proposed that omalizumab should be maintained for 5 years and then withdrawn, although this proposal is based upon a mathematic model.

Our empiric experience is at variance with these data. The effect of omalizumab is progressive, and for this reason the time to response is not uniform. IgE directly binds to and activates receptors present on eosinophils, neutrophils, and monocytes. Thus, the free IgE level may also be a key factor in patient control. Two aspects are involved in this process: the duration of the inflammatory process, and the triggering factor, that is, the free IgE. We addressed the time-dependent aspect using a progressive decreasing-dose protocol, and the level-dependent factor by measuring the free IgE. Our preliminary results suggested that, in some patients, the drug can be stopped long before 5 years while in others, it seems that the drug may never be withdrawn [59, 60]. Therefore, the moment at which the drug should be stopped is far from clear.

Corticosteroids are the mainstay of asthma therapy and many of their beneficial effects result from the modulation of Th2 cytokines and associated inflammation, but their activity is broad and nonspecific. Despite this lack of specificity, there is some evidence that corticosteroids are most effective in individuals in whom there is evidence of Th2 inflammation as manifested by high fractional exhaled nitric oxide (FeNO), sputum eosinophils (≥2 % all sputum

inflammatory cells), and increased airway periostin. All of these factors have been proposed as biomarkers for Th2 asthma [61].

The evolving data surrounding the heterogeneity of asthma and its associated phenotypes have made the development and use of biomarkers of utmost importance. Periostin (encoded by POSTN) is a secreted, 90-kDa, extracellular protein. Microarray studies of gene expression in the airway epithelium of asthmatic patients have shown a greater than four-fold increase in POSTN compared with healthy controls [62], making periostin among the most highly expressed genes in asthma.

The importance of periostin as a biomarker for Th2 inflammation was initially highlighted in a study by Woodruff et al. [62]. The authors used gene-expression microarrays to demonstrate that POSTN, along with SERPINB2 and CLCA1, was upregulated in the airway epithelial cells of asthmatic patients. Baseline expression of POSTN, SERPINB2, and CLCA1 was associated with good clinical response to corticosteroids, and treatment with corticosteroids led to the down-regulation of these three genes [62]. The same group of investigators subsequently used this three-gene signature to identify Th2-high and Th2-low phenotypes in asthmatic patients and validated their findings with bronchial biopsy specimens [63]. The three-gene mean obtained from the airway epithelial brushings of asthmatic patients identified Th2-high and Th2-low populations, correlated with other Th2 biomarkers [FENO, blood eosinophils, and provocative concentration of methacholine causing a 20 % drop in FEV₁ (PC20)], and predicted FEV₁ improvement with inhaled corticosteroids [64]. Other convincing data have contributed to the interest in using periostin as a biomarker in asthma. A study by Jia et al. [65] identified serum periostin as a systemic biomarker of airway eosinophilia in severe, uncontrolled asthmatic patients. Peripheral blood and induced sputum were collected and bronchoscopy was performed on severe, uncontrolled asthmatic patients treated with high doses of inhaled corticosteroids. Serum periostin was the single best predictor of sputum and tissue eosinophilia, showing superiority to blood eosinophils, IgE, and FENO. Importantly, serum periostin did not correlate with sputum or tissue neutrophilia [65]. These findings further support the role of periostin as a biomarker in Th2 or eosinophilic inflammation. Supporting the previous work by Jia et al. [65], Kanemitsu et al. [66] observed that serum periostin levels were significantly higher in patients taking high-dose inhaled corticosteroids, suggesting that serum periostin may be a biomarker of eosinophilic airway inflammation that is at least partly refractory to inhaled corticosteroids.

The ability of periostin to predict treatment response in Th2-driven asthma has mainly been considered but not limited to inhaled corticosteroids and lebrikizumab. In a

post hoc analysis of patients enrolled in the EXTRA study, Hanania et al. [67] explored the potential of Th2 inflammatory biomarkers (FeNO, blood eosinophils, and serum periostin) to serve as baseline predictors of the therapeutic benefit of omalizumab treatment in patients with inadequately controlled, severe, allergic asthma. In this study of uncontrolled, severe, persistent, allergic asthmatic patients, exacerbation rate decreased by 30 % in the high serum periostin group (50 ng/mL) compared with 3 % in the low serum periostin group (<50 ng/mL) following treatment with omalizumab. In any case the investigators were very cautious, and concluded that their observations provided preliminary information suggesting the presence of biomarkers able to identify patients most likely to benefit from omalizumab in relation to preventing exacerbations. Finally, the role of free IgE levels as a possible biomarker still needs to be established.

4 Omalizumab in Non-atopic Patients: Implications for Current Clinical Practice

4.1 Gray Areas between Allergic and Non-allergic Asthma: Atopy vs. Entopy

Atopic patients show a predisposition for allergic disease. By definition, patients with an allergy have an IgE-mediated allergic response involving a Th2 inflammatory pathway. Allergic patients characteristically show affirmative responses to clinical tests for atopy, including allergen skin prick tests and serum allergen-specific and increased total IgE levels. Allergen-specific IgE was detected many years ago in nasal secretions of nonatopic patients with rhinitis [68]. Thus, the concept of localized mucosal allergic disease in the absence of systemic atopy is not new. Furthermore, when subjected to allergen nasal provocation, a sub-group of non-allergic idiopathic patients show nasal airway responses similar to those seen in allergic rhinitis [69].

Powe et al. [70] reported for the first time mucosal allergen capture in non-atopic rhinitis patients. They proposed the term “entopy” (Greek ‘entopos’ meaning local resident) to describe the phenomenon of a localized mucosal response independent of systemic atopic responses. We believe that this concept has a wider implication and may occur in allergic diseases of the skin, gastrointestinal tract, eye, and upper respiratory airways [70–73]. Interestingly, the study of Powe et al. [70] also suggests that differential IgE longevity may occur, depending on the nature of the allergen causing the immune response; thus atopic status may change over time.

The distinction between atopic and non-atopic asthma has also come under scrutiny and may not be as clear cut as

originally thought. Recent publications show that IgE may be produced by T lymphocytes in non-allergic subjects owing to the presentation of the allergen through the mucosa. The observation of local IgE production (entropy) not detectable by skin-prick testing) also suggests a possible role for IgE in non-atopic asthma. This IgE may bind to the high-affinity receptors on the mast cells or basophils and produce the same type of inflammation as in patients considered allergic [74, 75]. As in atopic asthma, bronchial biopsies from non-atopic asthmatic patients showed enhanced expression of Th2-type cytokines (IL-4, IL-5, and IL-13) and FcεRI compared with controls [76]. The finding that the immunopathology of atopic and non-atopic asthma shares more similarities than differences [77] somewhat blurs the distinction between the two forms.

4.2 Experience in Nasal Polyposis

Nasal polyps (NP) are benign edematous masses in the nasal cavities, paranasal cavities, or both, with a probable overall prevalence of approximately 2–4 %. The pathophysiology of NP is characterized by a prominent, local eosinophilic inflammation with high production of eosinophil cationic protein, IL-5, and tissue IgE; mediators also observed in asthma inflammation. Thus, in addition to classic treatment options (local or systemic corticosteroids and/or endoscopic sinus surgery), strategies to antagonize IgE antibodies have been considered as possible alternatives. Some reports have suggested the beneficial effect of omalizumab in patients with NP and allergic asthma [78]. It has also been shown that the level of tissue inflammation and local IgE formation in patients with NP is independent of the presence of allergy. The next challenge was to test whether omalizumab might be effective in allergic and non-allergic patients with NP and asthma. Gevaert et al. [79] conducted a randomized, double-blind, placebo-controlled study of 24 allergic and non-allergic patients with NP and co-morbid asthma. Omalizumab demonstrated clinical efficacy in the treatment of NP with co-morbid asthma, supporting the importance and functionality of local IgE formation in the airways. The omalizumab group comprised seven allergic and eight non-allergic patients; both groups experienced similar benefits.

4.3 Hypothetical Mechanisms of Action

To date, many similarities have been found between allergic and non-allergic asthma, including eosinophilic inflammation and increased levels of IL-5, IL-4, and IL-13 [80, 81]. As stated previously [74–76] the presence of asthma associated with increased local IgE levels is called intrinsic asthma. Some publications have shown that IgE may be produced by T lymphocytes in non-allergic patients

because of the presentation of the allergen through the mucosa. This IgE may bind to the high-affinity receptors on the mast cells or basophils and produce the same type of inflammation as in the patients considered allergic [74, 75]. Recent evidence suggests that *Staphylococcus aureus* enterotoxins act as superantigens and induce local polyclonal IgE formation combined with severe eosinophilic inflammation [82, 83]. The marked local production of IgE antibodies appears to be functional and involved in the regulation of chronic inflammation [84].

The rationale for the use of omalizumab in non-allergic patients is based on the relatively recent finding that IgE can be produced locally in mucosal tissue, without any increase in IgE levels in the blood. In allergic patients, a significant decrease in surface FcεRI expression caused by omalizumab is also seen in dendritic cells, which are potent antigen-presenting cells. In both basophils and dendritic cells, the decrease in FcεRI expression is proportional to the reduction in serum free IgE [30]. In a very recent randomized study, García et al. [76] evaluated the changes in the expression of the FcεRI in non-atopic patients. The results clearly showed that, compared with placebo, omalizumab decreased the level of FcεRI on basophils and plasmacytoid dendritic cells as much as it does in severe atopic asthma.

At the present moment, three hypotheses have been proposed to explain the possible mechanisms of anti-IgE treatment in intrinsic asthma [85–87]. The first one assumes that patients with intrinsic asthma have a localized allergy with high levels of allergen-specific IgE antibodies in the airways. In this scenario, anti-IgE treatment would reduce local allergic inflammation in the airways, a mechanism similar to that found in allergic patients, with the difference that the phenomenon occurs locally rather than generally. Interestingly, an alternative or additional explanation may be provided by Kalesnikoff et al. [87] who observed that by binding to its high-affinity receptor (FcεRI) IgE was able to induce intracellular signaling pathways, resulting in the production of cytokines (e.g., IL-4, IL-6, IL-13, tumor necrosis factor-α) and the enhancement of mast cell survival without cross linking by allergens. In addition, IgE can directly bind and activate receptors present on eosinophils, neutrophils, and monocytes [85]. The third hypothesis deals with the possibility that omalizumab modulates innate immunity. It is known that plasmacytoid dendritic cells (pDCs), involved in the allergic immune response, play a crucial role in innate immune defenses against (predominantly viral) infections. Dendritic cells of patients with asthma display increased expression of the high-affinity IgE receptor. Thus, pDCs play a role in both innate and adaptive immunity; both pathways seem to influence each other. By reducing the FcεRI, omalizumab seems to favor the anti-viral immune responses of the

pDCs, and thus helps to prevent exacerbations of airway diseases triggered by viral infections [86].

4.4 Clinical Evidence

The clinical evidence is still scarce. Some case reports [88, 89] were followed by real-life observations suggesting that omalizumab could be clinically effective in patients with intrinsic asthma [85, 90]. In a 2-year study, Pérez de Llano et al. [90] analyzed 29 patients with intrinsic asthma treated with omalizumab, finding that omalizumab helped to increase asthma control, was associated with a trend towards reduced exacerbation rates, and improved lung function. As the authors noted, the study had several limitations; the results were obtained from a registry of patients with severe asthma in whom participation was optional (and were therefore unlikely to be representative of the country's severe asthma population), and the diagnosis of asthma was based solely on the judgment of the chest physician caring for the patient. In a study by our group, six non-atopic, oral corticosteroid-dependent asthma patients were followed for 1 year. We did not observe changes in eosinophil count, spirometry, or FeNO values, but oral corticosteroid requirement decreased: three patients considered responders did not need prednisolone during the follow-up, and the mean daily dose of prednisolone and the mean monthly accumulated dose fell notably but did not reach statistical significance probably because of the small number of patients. We concluded that in some non-allergic asthma patients, omalizumab might have a certain oral corticosteroid-sparing effect [85]. More recently, García et al. [76] performed the first randomized study designed to show immunobiologic changes in non-allergic patients randomly treated with omalizumab and placebo but the study lacked power to detect differences in secondary endpoints. In addition to the well-documented, primary outcome benefits already outlined above, the authors observed a statistically significant overall increase in FEV₁ compared with baseline of 250 mL (9.9 %), as well as a trend toward improvement in the global evaluation of treatment effectiveness in the omalizumab group. A meticulous analysis of the manuscript shows that the group of patients receiving omalizumab had an FEV₁ lower than the placebo group (400 mL, 10 %) and therefore may have presented greater room for improvement. To summarize, it seems that at least some non-allergic patients can benefit from omalizumab, although to date there is no clinically irrefutable evidence (as there is in the case of allergic patients) to systematically recommend the use of omalizumab in this population. The preliminary findings highlight the need for further investigation to better assess the drug's clinical efficacy.

5 Anti-IgE: A Disease-Modifying Therapy?

Initially presented as an IgE-blocking drug, omalizumab seems to offer many more benefits to patients. Two types of receptor mediate the biologic activities of IgE: a high-affinity receptor (FcεRI) and a low-affinity receptor (FcεRII or CD23). After blocking free IgE, omalizumab causes a down-regulation of FcεRI on basophils owing to the fact that the very low level of free IgE molecules becomes too sparse to bind the receptors, and unoccupied receptors on basophils are endocytosed and not replenished (Fig. 2). Basophils have a life span of about 2 weeks; thus, in longer periods, the old pool of basophils in the blood will be replaced by a new pool which, because of the low free IgE levels, has not undergone up-regulation of FcεRI [27].

Acting mostly through FcεRII, IgE appears to play a role in the induction of a Th2-type response and forms part of a positive feedback loop leading to further increases in IgE in the airway. By down-regulating FcεRII expression, anti-IgE may inhibit allergen presentation to T cells, possibly resulting in decreased allergen-specific T-cell activation and thus being able to block both the sensitization and effector phases of allergen-specific immune responses (Fig. 2).

The observation that omalizumab also downregulates FcεRII expression and the relationship established between FcεRII and IgE production suggests one possible way in which treatment with omalizumab might reduce IgE production (Fig. 2). Moreover, the binding of anti-IgE antibodies to cell surface membrane IgE on B cells can alter B-cell function, leading to changes in IgE production in vitro [91]. In vivo, down-regulation was demonstrated using the chimeric monoclonal anti-IgE CGP 51901, which reduced both circulating IgE and IgE-expressing cells in a mouse model system [92]. In turn, IgE acts as a trigger factor in the releasing process of ILs. Anti-IgE has shown to selectively decrease IL-5 production from mononuclear cells in response to both mite allergen and ionomycin/PMA (interferon-γ production was unchanged) [93]. Finally, the concentration of eosinophils, proinflammatory cells that make a major contribution to the inflammation seen in allergic diseases such as asthma, is also modulated by omalizumab [94, 95].

6 Perspectives for Anti-IgE Blockers

Future research on omalizumab should focus on several different levels. The drug's effect on the down-regulation of low-affinity receptors (FcεRII or CD23) and the role of free IgE and periostin [96] levels in patients treated with the drug will have to be determined. A retrospective

analysis of the omalizumab database corroborates the observation that deeper IgE suppression may be linked to better outcomes in asthma [97]. Several markers have been documented in addition to the absolute level of IgE, such as a threefold variation in receptor expression for the same level of IgE [98] and significant changes in cellular sensitivity because of differences in receptor occupancy by allergen-specific IgE, antigen valency, and IgE affinity for allergen [99]. Taken together, the above data provide additional justification for the development of a more potent (i.e., higher affinity) anti-IgE monoclonal antibody for the treatment of a variety of IgE-mediated allergic diseases, including asthma [100]. Clinical studies will have to investigate the criteria for starting a step-down process in omalizumab dose in stabilized patients. The company marketing the drug will be particularly interested in showing that many patients eligible for omalizumab treatment are still to be identified [101] and will try to establish the association between regular omalizumab treatment and asthma control. They will need to demonstrate the reductions in severe exacerbations in oral corticosteroid-dependent patients and in emergency department visits and hospitalizations [102] to persuade health insurance companies and National Health Services to cover the costs.

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