

### The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation

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Anti-IgE therapy with omalizumab reduces serum levels of free IgE and downregulates expression of IgE receptors (FcεRI) on mast cells and basophils. In the airways of patients with mild allergic asthma, omalizumab reduces FcεRI<sup>+</sup> and IgE<sup>+</sup> cells and causes a profound reduction in tissue eosinophilia, together with reductions in submucosal T-cell and B-cell numbers. In patients with seasonal allergic rhinitis, omalizumab inhibits the allergen-induced seasonal increases in circulating and tissue eosinophils. Omalizumab decreases FcεRI expression on circulating dendritic cells, which might lead to a reduction in allergen presentation, T<sub>H</sub>2 cell activation, and proliferation. As a systemic anti-IgE agent, omalizumab has demonstrated clinical efficacy in patients with moderate and severe allergic asthma and in those with seasonal and perennial allergic rhinitis, as well as in patients with concomitant allergic asthma and allergic rhinitis. The anti-inflammatory effects of omalizumab at different sites of allergic inflammation and the clinical benefits of anti-IgE therapy in patients with allergic asthma and allergic rhinitis emphasize the fundamental importance of IgE in allergic inflammation. (*J Allergy Clin Immunol* 2005;115:459-65.)

**Key words:** IgE, omalizumab, anti-inflammatory, FcεRI, FcεRII, T cell, B cell, allergic inflammation

#### IgE AND ASTHMA

The airflow limitation and episodic worsening that typify asthma are the clinical manifestations of a complex pattern of chronic and continuing inflammation in the airways tissue in which IgE plays a key role. The concept that IgE was only central in allergic asthma was first challenged by data from a population-based study, which showed a close and highly significant relationship between serum IgE levels and the prevalence of all asthma.<sup>1</sup> Since then, others have confirmed the view that most asthma is in some way allergic in nature.<sup>2,3</sup>

The dominant clinical phenotype in severe asthma tends to be nonallergic asthma, with IgE levels lower than those seen in subjects with mild-to-moderate asthma. However, more than half of patients with severe asthma in a recent study still demonstrated skin prick test positivity to common aeroallergens.<sup>4</sup> In patients with severe asthma, local IgE production might be more relevant than circulating IgE levels. A recent study of postmortem human lung tissue showed that cases of fatal asthma were associated with higher levels of FcεRI<sup>+</sup> cells within the lamina propria compared with levels seen in subjects who died of other causes or with biopsy tissue from patients with mild asthma.<sup>5</sup> More than 60% of FcεRI<sup>+</sup> cells were mast cells, and none were eosinophils.

#### IgE RECEPTORS

The interaction between IgE and mast cells and basophils is the best characterized, although it is not fully elucidated. Mature mast cells resident in airway tissue are primed with IgE molecules bound to FcεRI receptors. Mast cells activated by antigen complexed with IgE through the FcεRI release an array of products that can have effector, immunoregulatory, or autocrine effects.

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*Abbreviations used*

BHR: Bronchial hyperresponsiveness  
 EAR: Early asthmatic response  
 ICS: Inhaled corticosteroid  
 LAR: Late asthmatic response  
 pDC: Precursor dendritic cell  
 SAR: Seasonal allergic rhinitis

These products have not yet been fully identified. By using complementary DNA microarrays, stimulation of FcεRI in human umbilical cord mast cells resulted in substantial change in expression of more than 2400 genes, including 18 cytokines, 13 chemokines, several adhesion molecules, and several genes involved in potential interactions with T cells, B cells, or dendritic cells.<sup>6</sup> On activation, basophils produce a similar but not identical range of proinflammatory mediators to mast cells. For example, lipid mediators produced by mast cells include prostaglandin D<sub>2</sub>, leukotriene C<sub>4</sub>, and platelet-activating factor, whereas basophils only produce leukotriene C<sub>4</sub>. Similarly, mast cells produce a larger number of cytokines than basophils.<sup>7</sup>

A second important feature of the interaction between IgE and mast cells—basophils is that IgE itself regulates the expression of FcεRI receptors on these cells.<sup>8,9</sup> The upregulation of FcεRI expression in the presence of higher concentrations of serum IgE results in mast cell stimulation and mediator release at lower concentrations of allergen, in the release of increased amounts of mediators and cytokines for a given level of stimulus, or both.<sup>10</sup>

Recent *in vitro* data have also suggested that IgE can enhance mast cell survival; monomeric IgE (in the absence of cross-linking) appears to make mouse mast cells resistant to apoptosis.<sup>11</sup>

A close correlation has also been observed between serum IgE levels and FcεRI expression on precursor dendritic cells (pDC1 and pDC2) from subjects with allergic asthma.<sup>12</sup> FcεRI expression on pDC1 cells was approximately 50% the level of basophil expression and higher than pDC2 expression.

FcεRI expression has been observed on other cells, including eosinophils, neutrophils, platelets, and epithelial cells, but there is little or no clarification of their functional role in allergic asthma.

## EFFECT OF OMALIZUMAB ON IgE RECEPTORS

The recently developed humanized monoclonal anti-IgE antibody omalizumab decreases levels of circulating IgE by binding to the constant region (Cε3) of the IgE molecule, which prevents free IgE from interacting with IgE receptors (FcεRI and FcεRII). Because omalizumab does not bind to the variable allergen-specific region of the IgE molecule, it will inhibit allergen-induced responses

regardless of allergen specificity. Omalizumab does not bind to cell-bound IgE, thus avoiding the FcεRI cross-linking that could potentially lead to anaphylaxis.

An early study in a group of 15 subjects who were allergic to dust mite showed that administration of omalizumab produced a rapid 99% reduction in serum levels of free IgE.<sup>13</sup> FcεRI density on circulating basophils decreased by 97% during treatment, and *ex vivo* responsiveness of these cells to challenge with dust mite allergen reduced by 90% (both  $P = .0022$ ). In the same subjects a 100-fold increase in antigen dose was required to produce a skin prick test response equal to pretreatment levels ( $P = .0007$ ), indicating an effect on tissue mast cell function. The dual effects on IgE levels and receptor expression are important because without the FcεRI downregulation, near-total removal of free IgE would be necessary to elicit these functional consequences on mast cells and basophils.<sup>13</sup>

In a recent study in 24 subjects with ragweed allergy-induced rhinitis, mean IgE levels decreased by 96% from baseline within 3 days, and basophil FcεRI expression decreased by 73% within 7 days (the earliest time of measurement).<sup>14</sup> These 2 effects were highly correlated. The nasal response (nasal volume) to ragweed allergen was significantly blunted during treatment ( $P < .001$ ). Two large studies in subjects with seasonal allergic rhinitis (SAR) showed that clinical outcomes (nasal symptom severity and rescue antihistamine use) correlated with the reduction in serum levels of free IgE.<sup>15,16</sup>

These results show that omalizumab reduces serum levels of free IgE and downregulates FcεRI expression on basophils—and probably on mast cells too—because basophil expression might be regarded as a surrogate marker of similar changes in mast cells.<sup>14</sup> The downregulation of FcεRI expression is associated with a loss of sensitivity of basophils to allergen challenge and a reduction in mediator release.<sup>14</sup>

Omalizumab therapy also resulted in downregulation of FcεRI expression on dendritic cells (pDC1 and pDC2) taken from 24 subjects with ragweed-sensitive SAR (out of season).<sup>17</sup> In contrast to placebo, omalizumab downregulated FcεRI expression on both subsets, with a significant effect ( $P \leq .002$ ) from day 7 onward. Maximal downregulation of FcεRI expression was 52% and 83% on pDC1 and pDC2 cells, respectively. The change in FcεRI expression was highly correlated ( $P < .0001$ ) with the change in free IgE levels (and with basophil FcεRI downregulation). The similarity in the time frame for the effects on basophils and dendritic cells suggests that omalizumab might decrease FcεRI expression on all FcεRI<sup>+</sup> cells at the same rate. By downregulating FcεRI expression on dendritic cells, omalizumab might be inhibiting antigen processing and presentation to T cells. Consequently, this could lead to a reduction in T<sub>H</sub>2 cell differentiation, inhibition of T<sub>H</sub>2 cell activation and reduction in the generation of T<sub>H</sub>2 cytokines. Thus omalizumab therapy could potentially block both the sensitization and effector phases of the allergen-specific immune response.

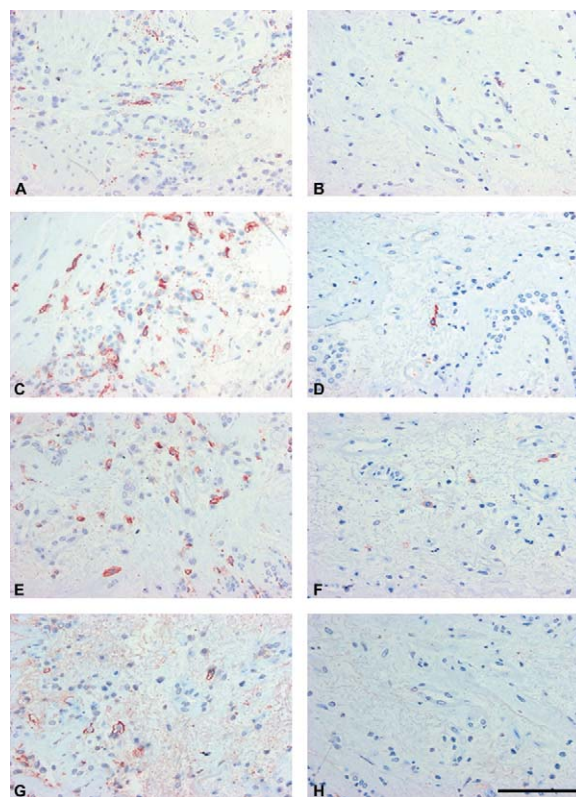
In a placebo-controlled study evaluating the effects of omalizumab in 20 patients with atopic dermatitis, Hayek et al<sup>18</sup> reported a reduction in FcεRI expression, receptor saturation, and IgE-binding capacity on basophils and circulating dendritic cells, together with a decrease in circulating and cell-bound IgE levels.

## ANTI-INFLAMMATORY ACTIVITY OF OMALIZUMAB IN CLINICAL STUDIES

### Inflammation in asthma

Early proof-of-concept studies showed that omalizumab inhibited both early asthmatic responses (EARs) and late asthmatic responses (LARs) to inhaled allergen in patients with asthma. Assessed as the mean maximal decrease in FEV<sub>1</sub>, the EAR was reduced by 85% ( $P = .01$ ) and the LAR by more than 65% ( $P = .047$ ) compared with results with placebo in a study of 19 subjects with mild allergic asthma.<sup>19</sup> Sputum eosinophilia was reduced 11-fold from baseline ( $P = .02$  vs baseline; not significant vs placebo). These findings demonstrate that IgE contributes to both the EAR and LAR and suggest a role for IgE in orchestrating the airway narrowing and tissue eosinophilia of the LAR.

Definitive evidence of the anti-inflammatory activity of omalizumab was provided in a recent placebo-controlled study in 45 patients with corticosteroid-naïve, mild persistent asthma by using bronchial biopsy and induced sputum sampling.<sup>20</sup> Subjects were treated with omalizumab or placebo for 16 weeks. Treatment with omalizumab led to a major depletion in eosinophils in both sputum and biopsy specimens. Sputum eosinophilia decreased from a mean of 4.8% to 0.6% ( $P = .05$  vs placebo), which was mirrored by significant reductions in tissue eosinophils (8.0 to 1.5 cells/mm<sup>2</sup>,  $P = .03$  vs placebo; Fig 1, A and B). Significant changes in IgE<sup>+</sup> and FcεRI<sup>+</sup> cells in the bronchial mucosa ( $P \leq .001$  vs placebo) provided reassuring evidence that omalizumab demonstrated the effects at a cellular level in the bronchial mucosa (Fig 1, C-F). The FcεRI<sup>+</sup> cells would be expected to comprise a majority of tissue-resident mast cells, but an effect on other FcεRI<sup>+</sup> cells, such as antigen-presenting cells, cannot be excluded. The number of mast cells was reduced, but the change was not significantly different versus that brought about by placebo. However, further investigation to explore the effect of omalizumab on survival of different mast cell subtypes is warranted. There was no decrease in FcεRII<sup>+</sup> cells. A decrease in cells staining for IL-4, a central T<sub>H</sub>2-type cytokine, was observed ( $P \leq .001$  vs placebo; Fig 1, G and H). This is of interest because increased IL-4 expression has been shown to be associated with steroid-resistant asthma and is not decreased with corticosteroid treatment.<sup>21</sup> Numbers of T cells (CD4<sup>+</sup> and CD8<sup>+</sup>) and B cells in the submucosa were all significantly reduced with treatment ( $P \leq .05$  vs placebo), although to a more modest extent (Table I). In the epithelium omalizumab significantly reduced numbers of IgE<sup>+</sup> cells ( $P \leq .001$  vs placebo), FcεRI<sup>+</sup> cells ( $P \leq .01$ ), IL-4<sup>+</sup> cells, and CD3<sup>+</sup> (total) T cells (both  $P \leq .05$  vs placebo).



**FIG 1.** Immunohistochemical staining of bronchial biopsy specimens before (left) and after (right) 16 weeks of omalizumab treatment. Representative sections from one subject show eosinophils staining with antibody against eosinophil cationic protein (ECP; A and B), cell-surface IgE (C and D), high-affinity IgE receptor (E and F), and IL-4 (G and H). The scale bar is 100  $\mu$ m. Reprinted with permission from Djukanović et al.<sup>20</sup>

This study confirms the central role of IgE in the inflammatory response in asthma and confirms that suppression of IgE results in extensive downregulation of multiple effector cells, both in the peripheral blood and at the cellular level, in target organs. It is noteworthy here that the large reductions in eosinophils achieved with omalizumab are similar to those observed with inhaled corticosteroid (ICS) treatment. Paradoxically, bronchial hyperresponsiveness (BHR; methacholine PC<sub>20</sub>) was not significantly changed during the 16 weeks of treatment in this study, yet early challenge studies have shown small but significant increases in methacholine PC<sub>20</sub> values in omalizumab-treated subjects,<sup>19,22</sup> and a later study in patients with more severe allergic asthma showed an improvement in BHR after 16 weeks of treatment.<sup>23</sup> A challenge model using a stimulus such as AMP that more closely and sensitively mimics the conditions of asthmatic allergic inflammation<sup>24</sup> might be useful in determining the effect of omalizumab therapy on BHR.

### Inflammation in allergic rhinitis

The effect of omalizumab on eosinophilic allergic inflammation was studied in a group of 30 adults with

**TABLE I.** Change from baseline in cell counts of the bronchial submucosa after 16 weeks of treatment with omalizumab or placebo

Cell	Omalizumab (n = 14)	Placebo (n = 14)
Basophils	-1.02 (-8.49 to 3.89)	1.07 (-9.86 to 6.83)
Mast cells	-8.77 (-20.94 to 29.42)	3.24 (-10.76 to 31.28)
Eosinophils	-3.95* (-20.95 to -0.10)	0.35 (-40.80 to 38.47)
T lymphocytes		
CD3 <sup>+</sup>	-36.96† (-258.00 to 79.54)	40.52 (-50.00 to 199.09)
CD4 <sup>+</sup>	-27.81† (-149.15 to 56.17)	40.90 (-28.02 to 138.89)
CD8 <sup>+</sup>	-8.95* (-78.31 to 32.22)	15.71 (-22.07 to 35.92)
B lymphocytes (CD20 <sup>+</sup> )	-0.83* (-20.02 to 6.53)	3.36 (-11.62 to 82.09)
FcεRI receptor	-21.26‡ (-48.00 to 3.13)	2.44 (-16.15 to 25.65)
FcεRII receptor	-0.76 (-5.98 to 0)	-0.73 (-5.02 to 1.55)
IL-4 <sup>+</sup> (cell surface)	-15.28‡ (-37.74 to 0.29)	0 (-20.21 to 14.67)
IL-4 <sup>+</sup> (cytoplasmic)	0.47 (-7.61 to 13.96)	0.72 (-8.69 to 15.26)
IL-5 <sup>+</sup> cells	-0.44 (-11.06 to 6.33)	1.41 (-12.22 to 18.69)
IgE <sup>+</sup> (cell surface) cells	-31.33‡ (-92.45 to -6.44)	6.16 (-89.39 to 35.24)

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\* $P \leq .05$ , † $P \leq .01$ , and ‡ $P \leq .001$  versus placebo (Wilcoxon test).

SAR.<sup>25</sup> Serum levels of free IgE decreased significantly with omalizumab but were stable in the placebo-treated patients ( $P = .0001$  between groups). Blood eosinophils increased significantly in the placebo group but remained unchanged with omalizumab treatment, with a significant difference ( $P = .04$ ) between the groups. This seasonal increase and inhibitory effect of treatment were mirrored in the changes in eosinophils (staining positively for eosinophil peroxidase) in nasal biopsy specimens. The number of nasal tissue eosinophils correlated significantly with serum IgE levels. It appears that patients with SAR experience inflammatory flares on allergen exposure and that such flares might be preventable with omalizumab therapy.

Another report<sup>26</sup> showed that omalizumab reduced the numbers of pDC1 cells relative to placebo ( $P = .0137$ ) in 49 children with SAR treated with omalizumab and concomitant specific immunotherapy. The reduction occurred in the grass pollen season and was not seen in the birch pollen season (children were sensitized to both allergens). These results are difficult to interpret but augment the theory that omalizumab therapy has immunomodulatory effects associated with changes in dendritic cells at a stage of development preceding their trafficking into tissues and maturation.

### Inflammatory responses in skin

Omalizumab treatment significantly reduced the magnitude of cutaneous responses to allergen at 15 minutes and 6 hours in a placebo-controlled study in 24 allergic volunteers.<sup>27</sup> The effect of omalizumab on the late skin response was more marked and more rapid than its effect on the early response, suggesting that IgE also has an important role in the late response. Skin biopsy specimens taken after repeat allergen challenge showed increases in CD3<sup>+</sup> (total) T cells and eosinophils with placebo compared with omalizumab ( $P = .046$  and  $P = .019$

between groups, respectively). Thus omalizumab appeared to prevent eosinophil influx and the T-cell priming response, suggesting that it might play an important role in reducing sensitization on initial exposure to allergen.

In a study involving 35 asthmatic patients,<sup>23</sup> a significant decrease in wheal diameter at 15 minutes after skin prick testing with relevant allergen was also observed ( $P < .01$  vs placebo). In another study in 20 patients with atopic dermatitis, omalizumab decreased levels of IgE in the skin and, as in previous studies, reduced sensitivity to allergen skin prick testing. However, there was no change in inflammatory skin infiltrate and no clinical improvements in these patients.<sup>18</sup> It appears that the effects of omalizumab in the skin are less pronounced than the effects on airway mucosal responses and cells. This might be related to differences in drug penetration, cellular environment, or mast cells. For example, the decrease in basophil FcεRI receptor expression was more rapid than the decrease in FcεRI expression on skin mast cells.<sup>28</sup> The effects of omalizumab in the skin provide clear evidence of a systemic effect in tissue sites of allergic inflammation, but its precise activity and potential clinical benefits in conditions such as atopic dermatitis require further investigation.

### CLINICAL EFFICACY OF OMALIZUMAB

The efficacy of omalizumab has been demonstrated in patients with moderate-to-severe and severe allergic asthma, in patients with SAR<sup>15,16</sup> and perennial allergic rhinitis,<sup>29</sup> and in subjects with concomitant allergic asthma and allergic rhinitis.<sup>30</sup> In large placebo-controlled studies in children and adults with moderate-to-severe allergic asthma,<sup>31-33</sup> omalizumab significantly reduced the level of asthma exacerbations, and patients significantly reduced their intake of ICSs, with median reductions in ICS dose of 100%,<sup>31</sup> 83%,<sup>32</sup> and 75%<sup>33</sup> with omalizumab compared



Omalizumab has profound and significant effects on airway and tissue eosinophilia in patients with mild allergic asthma<sup>20</sup> and on allergen-induced seasonal increases in circulating and tissue eosinophils in subjects with SAR.<sup>25</sup> The effect of omalizumab on eosinophils might be explained in part by inhibition of the allergen-IgE-mast cell response, preventing mast cell activation and cytokine release and subsequent eosinophil chemotaxis. Because mast cells release a repertoire of mediators, and cytokines undoubtedly contribute to both the acute and continuing aspects of allergic inflammation, omalizumab might not only be inhibiting acute allergic reactions but also preventing the development of long-term consequences of allergen exposure, such as inflammatory cell

recruitment, tissue remodeling, and functional changes in the airways. The anti-inflammatory activity of omalizumab and its efficacy in patients with moderate-to-severe and severe asthma, particularly in terms of ICS dose reduction and prevention of asthma exacerbations, help to confirm that the role of IgE extends beyond the acute allergic response.<sup>19,31-33,37,38</sup>

The inhibitory effects of omalizumab on dendritic cell FcεRI expression<sup>17,18,26</sup> and numbers<sup>26</sup> are of particular interest. This research suggests that omalizumab can alter allergen presentation, a fundamental event in allergic processes. This is likely to be a unique and important step forward in treating asthma and other allergic diseases.

## CONCLUSION

Omalizumab has a central role in inhibiting the allergic inflammatory cascade. Evidence to date supports a marked effect on underlying steady-state inflammation and a preventive effect on the worsening inflammation (on allergen exposure) that underlies disease flares or exacerbations. Taken together, the activity of omalizumab against IgE, eosinophils, basophils, mast cells, and dendritic cells suggests that the effects of omalizumab therapy encompass not only inhibition of IgE-mediated hypersensitivity but also might extend to immunomodulatory effects on allergen-specific T cells. This confers on omalizumab a unique capacity to block sensitization and both the acute and chronic effector phases of the allergic inflammatory process. Its activities at different sites of allergic inflammation combine to provide a systemic but nonsteroidal anti-inflammatory agent with clinical benefits in allergic diseases, notably in patients with moderate-to-severe allergic asthma. However, because of its multiplicity of effects on inflammation, it will likely play a role in the therapy of other IgE-mediated disorders.

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