Update review

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 $FcεRI^+$ and IgE^+ 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_H2 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.)

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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.[1] Since then, others have confirmed the view that most asthma is in some way allergic in nature.[2,3]

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.[4] 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 $FcεRI^+$ 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.[5] More than 60% of $FcεRI^+$ 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.

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.[6] 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_2, leukotriene C_4, and platelet-activating factor, whereas basophils only produce leukotriene C_4. Similarly, mast cells produce a larger number of cytokines than basophils.[7]

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.[8,9] 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.[10]

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.[11]

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.[12] 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.[13] 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.[13]

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).[14] 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.[15,16]

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.[14] The downregulation of FcεRI expression is associated with a loss of sensitivity of basophils to allergen challenge and a reduction in mediator release.[14]

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).[17] 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 $FcεRI^+$ 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_H2 cell differentiation, inhibition of T_H2 cell activation and reduction in the generation of T_H2 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[18] 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_1, 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.[19] 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-naive, mild persistent asthma by using bronchial biopsy and induced sputum sampling.[20] 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^2, $P = .03$ vs placebo; Fig 1, *A* and *B*). Significant changes in IgE^+ and $Fc\epsilon RI^+$ 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 $Fc\epsilon RI^+$ cells would be expected to comprise a majority of tissue-resident mast cells, but an effect on other $Fc\epsilon RI^+$ 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 $Fc\epsilon RII^+$ cells. A decrease in cells staining for IL-4, a central T_H2-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.[21] Numbers of T cells ($CD4^+$ and $CD8^+$) 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^+ cells ($P \leq .001$ vs placebo), $Fc\epsilon RI^+$ cells ($P \leq .01$), IL-4^+ cells, and $CD3^+$ (total) T cells (both $P \leq .05$ vs placebo).

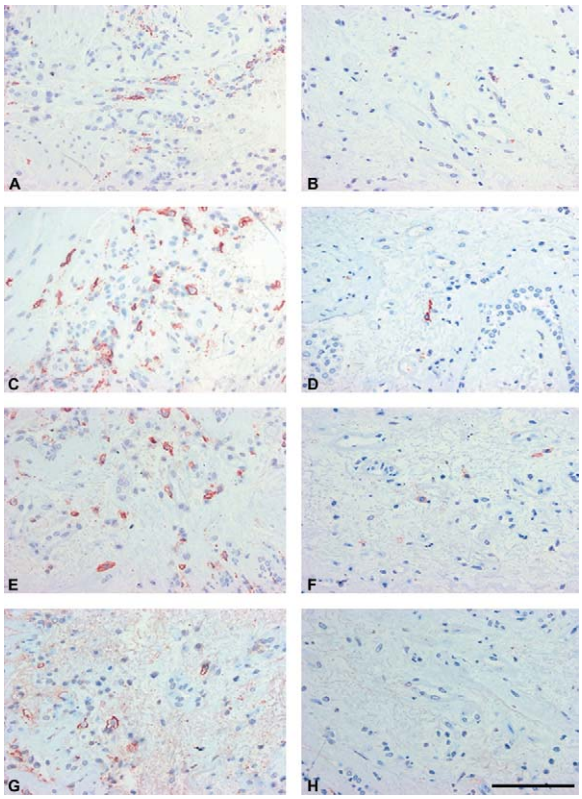

FIG 1. Immunohistochemical staining of bronchial biopsy specimens before *(left)* and after *(right)* 16 weeks of omalizumab treatment. Representative sections from one subject show eosinophils staining with antibody against eosinophil cationic protein (*ECP*; **A** and **B**), cell-surface IgE (**C**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

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_{20}) 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_{20} values in omalizumab-treated subjects,[19,22] and a later study in patients with more severe allergic asthma showed an improvement in BHR after 16 weeks of treatment.[23] A challenge model using a stimulus such as AMP that more closely and sensitively mimics the conditions of asthmatic allergic inflammation[24] 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		
$CD3^+$	−36.96† (−258.00 to 79.54)	40.52 (−50.00 to 199.09)
$CD4^+$	−27.81† (−149.15 to 56.17)	40.90 (−28.02 to 138.89)
$CD8^+$	−8.95* (−78.31 to 32.22)	15.71 (−22.07 to 35.92)
B lymphocytes ($CD20^+$)	−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)
$IL\text{-}4^+$ (cell surface)	−15.28‡ (−37.74 to 0.29)	0 (−20.21 to 14.67)
$IL\text{-}4^+$ (cytoplasmic)	0.47 (−7.61 to 13.96)	0.72 (−8.69 to 15.26)
$IL\text{-}5^+$ cells	−0.44 (−11.06 to 6.33)	1.41 (−12.22 to 18.69)
IgE^+ (cell surface) cells	−31.33‡ (−92.45 to −6.44)	6.16 (−89.39 to 35.24)

Reprinted with permission from Djukanović et al.[20] Units are presented as cells per square millimeter (median [range]).
*$P \leq .05$, †$P \leq .01$, and ‡$P \leq .001$ versus placebo (Wilcoxon test).

SAR.[25] 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[26] 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.[27] 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 $CD3^+$ (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,[23] 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.[18] 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.[28] 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[15,16] and perennial allergic rhinitis,[29] and in subjects with concomitant allergic asthma and allergic rhinitis.[30] In large placebo-controlled studies in children and adults with moderate-to-severe allergic asthma,[31-33] omalizumab significantly reduced the level of asthma exacerbations, and patients significantly reduced their intake of ICSs, with median reductions in ICS dose of 100%,[31] 83%,[32] and 75%[33] with omalizumab compared

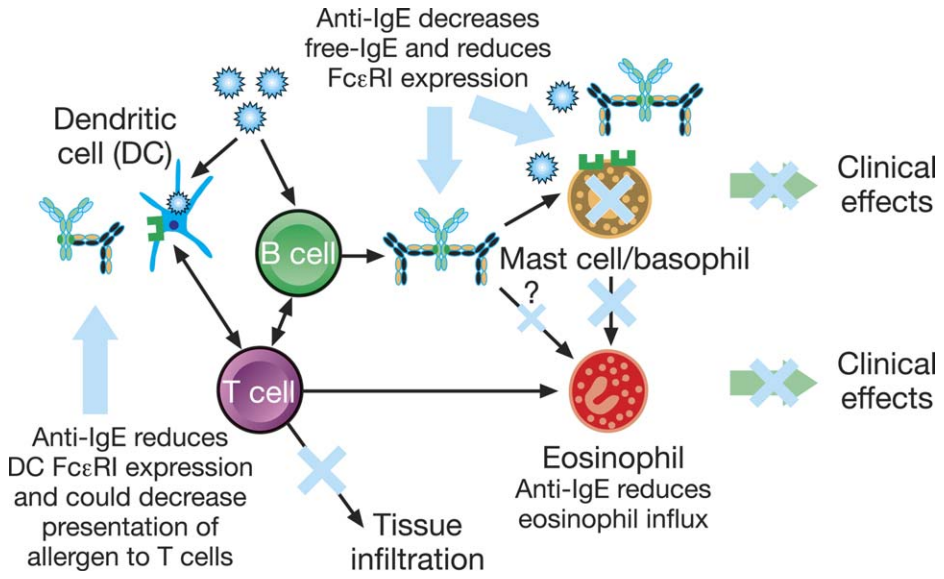

FIG 2. Proposed mechanisms of action of omalizumab. Omalizumab decreases free IgE levels and reduces FcεRI receptor expression on mast cells and basophils. This results in decreased mast cell activation and sensitivity, leading to a reduction in eosinophil influx and activation. Anti-IgE treatment with omalizumab might result in decreased mast cell survival. Omalizumab also reduces dendritic cell FcεRI receptor expression.

with 66.7%,[31] 43%,[32] and 50%[33] with placebo. More recent studies have demonstrated the efficacy of omalizumab in patients with severe asthma[34] and in those patients whose symptoms remain poorly controlled despite best standard therapy for asthma.[35]

Significant reductions of asthma exacerbations with omalizumab treatment were reported in an analysis of 254 patients (135 treated with omalizumab) who were at high risk of serious asthma-related morbidity and mortality on the basis of prior intubation or recent emergency or intensive care unit treatment or hospitalization for asthma.[36] When omalizumab was added to baseline ICS treatment, omalizumab halved the incidence and frequency of exacerbations in this high-risk population ($P = .007$ vs placebo). A further analysis of pooled data from adult and pediatric patients[37] showed that omalizumab significantly reduced the rate (per 100 patient-years) of serious asthma exacerbations requiring unscheduled outpatient visits (21.3 vs 35.5, $P < .001$), emergency department treatment (1.8 vs 3.8, $P = .05$), and hospitalizations (0.26 vs 3.42, $P < .01$).

Factors increasing the likelihood of responding to omalizumab compared with placebo are those that reflect more severe asthma.[38] Regression analysis of pooled data from the 2 studies in adults with moderate-to-severe asthma[32,33] showed that the most marked benefit of omalizumab therapy was observed in patients with a history of frequent emergency asthma treatment and in patients receiving high ICS doses (ie, those with more severe disease).[38] Both these factors were predictive ($P = .015$ and $P = .037$, respectively) of response to omalizumab therapy.

SUMMARY

IgE plays a central role in allergic asthma, and there is also growing evidence suggestive of a role in nonallergic (intrinsic) asthma. The central role of IgE in allergic inflammation and the proposed mechanisms of action of omalizumab in inhibiting IgE-mediated processes are depicted schematically in Fig 2. Omalizumab treatment results in a rapid reduction in free IgE levels and down-regulation of FcεRI on basophils, mast cells, and other inflammatory cells.[13,14,17,31-33] Recent research has shown that the effects of omalizumab on circulating IgE and cellular IgE receptor expression are accompanied by a reduction in $FcεRI^+$ cells and IgE^+ cells in the airways of patients with asthma,[20] and because Fregonese et al[5] have highlighted a possible relationship between FcεRI expression and fatal asthma, it is interesting to speculate whether omalizumab could have an effect on mortality.

Omalizumab has profound and significant effects on airway and tissue eosinophilia in patients with mild allergic asthma[20] and on allergen-induced seasonal increases in circulating and tissue eosinophils in subjects with SAR.[25] 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.[19,31-33,37,38]

The inhibitory effects of omalizumab on dendritic cell FcεRI expression[17,18,26] and numbers[26] 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.

REFERENCES

1. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. N Engl J Med 1989;320:271-7.
2. Kay AB. Allergy and allergic diseases. N Engl J Med 2001;344:109-13.
3. Holt PG, Macaubas C, Stumbles PA, Sly PD. The role of allergy in the development of asthma. Nature 1999;402(suppl):B12-7.
4. European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA). The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. Eur Respir J 2003;22:470-7.
5. Fregonese L, Patel A, van Schadewijk A, Santos MA, Dolhnikoff M, Sterk PJ, et al. Expression of the high-affinity IgE receptor (FcεRI) is increased in fatal asthma [abstract]. Am J Respir Crit Care Med 2004; 169:A297.
6. Sayama K, Diehn M, Matsuda K, Lunderius C, Tsai M, Tam SY, et al. Transcriptional response of human mast cells stimulated via the Fc(epsilon)RI and identification of mast cells as a source of IL-11. BMC Immunol 2002;3:5.
7. Kawakami T, Galli SJ. Regulation of mast-cell and basophil function and survival by IgE. Nat Rev Immunol 2002;2:773-86.
8. MacGlashan D Jr, Lichtenstein LM, McKenzie-White J, Chichester K, Henry AJ, Sutton BJ, et al. Upregulation of FcepsilonRI on human basophils by IgE antibody is mediated by interaction of IgE with FcepsilonRI. J Allergy Clin Immunol 1999;104:492-8.
9. MacGlashan DW Jr, Bochner BS, Adelman DC, Jardieu PM, Togias A, Lichtenstein LM. Serum IgE level drives basophil and mast cell IgE receptor display. Int Arch Allergy Immunol 1997;113:45-7.
10. Williams CM, Galli SJ. The diverse potential effector and immunoregulatory roles of mast cells in allergic disease. J Allergy Clin Immunol 2000;105:847-59.
11. Kitaura J, Song J, Tsai M, Asai K, Maeda-Yamamoto M, Mocsai A, et al. Evidence that IgE molecules mediate a spectrum of effects on mast cell survival and activation via aggregation of the FcepsilonRI. Proc Natl Acad Sci U S A 2003;100:12911-6.
12. Foster B, Metcalfe DD, Prussin C. Human dendritic cell 1 and dendritic cell 2 subsets express FcεRI: correlation with serum IgE and allergic asthma. J Allergy Clin Immunol 2003;112:1132-8.
13. MacGlashan DW Jr, Bochner BS, Adelman DC, Jardieu PM, Togias A, McKenzie-White J, et al. Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. J Immunol 1997;158:1438-45.
14. Lin H, Boesel KM, Griffith DT, Prussin C, Foster B, Romero FA, et al. Omalizumab rapidly decreases nasal allergic response and FcεRI on basophils. J Allergy Clin Immunol 2004;113:297-302.
15. Ädelroth E, Rak S, Haahtela T, Aasand G, Rosenhall L, Zetterstrom O, et al. Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. J Allergy Clin Immunol 2000; 106:253-9.
16. Casale TB, Condemi J, LaForce C, Nayak A, Rowe M, Watrous M, et al. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. JAMA 2001;286:2956-67.
17. Prussin C, Griffith DT, Boesel KM, Lin H, Foster B, Casale TB. Omalizumab treatment downregulates dendritic cell FcεRI expression. J Allergy Clin Immunol 2003;112:1147-54.
18. Hayek B, Heil PM, Laimer M, Maurer D, Hultsch T, Stingl G. Omalizumab-induced downregulation of IgE/FcεRI on dendritic cells in patients with atopic dermatitis. Abstract presented at: XXIII EAACI Congress; June 12-16, 2004; Amsterdam, The Netherlands. 2004;224: 744.
19. Fahy JV, Fleming HE, Wong HH, Liu JT, Su JQ, Reimann J, et al. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. Am J Respir Crit Care Med 1997;155:1828-34.
20. Djukanović R, Wilson SJ, Kraft M, Jarjour NN, Steel M, Chung KF, et al. The effects of anti-IgE (omalizumab) treatment on airways inflammation in allergic asthma. Am J Respir Crit Care Med 2004;170:583-93.
21. Leung DY, Martin RJ, Szefler SJ, Sher ER, Ying S, Kay AB, et al. Dysregulation of interleukin 4, interleukin 5, and interferon gamma gene expression in steroid-resistant asthma. J Exp Med 1995;181:33-40.
22. Boulet LP, Chapman KR, Côté J, Kalra S, Bhagat R, Swystun VA, et al. Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. Am J Respir Crit Care Med 1997;155:1835-40.
23. Noga O, Hanf G, Kunkel G. Immunological and clinical changes in allergic asthmatics following treatment with omalizumab. Int Arch Allergy Immunol 2003;131:46-52.
24. Currie GP, Jackson CM, Lee DK, Lipworth BJ. Allergen sensitization and bronchial hyper-responsiveness to adenosine monophosphate in asthmatic patients. Clin Exp Allergy 2003;33:1405-8.
25. Plewako H, Arvidsson M, Petruson K, Oancea I, Holmberg K, Adelroth E, et al. The effect of omalizumab on nasal allergic inflammation. J Allergy Clin Immunol 2002;110:68-71.
26. Feuchtinger T, Bartz H, von Berg A, Riedinger F, Brauburger J, Stenglein S, et al. Treatment with omalizumab normalizes the number of myeloid dendritic cells during the grass pollen season. J Allergy Clin Immunol 2003;111:428-30.
27. Ong Y, Menzies-Gow A, Matthews J, Kay AB. A randomised double-blind, placebo-controlled study to assess the effects of omalizumab (humanised monoclonal anti-IgE antibody) on the early- and late-phase skin reactions and cellular infiltrate after multiple intradermal allergen challenges. Abstract presented at: XXIII EAACI Congress; June 12-16, 2004; Amsterdam, The Netherlands. 2004;96:305.
28. Beck LA, Marcotte GV, MacGlashan D, Togias A, Saini S. Omalizumab-induced reductions in mast cell FcεRI expression and function. J Allergy Clin Immunol 2004;114:527-30.

29. Chervinsky P, Casale T, Townley R, Tripathy I, Hedgecock S, Fowler-Taylor A, et al. Omalizumab, an anti-IgE antibody, in the treatment of adults and adolescents with perennial allergic rhinitis. Ann Allergy Asthma Immunol 2003;91:160-7.
30. Vignola AM, Humbert M, Bousquet J, Boulet LP, Hedgecock S, Blogg M, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. Allergy 2004;59:709-17.
31. Milgrom H, Berger W, Nayak A, Gupta N, Pollard S, McAlary M, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). Pediatrics 2001;108:E36.
32. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Della-Cioppa G, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol 2001;108:184-90.
33. Solér M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics [published erratum appears in Eur Respir J 2001; 18:739-40]. Eur Respir J 2001;18:254-61.
34. Holgate ST, Chuchalin AG, Hebert J, Lotvall J, Persson GB, Chung KF, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. Clin Exp Allergy 2004;34: 632-8.
35. Ayres JG, Higgins B, Chilvers ER, Ayre G, Blogg M, Fox H. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. Allergy 2004;59:701-8.
36. Holgate S, Bousquet J, Wenzel S, Fox H, Liu J, Castellsague J. Efficacy of omalizumab, an anti-immunoglobulin E antibody, in patients with allergic asthma at high risk of serious asthma-related morbidity and mortality. Curr Med Res Opin 2001;17:233-40.
37. Corren J, Casale T, Deniz Y, Ashby M. Omalizumab, a recombinant humanized anti-IgE antibody, reduces asthma-related emergency room visits and hospitalizations in patients with allergic asthma. J Allergy Clin Immunol 2003;111:87-90.
38. Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. Chest 2004;125:1378-86.