

## Asthma diagnosis and treatment

### *Perspectives in asthma*

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## Anti-IgE: Lessons learned from effects on airway inflammation and asthma exacerbation

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Omalizumab is an mAb that binds free IgE and ultimately reduces the density of IgE-loaded receptors on IgE effector cells. Because IgE effector cells, such as mast cells and basophils, are a source of proinflammatory chemokines, cytokines, and proteases, it is not surprising that omalizumab has anti-inflammatory effects, most notably large effects in reducing airway eosinophilia. What has been surprising is the nature of the clinical effects of omalizumab. Rates of exacerbation in omalizumab-treated patients are approximately half those in placebo-treated patients. This important clinical effect has occurred despite the fact that omalizumab does not improve nonspecific bronchial hyperresponsiveness and does not have large effects on airflow. The unsuspected dissociations among asthma outcomes uncovered during clinical trials of omalizumab remind us that mysteries remain for how inflammation, remodeling, and airway function are linked in asthma. (*J Allergy Clin Immunol* 2006;117:1230-2.)

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IgE is an important mediator in the pathophysiology of asthma.<sup>1</sup> IgE binds to effector cells through its high-affinity (FcεR1) and low-affinity (FcεR2, CD23) receptors. The binding of IgE to its receptors on these cells primes them to respond to allergen. Mast cells and basophils are the best known of the IgE effector cells, but the number of cells expressing IgE receptors is large and includes structural cells in the airway, such as epithelial cells and smooth muscle cells. Allergen-induced activation of mast cells and basophils results in secretion of preformed mediators, such as chymase, tryptase, and histamine, and the generation of newly formed mediators, such as

arachidonic acid metabolites and cytokines. These secreted proteins mediate multiple inflammatory effects, including increases in vascular permeability and chemotaxis of inflammatory cells. Other IgE-mediated effects of relevance in asthma include IgE-dependent focusing of antigen to dendritic cells<sup>2</sup> and mobilization of calcium in airway smooth muscle cells.<sup>3</sup> Thus the biologic effects of IgE are diverse and far reaching, and inhibiting IgE can be expected to inhibit multiple allergic mechanisms and to have multiple anti-inflammatory effects. In this brief review I will focus on the clinical data that are available to support an anti-inflammatory effect for anti-IgE in asthmatic patients. In reviewing the data, I will point out unexpected and interesting dissociations in outcomes of treatment with omalizumab (Xolair; Novartis, Basel, Switzerland). These dissociations prompt some rethinking about conventional wisdom for relationships among inflammation, remodeling, and asthma control.

### ANTI-INFLAMMATORY EFFECTS OF OMALIZUMAB

Omalizumab is currently the only anti-IgE drug approved for use in human subjects. Omalizumab is an mAb that binds free IgE at the Cε3 domain of its Fc fragment, a site usually recognized by IgE's own high- and low-affinity receptors. Omalizumab cannot bind IgE already bound to its natural receptors and is therefore non-anaphylactogenic. Early clinical trials with omalizumab showed that pretreatment of allergic asthmatic subjects prevented both the early- and late-phase responses to inhaled allergen.<sup>4,5</sup> The inhibitory effect of omalizumab on the early phase was predictable because the early asthmatic response is a classic type 1 hypersensitivity reaction that is IgE mediated. The effect on the late phase was not as predictable, but it was surprisingly robust and unambiguously established IgE's role as a mediator of late asthmatic responses. Later clinical trials of omalizumab focused on documenting efficacy on asthma control. The phase 2 trial showed a modest effect in asthma symptoms but suggested a larger effect on asthma exacerbations.<sup>6</sup> Consequently, the phase 3 trials used asthma exacerbations as the primary outcome, and all showed large

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effects on this outcome.<sup>7-9</sup> A postapproval study similarly documented the efficacy of omalizumab as a treatment for reducing asthma exacerbations.<sup>10</sup>

Secondary outcomes in the early proof-of-concept studies of omalizumab hinted at an anti-inflammatory effect. Specifically, omalizumab was shown to inhibit allergen-induced increases in sputum eosinophils and to reduce peripheral blood eosinophilia.<sup>6</sup> More definitive data for anti-inflammatory effects came from later studies specifically designed to study airway inflammation. One clinical study focused on whether omalizumab reduces eosinophil numbers in the airway.<sup>11</sup> The primary outcome was sputum eosinophil percentage and included subjects needed to have at least 2% eosinophils in their induced sputum. All subjects also underwent bronchoscopy for collection of endobronchial biopsy specimens. The reduction in the mean percentage of sputum eosinophils in the omalizumab-treated subgroup (6.6% to 1.7%) was significantly greater than the reduction in the placebo-treated subgroup (8.5% to 7.0%). The omalizumab-induced reduction in eosinophil numbers in airway secretions was mirrored by significant reductions in eosinophil numbers in the epithelial and submucosal compartments of endobronchial biopsy specimens. T- and B- lymphocyte numbers also decreased in the biopsy tissue, as did the numbers of IL-4<sup>+</sup> cells. Surprisingly, despite this broad range of anti-inflammatory activity, there was no improvement in bronchial hyperreactivity to methacholine.<sup>11</sup>

The mechanism whereby anti-IgE reduces eosinophil numbers in blood and in the airway is not known, but there are several possibilities. First, it should be noted that the density of IgE receptors on cell surfaces is regulated by IgE, and reducing IgE levels with omalizumab causes marked downregulation of IgE receptor density on basophils, mast cells, and dendritic cells.<sup>12-14</sup> Interestingly, although binding of IgE to its receptor on mast cells is thought to activate signaling mechanisms that improve mast cell survival,<sup>15</sup> omalizumab treatment does not decrease mast cell numbers in the skin after prolonged treatment.<sup>13</sup> Nevertheless, treatment with anti-IgE will cause cells normally coated with IgE-loaded IgE receptors to become disarmed, not only because the receptor is empty of IgE but because the receptors themselves are greatly reduced in number. Disarming dendritic cells might result in decreased IgE-facilitated antigen presentation to T cells and could ultimately lead to an antieosinophil effect. Disarming IgE effector cells will prevent IgE-dependent secretion of eosinophil-active inflammatory mediators by these cells, especially cells bearing high-affinity receptors, such as mast cells and basophils. These cells secrete eosinophil-active cytokines, such as IL-5, which can cause airway eosinophilia. Disarming cells bearing the low-affinity IgE receptor (CD23) might also account for some of the anti-inflammatory efficacy of omalizumab. The cellular distribution of CD23-bearing cells is broad and includes epithelial cells and smooth muscle cells. These cells secrete eosinophil-active chemokines, such as eotaxin, and inhibiting their activation by IgE could contribute to the antieosinophil effects of omalizumab.

The antieosinophil effects of omalizumab in the airway also occur in the upper airway and in the skin.<sup>13,16,17</sup> Interestingly, in the skin omalizumab more effectively prevents late-phase responses than early-phase responses, and its onset of action is faster for late-phase responses.<sup>17</sup> This might be because late-phase responses use IgE-CD23 complexes. Disarming cells of IgE bound to the low-affinity CD23 receptor will occur faster than disarming cells bearing IgE bound to the high-affinity FcεR1 receptor. Support for a primary role for CD23 in late asthmatic responses comes from a mouse model of allergic airway inflammation. Pretreatment of allergen-sensitized mice with anti-IgE just 6 hours before antigen challenge inhibits the production of T<sub>H</sub>2 cytokines and the recruitment of eosinophils to the lung.<sup>18</sup> Notably, studies with anti-CD23 and in CD23-deficient mice had the same effect, suggesting that the antieosinophil effect of anti-IgE might result from inhibition of IgE-CD23.<sup>18</sup> The clinical importance of this observation is that although some effects of omalizumab might take several weeks to manifest because they depend on disrupting strong IgE-FcεR1 interactions, others might only take days because they depend on disrupting weaker IgE-CD23 interactions.

## RELATIONSHIP BETWEEN THE EFFECTS OF OMALIZUMAB ON AIRWAY INFLAMMATION AND ASTHMA CONTROL

As documented above, omalizumab treatment is associated with large reductions in airway eosinophilia in asthma. The size of the reductions in airway eosinophils is similar to that reported after treatment with corticosteroids. Despite similarity in the effect of corticosteroids and anti-IgE on airway eosinophilia, the asthma control profiles of these 2 drug classes are different. For example, whereas omalizumab treatment is not consistently associated with improvements in airway hyperresponsiveness, corticosteroid treatment consistently improves methacholine or histamine hyperresponsiveness by 1 or 2 doubling doses. In addition, whereas omalizumab's effects on measures of airflow obstruction in asthma are modest and of questionable clinical significance (2% to 5% improvements), the effects of corticosteroids are larger and more clinically significant (5% to 15% improvements). In contrast, omalizumab decreases asthma exacerbation rates by 50% and achieves this effect in populations already treated with significant doses of corticosteroids. Thus omalizumab has a large effect on asthma exacerbations, even though its effects on other outcomes of asthma control are modest. This clinical effect profile of omalizumab has implications for the design of clinical trials to test novel or existing treatments for asthma. Clearly, neither FEV<sub>1</sub> nor PC<sub>20</sub> can be used as surrogate outcomes of asthma exacerbations.

Concepts about relationships among inflammation, remodeling, hyperresponsiveness, airflow limitation, and clinical exacerbations in asthma have been informed by the clinical trial experience with corticosteroids. Although data for remodeling are not robust, corticosteroids clearly

improve most other asthma outcomes, and the treatment effects of steroids suggested that improvements in clinical outcomes, such as hyperresponsiveness and airflow, are linked to improvements in airway eosinophilic inflammation. Furthermore, the data implied that reductions in asthma exacerbation rates are linked to improvements in hyperresponsiveness. The experience with omalizumab teaches us that airflow and hyperresponsiveness might not change much despite large improvements in eosinophilia and that large improvements in exacerbation frequency can occur without large improvements in hyperresponsiveness. Thus we need to rethink pathophysiologic relationships between IgE and hyperresponsiveness and eosinophilic inflammation and hyperresponsiveness. We also need to reconsider how hyperresponsiveness is linked to the risk of exacerbation in asthma. The effectiveness of omalizumab in preventing exacerbations demonstrates that IgE-related mechanisms are important in the pathophysiology of exacerbations. But these IgE-related mechanisms of exacerbation might have less to do with hyperreactivity of airway smooth muscle and more to do with other pathologies implicated in exacerbation, such as bronchovascular leakiness and mucus hypersecretion.

In summary, anti-IgE treatment results in decreased airway eosinophilia and decreased exacerbation frequency in asthma. Anti-IgE has more modest effects on other asthma outcomes, such as FEV<sub>1</sub> and PC<sub>20</sub> methacholine. The unsuspected dissociations among outcomes uncovered during clinical trials of omalizumab demonstrate that the links between airway inflammation, airway remodeling, and airway function in asthma are not clear-cut.

## REFERENCES

- Platts-Mills TA. The role of immunoglobulin E in allergy and asthma. *Am J Respir Crit Care Med* 2001;164(suppl):S1-5.
- Kehry MR, Yamashita LC. Low-affinity IgE receptor (CD23) function on mouse B cells: role in IgE-dependent antigen focusing. *Proc Natl Acad Sci U S A* 1989;86:7556-60.
- Gounni AS, Wellemans V, Yang J, Bellesort F, Kassiri K, Gangloff S, et al. Human airway smooth muscle cells express the high affinity receptor for IgE (Fc epsilon RI): a critical role of Fc epsilon RI in human airway smooth muscle cell function. *J Immunol* 2005;175:2613-21.
- Boulet LP, Chapman KR, Cote 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.
- 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.
- Milgrom H, Fick RB Jr, Su JQ, Reimann JD, Bush RK, Watrous ML, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. *N Engl J Med* 1999;341:1966-73.
- Solèr 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. *Eur Respir J* 2001;18:254-61.
- 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.
- Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001;108:184-90.
- Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005;60:309-16.
- Djukanovic R, Wilson SJ, Kraft M, Jarjour NN, Steel M, Chung KF, et al. Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. *Am J Respir Crit Care Med* 2004;170:583-93.
- MacGlashan D Jr, Bochner B, Adelman D, 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.
- Beck LA, Marchotte GV, MacGlashan D, Togias A, Saini S. Omalizumab-induced reductions in mast cell FcεR1 expression and function. *J Allergy Clin Immunol* 2004;114:527-30.
- Prussin C, Griffith DT, Boesel KM, Lin H, Foster B, Casale TB. Omalizumab treatment downregulates dendritic cell FcεR1 expression. *J Allergy Clin Immunol* 2003;112:1147-54.
- Kalesnikoff J, Huber M, Lam V, Damen JE, Zhang J, Siraganian RP, et al. Monomeric IgE stimulates signaling pathways in mast cells that lead to cytokine production and cell survival. *Immunity* 2001;14:801-11.
- 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.
- Ong YE, Menzies-Gow A, Barkans J, Benyahia F, Ou TT, Ying S, et al. Anti-IgE (omalizumab) inhibits late-phase reactions and inflammatory cells after repeat skin allergen challenge. *J Allergy Clin Immunol* 2005;116:558-64.
- Coyle AJ, Wagner K, Bertrand C, Tsuyuki S, Bews J, Heusser C. Central role of immunoglobulin (Ig) E in the induction of lung eosinophil infiltration and T helper 2 cell cytokine production: inhibition by a non-anaphylactogenic anti-IgE antibody. *J Exp Med* 1996;183:1303-10.