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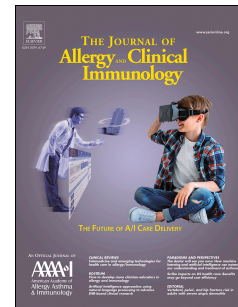
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Omalizumab in “non-IgE mediated” diseases

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30 Omalizumab is an anti-IgE antibody developed for the treatment of atopic diseases.¹ It is
31 approved for moderate-severe persistent allergic asthma and appears to be effective for other
32 atopic diseases such as allergic rhinitis, food allergy, allergic bronchopulmonary aspergillosis,
33 atopic dermatitis, and anaphylaxis. Surprisingly, omalizumab has also been found to be effective
34 for “non-IgE mediated” diseases, such as chronic spontaneous urticaria (CSU), bullous
35 pemphigoid (BP), virally-induced asthma exacerbations, and mastocytosis. It is now also
36 approved as treatment for CSU. Although omalizumab’s mechanism of action in atopic diseases
37 is well understood, its mechanism of action in non-atopic diseases is still unclear.¹

38 In atopy, onset of allergic symptoms requires prior sensitization (antigen-specific IgE
39 binding to FcεRI receptors on effector cells (mast cells and basophils)). Omalizumab, by binding
40 to free IgE, prevents it from binding to FcεRI receptors on effector cells, interfering with
41 degranulation and release of proinflammatory mediators. Further, by reducing free IgE,
42 omalizumab decreases FcεRI expression on these cells, leading to decreased degranulation. In
43 general, omalizumab does not bind to FcεRI-bound IgE or IgE receptors, an important safety
44 aspect for avoiding degranulation by effector cells.² However, in rare cases (approximately
45 0.09%), omalizumab induces an anaphylaxis-like reaction through unknown mechanism(s).²

46 In addition to the high-affinity FcεRI receptor, IgE can also bind to low-affinity FcεRII
47 receptors (CD23), which can facilitate up- or down-regulation of IgE synthesis. Although FcεRII
48 is considered a low-affinity receptor, cell surface oligomerization of CD23 has a potential IgE
49 affinity similar to that of FcεRI. Omalizumab also has been shown to downregulate FcεRII,
50 making cells insensitive to incoming allergen.³ Another mechanism by which anti-IgE antibodies
51 decrease allergic reactions is through decreasing IgE production by targeting CD23 or CD23-

bound IgE on B-cells. For example, ligelizumab, a more recently developed anti-IgE antibody, is more effective than omalizumab in binding CD23-bound IgE.³

Ligelizumab differs from omalizumab in its binding epitopes and appears to be more efficient in suppressing FcεRI-dependent allergic reactions; by contrast, omalizumab may have advantages in blocking antigen presentation and transport processes that are dependent on IgE:CD23 interactions.^{3,4} Further clinical studies with these drugs may help to elucidate specific immune cell contributions in IgE versus non-IgE mediated diseases.

Although omalizumab's role in preventing immediate allergic reactions in established IgE-dependent diseases is well recognized, there is accumulating evidence of omalizumab's effectiveness in other diseases currently regarded as "non-IgE mediated". These include chronic spontaneous urticaria (CSU), bullous pemphigoid (BP), nasal polyposis, idiopathic angioedema, non-allergic asthma, virally-induced asthma exacerbations, and mastocytosis.¹ Here we review the apparent IgE-independence of some of these omalizumab-responsive disorders.

In CSU, the dosage of omalizumab is fixed and appears not to be as dependent on serum IgE levels (although total IgE before and during therapy can predict disease responsiveness) and clinical responses are seen early (after only 12 h). IgG autoantibodies against FcεRI, IgE, or both have been observed, and these autoantibodies can crosslink FcεRI, leading to subsequent degranulation of effector cells. Another possible mechanism is that some patients with CSU have IgE antibodies against auto-allergens, and omalizumab can reduce the level of these auto-antibodies. Omalizumab also has shown efficacy in several other types of urticaria, supporting a role for IgE in these disorders.⁵ Even though no relevant evidence has yet been generated in such

settings, we think it likely that omalizumab mediates its effects by decreasing free IgE and down-regulating FcεRI, although this remains to be shown.

In BP, detection of serum anti-BP180 (type XVII collagen) IgE, and correlation with disease activity, support the notion that anti-BP180 IgE is of pathogenic relevance and may distinguish the subset in which omalizumab may have the most benefit.⁶ Indeed, in a case report of two patients with BP, omalizumab led to down-regulation of FcεRI, and IgE in lesional skin and on circulating basophils, with clinical improvement.⁷

In adults with virus-induced asthma exacerbations, omalizumab improved anti-viral responses and decreased asthma exacerbations, raising questions regarding the role of IgE and omalizumab in these responses. Viruses such as respiratory syncytial virus, parainfluenza virus, and Epstein-Barr viruses can induce specific IgE antibody responses. Plasmacytoid dendritic cells (pDCs) can express FcεRI receptors, and are thought to be critical for mediating anti-viral effects via production of IFN-α.

It is currently hypothesized that virus-induced asthma exacerbations associated with allergic asthma reflect both increased IgE levels and inhibition of critical virus-induced IFN-α responses by pDCs. Omalizumab is thought to mitigate these actions by preventing IgE binding to its receptor and reducing cross-linking of FcεRI-bound IgE, and by decreasing expression of FcεRI on pDCs while increasing their release of IFN-α. More recently, omalizumab also has been shown to restore the ability of pDCs to induce T regulatory cells, in vitro.⁸ A study of inner-city asthmatic children who underwent pre-seasonal treatment with omalizumab showed a decreased incidence of fall asthma exacerbations. In these patients, PBMCs increased their IFN-α responses in response to rhinovirus.⁹

Omalizumab also has been shown to be effective in steroid-resistant asthma with high eosinophil levels. In these patients, omalizumab decreased asthma exacerbations, oral corticosteroid intake, and blood eosinophils. Both high- and low-affinity IgE receptors have been found on eosinophils. Omalizumab, by decreasing free IgE, may influence eosinophil function and survival. A study by Noga et al.¹⁰ found that eosinophilic apoptosis, as determined by the presence of annexin V, increased after administration of omalizumab. Furthermore, omalizumab was associated with decreased production of GM-CSF, an eosinophilic growth factor.¹⁰

In summary, by decreasing free IgE, omalizumab can mediate a number of effects in part via downregulation of FcεRI and/or FcεRII receptors on mast cells, basophils, and B cells, as well as on pDCs and perhaps eosinophils (Figure 1). Additional research on the effects of omalizumab in “non-atopic” diseases not only is likely to shed light on its mechanism of action in these diseases, but also will help to clarify further the roles of IgE and FcεRI in these so-called “non-IgE-mediated” disorders.

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139 **Figure 1.** Omalizumab and downstream effects on allergic inflammation. Omalizumab inhibits
140 binding of IgE to FcεRI and FcεRII receptors, leading to down-regulation of receptors. In turn,
141 mast cells and basophils have decreased pro-inflammatory mediators; B cells decrease IgE
142 production and may become anergic; plasmacytoid dendritic cells (pDCs) have improved viral
143 responses and can induce Tregs; and eosinophils may apoptose.