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New insights into the utility of omalizumab

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Abstract

Cells that express FcεRIα, including mast cells, basophils, and plasmacytoid dendritic cells (pDCs), are regulated by IgE binding to FcεRIα. Omalizumab binds IgE and prevents its engagement with FcεRIα, thereby downregulating its expression and modulating cell function. Because these cells are implicated in the pathobiology of many allergic and immunologic diseases, as well as host defense mechanisms, it is unsurprising that omalizumab studies continue yielding biologic insights and treatment break-throughs for many diseases. Several recent updates in the biology and use of omalizumab will be presented here, and others will be summarized in Table I, highlighting available biomarker-based personalized approaches.

Keywords

IgE; FcεRIα; mAb; biologic therapy; allergy; antiviral immunity; asthma; chronic urticaria; food allergy; immunotherapy

ANTIVIRAL EFFECTS

One exciting contribution from recent studies on omalizumab has been the demonstration that omalizumab can ameliorate the inadequate antiviral response observed in patients with allergic asthma. Children with severe asthma are more susceptible to virus-induced asthma exacerbations, particularly those with higher serum IgE levels.[1,2] This relationship has been postulated to be due to impaired interferon responses to viruses in patients with allergic asthma based on cell-based studies using peripheral blood–derived pDCs coincubated with viruses. Furthermore, these studies demonstrated a counterregulatory mechanism between FcεRIα and Toll-like receptor 7 (TLR7; an important receptor for sensing viruses and mounting innate immune responses), whereby their protein expression is inversely proportional.[3,4]

These observations have now been expanded by 2 recent studies using biospecimens and data from the Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations (PROSE) study, which examined whether preventive administration of omalizumab could dampen the seasonal increase in asthma exacerbations seen in children.[5] First, these studies

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revealed that omalizumab decreased the duration of human rhinovirus (HRV) infections, viral shedding, and risk of HRV-related illnesses compared with guideline-driven care alone.[6] Second, omalizumab attenuated pDC FcεRIα protein expression while simultaneously augmenting pDC IFN-α responses to HRV and influenza virus.[7] Together, these findings provide direct evidence that blocking IgE decreases susceptibility to respiratory viral illnesses through enhanced IFN-α responses in pDCs (Fig 1).[5–7] These findings can provide a mechanistic explanation to the results from the Inner-City Anti-IgE Therapy for Asthma study, in which omalizumab inhibited seasonal increases in asthma exacerbations thought to be caused by viral infections.[8]

In contrast, a recent study showed that mepolizumab administration (which blocks IL-5, the main driver of eosinophilic inflammation) did not abrogate lung function decreases provoked by HRV challenge in participants with mild asthma.[9] This suggests that enhancement of the antiviral response is specific to blocking IgE and not cytokines important in eosinophilic inflammation. Still, these recent studies raise new questions on allergy-antiviral immunity interactions and the counterregulatory relationship between FcεRIα and TLR7. Unexpectedly, omalizumab decreased TLR7 protein expression,[7] increases of which were presumed to be one mechanism that promoted greater IFN-α production. Whether type 1 interferons other than IFN-α (eg, IFN-β1) or IFN-γ (also deficient in patients with allergic asthma) are also upregulated and responsible for the enhanced viral clearance observed with omalizumab treatment remains unknown. Future omalizumab studies might identify intermediaries downstream of FcεRIα that could be targeted to further improve or restore interferon responses in patients vulnerable to viral respiratory tract infections.

RELATIONSHIP WITH EOSINOPHILS

Another interesting asthma-related finding has been the association between asthma exacerbation reductions and peripheral blood eosinophil counts.[10] In patients with blood eosinophil counts of greater than 300 or greater than 400 cells/μL, the reduction in exacerbations noted with omalizumab was 67% and 74%, respectively. Interestingly, data from this and the Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO) study suggest that exacerbation reductions relative to blood eosinophil counts are largely driven by the placebo arm because placebo-assigned participants with high blood eosinophil counts had substantially greater asthma exacerbation rates compared with placebo-assigned participants with low blood eosinophil counts.[E1]

URTICARIA

Omalizumab has transformed the treatment of chronic urticaria (CU) since US Food and Drug Administration approval for this indication in 2014. The majority of patients with CU experience substantial benefit from omalizumab, but not all are complete responders, and some are nonresponders. Recent small studies have identified several response biomarkers. The serum total IgE ratio of levels obtained before and 4 weeks after omalizumab therapy initiation demonstrated an area under the curve of 0.95, with ratios of less than 1.9 having

both a sensitivity and a specificity of 93% to predict nonresponse to omalizumab (n = 96).[E2] Baseline serum total IgE levels (threshold, <43 kU/L) alone showed a 95% negative predictive value for response. Others have also reported on low baseline serum IgE levels as negatively predictive of response.[E3] Conversely, greater baseline basophil FcεRIα expression was 100% sensitive and 72% specific for responsiveness to omalizumab.[E4] Importantly, this assay discriminated well between responders and nonresponders; a mean fluorescence intensity threshold of 5000 for FcεRIα by using flow cytometry completely distinguished responders from nonresponders.

Sera from patients with CU, which activates basophils (increased CD203c levels, as determined by using flow cytometry), associates with nonresponsiveness to omalizumab.[E5] Serum IL-31 levels were found to decrease with omalizumab treatment and not placebo, but baseline IL-31 levels did not correlate with CU disease activity indexes and did not distinguish responders from nonresponders.[E6] A large (n = 470) retrospective study showed no association between baseline D-dimer levels and omalizumab's therapeutic response,[E7] contradicting prior reports of this biomarker's predictive ability.[E8]

Improved patient selection is needed, and optimal duration of omalizumab therapy remains undetermined. Furthermore, its therapeutic mechanism remains unclear. Indeed, omalizumab response times in patients with CU seem slower in patients with autoantibodies,[E9] suggesting that variations in pathogenic mechanisms (IgE-mediated vs IgG-mediated FcεRIα activation) likely underlie differences in response times.

Finally, omalizumab's performance on several physical urticarias has been recently reviewed, with the strongest data available for symptomatic dermographism, cold-induced urticaria, and solar urticaria.[E10]

OTHER DISORDERS

Omalizumab has been shown to be beneficial in patients with various other disorders. Omalizumab facilitates immunotherapy to inhalant, food, and Hymenoptera venom allergens. A recent phase 2 randomized, double-blind, placebo-controlled trial of children with peanut allergy undergoing oral immunotherapy showed that omalizumab administration allowed for tolerance of 2000 mg of peanut on discontinuation of immunotherapy more often than placebo (23/27 [74%] vs 1/8 [13%], $P < .01$).[E11] Participants assigned to omalizumab were also less likely to experience adverse reactions to peanut immunotherapy. Omalizumab has also been shown to improve the safety of oral immunotherapy to other food allergens administered alone or in combination.[E12] Considering the high burden of disease posed by food allergy and the important role food desensitizations will likely play in clinical practice, omalizumab will probably be frequently used to improve safety and efficacy with oral immunotherapy.

Omalizumab has shown effectiveness in patients with nasal polyps,[E13] and phase 3 studies for this indication are under way. Many studies have demonstrated therapeutic benefit for omalizumab in seasonal[E14] and perennial[E15] allergic rhinitis. Small case series show positive therapeutic effects for patients with idiopathic anaphylaxis,[E16] mast cell activation

disorders,[E17] allergic bronchopulmonary aspergillosis,[E18] atopic dermatitis,[E19] eosinophilic gastrointestinal disorders,[E20] nonallergic asthma,[E21] and asthma–chronic obstructive pulmonary disease overlap.[E22] There is conflicting evidence on whether omalizumab can facilitate aspirin desensitization in patients with aspirin-sensitive asthma.[E23,E24]

Cost ($10,000–$70,000/year [minimum-maximum dose]) largely prevents omalizumab from wider use for a broader range of allergic, nonallergic, and immunologic conditions, although most analyses in asthma and CU cohorts have considered it cost-effective when targeted to select groups.[E25,E26] Considering the importance of IgE and cells that bear IgE receptors, omalizumab will likely continue gaining prominence in the treatment of disorders beyond allergic asthma and CU.

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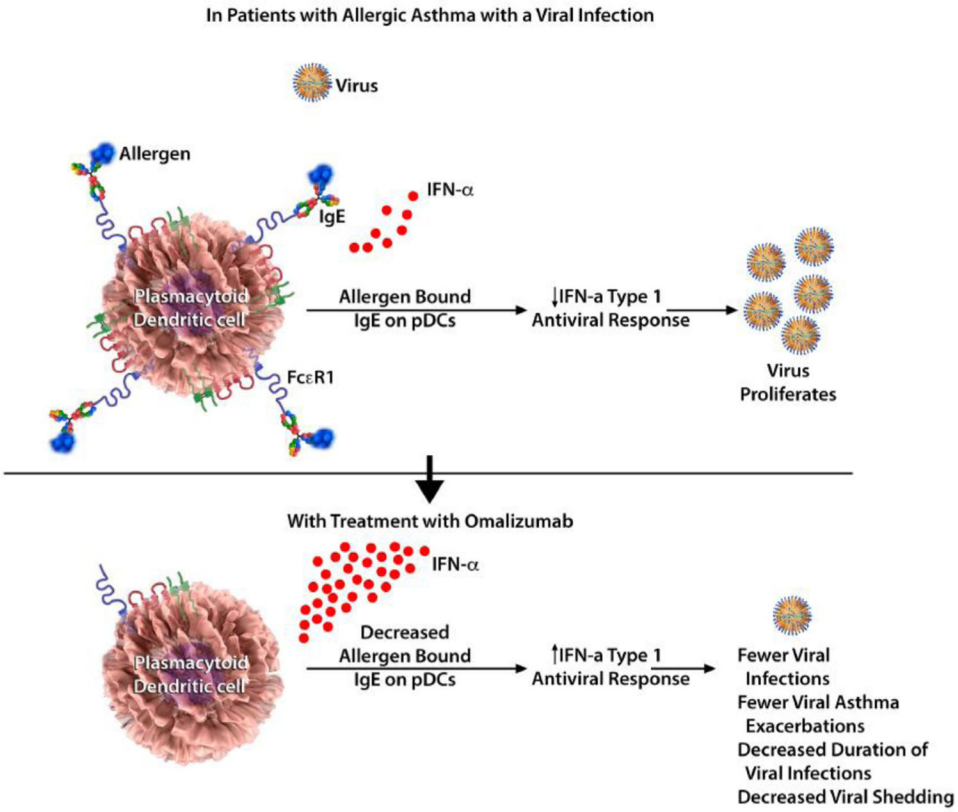

FIG 1.

Omalizumab and the antiviral response in pDCs. Omalizumab blocks IgE and enhances IFN-α responses in pDCs, thereby decreasing susceptibility to viral respiratory tract illness (based on results from the PROSE study).[5–7]

TABLE I.

Omalizumab and its uses

Indications by quality of supportive evidence	Findings	References
High (eg, large, double-blind, placebo-controlled clinical trials or meta-analyses)		
Allergic asthma	Reduction in asthma exacerbations	Busse et al. J Allergy Clin Immunol 2001;108:184–90
CU	Reduction in symptoms in patients whose symptoms were uncontrolled by antihistamines	Maurer et al. N Engl J Med 2013;368:924–35
Allergic rhinitis	Improvement in rhinitis symptoms and quality of life	Casale et al. JAMA 2001;286:2956–67
Moderate (eg, small clinical trials)		
Facilitation of oral food allergen immunotherapy	Facilitation of peanut oral immunotherapy	MacGinnitie et al. J Allergy Clin Immunol 2017;139: 873–81
Facilitation of subcutaneous immunotherapy to aeroallergens	Improvement in safety of rush immunotherapy to ragweed	Casale et al. J Allergy Clin Immunol 2006;117:134–40
Nonallergic asthma	Improvement in lung function and reduction of bronchial mucosal IgE cells	Pillai et al. Eur Respir J 2016;48:1593–1601
Nasal polyposis	Reduction in endoscopic and radiographic polyp scores	Gevaert et al. J Allergy Clin Immunol 2013;131:110–6
ABPA	Reduction in exacerbations	Voskamp et al. J Allergy Clin Immunol Pract 2015;3:192–9
Low (eg, case series or reports; anecdotal, retrospective, conflicting evidence)		
Mast cell activation syndrome	Reduction in anaphylactic episodes and skin symptoms	Broesby-Olsen et al. Allergy 2018;73:230–8
Idiopathic anaphylaxis	Reduction in anaphylactic episodes	Warrier et al. Ann Allergy Asthma Immunol 2009;102: 257–8
Atopic dermatitis	Conflicting responses to therapy	Belloni et al. J Allergy Clin Immunol 2007;120:1223–5
ACO	Improvement in asthma control and QoL	Maltby et al. Chest 2017;151:78–89
EoE	Clinical and histologic improvement in a minority of patients	Loizou et al. PLoS One 2015;10:e0113483
AERD	Conflicting evidence on whether omalizumab can facilitate aspirin desensitization	Lang et al. Ann Allergy Asthma Immunol 2018;121:98–104 Waldram et al. J Allergy Clin Immunol 2018;141:250–6

ABPA, Allergic bronchopulmonary aspergillosis; *ACO*, asthma-COPD overlap; *AERD*, aspirin-exacerbated respiratory disease; *COPD*, chronic obstructive pulmonary disease; *EoE*, eosinophilic esophagitis; *QoL*, quality of life

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