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REVIEW

Management of asthma with anti-immunoglobulin E: A review of clinical trials of omalizumab

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Summary Immunoglobulin E (IgE) is a key mediator of the inflammatory reactions that are central to the pathogenesis of allergic diseases such as asthma and rhinitis. The recognition of the importance of IgE in allergic disease led to the development of omalizumab, a humanized monoclonal anti-IgE antibody that binds free circulating IgE and prevents the interaction between IgE and high-affinity (FcεRI) and low-affinity (FcεRII) IgE receptors on inflammatory cells. By removing free IgE, omalizumab also markedly downregulates the expression of high-affinity receptors on basophils, mast cells and dendritic cells. Several studies have shown that omalizumab effectively reduces the risk of exacerbations and hospitalization and improves symptom control, lung function and quality of life in patients with severe persistent allergic asthma. Importantly, omalizumab has been shown to be effective in patients with poorly controlled severe persistent allergic asthma, a group of patients with few effective additional treatment options. In addition, omalizumab has been shown to provide effective relief from the symptoms of allergic rhinitis (including patients with concomitant asthma). Patients with uncontrolled severe persistent allergic asthma are a challenging and difficult-to-treat population for whom omalizumab might represent an important new treatment option. In addition, omalizumab may provide a means to address comorbid allergic disease in patients with asthma. Further investigation is also warranted to explore potential applications of omalizumab in occupational asthma.

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Introduction

Immunoglobulin E (IgE) has been known to be a key mediator of allergic reactions for more than 30 years and plays a central role in allergic responses to allergens in patients with asthma and rhinitis.[1,2] IgE is produced by B cells after sensitization to an allergen[3] and has a short half-life.[4] Despite low serum concentrations, IgE is immunologically highly active due to the large number of high-affinity IgE receptors on mast cells and basophils.[3] In addition, IgE up-regulates receptors on several cell types, including basophils and mast cells.[4,5] The binding of IgE to the receptors on these cells results in the formation of cross links between the allergen and the IgE molecule and initiates the inflammatory cascade through release of a variety of mediators, including histamine, leukotrienes (LT), and platelet-activating factor.[6]

Current evidence suggests that the majority of asthma has an allergic basis[7,8] and that IgE is central to the initiation of both allergic and non-allergic asthma.[9–11] Indeed, population studies indicate that almost all asthma is associated with elevated IgE levels.[12] In addition, IgE also plays a central role in many cases of occupational asthma[13] as well as in a variety of allergic conditions, including rhinitis.[14]

The central role of IgE in allergic disease created interest in developing treatments based on anti-IgE antibodies. In particular, it was hoped that new treatments based on anti-IgE approaches might provide a means to improve control of allergic asthma and better meet the goals set out in the Global Initiative for Asthma (GINA) guidelines.[15] According to the GINA guidelines, treatment should be adjusted using a stepwise approach based on asthma severity. Treatment for mild intermittent asthma (step 1) is based on use of rescue bronchodilators as needed, with increasing doses of inhaled corticosteroids (ICS) used to control mild (step 2), moderate (step 3), and severe (step 4) persistent asthma. Patients with moderate persistent asthma should also receive a long-acting β_2-agonists (LABA) or alternatively sustained-release theophylline, an oral β_2-agonists or a LT modifier. For patients with severe persistent asthma, high-dose ICS and LABA are recommended with additional agents added if required. The Gaining Optimal Asthma Control (GOAL) study showed that many patients fail to achieve control of asthma despite treatment with corticosteroids (fluticasone) or combination salmeterol/fluticasone therapy.[16] Although the GOAL study showed that using combined salmeterol and fluticasone increased the percentage of patients achieving control of their asthma, many patients remained inadequately controlled, especially in the group with the most severe asthma where 38% and 53% of patients remained inadequately controlled despite treatment with salmeterol/fluticasone and fluticasone, respectively (Table 1).

The association between an increased risk of death and factors characteristic of more severe

Table 1 Percentage of patients who were not totally controlled or well controlled in the GOAL study.[16]

Stratum	Patients not totally controlled or well controlled (%)	
	Fluticasone/salmeterol	Fluticasone
1. Corticosteroid naïve	22	30
2. $\leqslant$500 μg/day BDP or equivalent	25	40
3. $>$500 to $\leqslant$1000 μg/day BDP	38	53

BDP = beclometasone dipropionate.