Clinical Commentary Review

Omalizumab in Asthma: An Update on Recent Developments

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IgE is central to the pathophysiology of allergic asthma. Omalizumab, a humanized anti-IgE mAb, specifically binds free IgE and interrupts the allergic cascade by preventing binding of IgE with its high-affinity FcεRI receptors on mast cells, antigen-presenting cells, and other inflammatory cells. The clinical efficacy of omalizumab has been well documented in a number of clinical trials that involve adults, adolescents, and children with moderate-to-severe and severe allergic asthma. In these studies, omalizumab reduced exacerbations, asthma symptoms, inhaled corticosteroid and rescue medication use, and improved quality of life relative to placebo or best standard of care. Similar benefits have been reported in observational studies in "real-world" populations of patients. Results from recent pooled data from randomized clinical trials and from a large prospective cohort study provide reassurance about the long-term safety of omalizumab. Omalizumab dosing is individualized according to body weight and serum-IgE level, and recent adjustments to the dosing algorithm in Europe have enabled more patients to be eligible for treatment. Ongoing and future research is investigating the optimal duration of therapy, accurate predictors of response to treatment, and efficacy in nonatopic asthma as well as other IgE-mediated conditions. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:525-36)

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Asthma is one of the most common chronic diseases, which affects 235 million people worldwide and continues to be a significant public health concern.[1,2] Asthma is a heterogeneous disease characterized by different clinical and pathophysiologic profiles.[3-6] The chronic airway inflammation present with asthma is associated with reversible airflow obstruction and bronchial hyperresponsiveness, which manifest as symptoms such as wheezing, coughing, breathlessness, and chest tightness.[7] Approximately 70% of patients with asthma have an allergic phenotype, in which symptoms are triggered by allergens such as pollen, cat dander, or house dust mites, and which is characterized by elevated serum levels of allergen-specific IgE.[8] The National Asthma Education and Prevention Program and Global Initiative for Asthma (GINA) guidelines recommend a stepwise approach to asthma therapy to reduce current impairment and future risk, with treatment intensified until patients achieve symptom control.[7,9] Although many patients achieve asthma control with standard therapies, a significant proportion continue to experience symptoms and exacerbations despite the use of inhaled corticosteroids (ICS) and long-acting β_2-adrenoceptor agonists (LABA).[10-13]

Omalizumab, a humanized anti-IgE mAb, was approved by the US Food and Drug Administration (FDA) in 2003 for adults and adolescents (12 years of age and older) with moderate-to-severe persistent allergic asthma whose symptoms are inadequately controlled with ICS.[14] In the European Union, omalizumab is approved for the treatment of patients ages 6 years and older with severe persistent allergic asthma inadequately controlled with ICS and LABA.[15] A decade after its initial approval, it is timely to review the current state of knowledge about omalizumab, specifically its mechanism of action, the findings of recent clinical studies and real-world effectiveness studies, and emerging knowledge about predictors of response and the long-term safety of omalizumab. This review also will describe the latest research and ongoing trials with this agent, and highlight future directions for the clinical use of omalizumab.

ROLE OF IgE IN ALLERGIC ASTHMA

In allergic asthma, the immune system reacts to a foreign protein as if it were a potentially harmful invader and triggers

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Abbreviations used
ATE- Arterial thromboembolic event
ED- Emergency department
EXCELS- *The Epidemiologic Study of Xolair (omalizumab)*
FDA- US Food and Drug Administration
FeNO- Fraction of exhaled nitric oxide
GETE- Global Evaluation of Treatment Effectiveness
GINA- Global Initiative for Asthma
ICS- Inhaled corticosteroid
LABA- Long-acting β_2-agonist
OCS- Oral corticosteroid
QALY- Quality-adjusted life year

inflammatory events that contribute to asthma symptoms.[16] Allergens that enter the airway are presented to T lymphocytes by dendritic cells, which initiate the cell-mediated immune response, particularly the maturation and migration of Th cells (Figure 1).[16,17] Th2 cells stimulate B cells to produce IgE antibodies as well as stimulate secretion of proallergic cytokines, such as IL-4, IL-5, IL-9, and IL-13. IL-4 is essential for the production of IgE, whereas IL-5 is involved in the recruitment of eosinophils and basophils, which then promote inflammation.[18]

When IgE is released from B cells, it binds to the FCϵRI on the surface of mast cells and basophils; is cross-linked by allergen; and triggers degranulation and the release of prostaglandins, leukotrienes, histamine, proteases, exoglycosidases, proteoglycans, and cytokines, which leads to the early allergic response.[19] FCϵRIs also are present on dendritic cells, where the interaction with IgE and allergen contributes to the Th2 cell- and eosinophil-associated late-phase allergic response.[20] The recognition that IgE plays a pivotal role in allergic asthma has stimulated research into the therapeutic potential of targeting this antibody.

MECHANISM OF ACTION OF OMALIZUMAB

Omalizumab is composed of a human IgG framework and the complementarity-determining region from a murine anti-IgE antibody. Omalizumab specifically binds to free (unbound) IgE forming omalizumab:IgE complexes, thereby reducing free IgE levels and preventing IgE from interacting with FCϵRIs as well as low-affinity IgE receptors (Figure 1).[21] Because IgE bound to omalizumab cannot interact with FCϵRI, omalizumab is able to inhibit the IgE-induced release of inflammatory mediators from mast cells and basophils without stimulating degranulation. IgE regulates its own receptor; hence, by reducing free IgE, omalizumab also downregulates expression of FCϵRI (but interestingly, not of low-affinity IgE receptors) on mast cells, basophils, and circulating dendritic cells (Figure 1).[21,22] This effect also has been observed in nonatopic asthma.[23] Decreases in FCϵRI expression on mast cells will contribute to reduced mediator release in response to allergen and to reduced facilitated allergen presentation by dendritic cells.[21] Whether acting directly by capturing IgE and/or indirectly via effector cell desensitization, at the population level, the suppression of free IgE correlates with a reduction in the signs and symptoms of asthma.[24-26]

EFFECTS ON IgE

Serum-free IgE levels decline after omalizumab administration, but omalizumab forms a complex with previously unbound IgE, and this contributes to an increase in total IgE (made up of both free IgE and omalizumab:IgE complexes).[25] Consequently, it is not possible to assess the treatment response to omalizumab by measuring total IgE. Initially, it was thought that IgE production remained constant over time, but results of recent research indicate that IgE production decreases then equilibrates during omalizumab therapy.[27] After the initial accumulation, total IgE levels decrease in parallel with the reduction in IgE production (Figure 2), which suggests that IgE production is regulated through a feedback loop determined by the free-IgE level, which reaches a new equilibrium after approximately 5 years of omalizumab treatment (Figure 2, *insets*).[27] This model also predicts that, once omalizumab is withdrawn, IgE production will slowly return to baseline levels.

CLINICAL BENEFITS OF OMALIZUMAB THERAPY

The clinical efficacy of omalizumab in patients with moderate-to-severe and severe allergic asthma has been well documented in several large-scale clinical trials that involved adults, adolescents, and children.

Adults and adolescents

In 5 phase III studies in patients ages 12 to 75 years with severe allergic asthma, omalizumab reduced the rate of asthma exacerbations relative to control (placebo or best standard care),[16,28-32] with statistically significant reductions in 4 of the 5 studies.[28-30,32] A pooled analysis of data from 7 omalizumab studies (including 5 randomized, double-blind, placebo-controlled studies and 2 randomized open-label studies) confirmed the beneficial impact on asthma exacerbations (Figure 3, and Figure E1 in this article's Online Repository at www.jaci-inpractice.org), and demonstrated a consistent reduction in the incidence rates of unscheduled outpatient visits, emergency department (ED) treatments, and hospitalizations for asthma exacerbations during 1 year of omalizumab treatment compared with placebo.[31,33,34] In addition, omalizumab was associated with significant reductions in asthma symptoms [16,28-30,32] and improvements in quality of life (measured by the Asthma Quality of Life Questionnaire).[16,32]

In studies that included a corticosteroid-reduction phase, patients who used omalizumab were able to significantly reduce their use of ICS relative to the control groups during the steroid-reduction phases, and some even discontinued ICS altogether.[16,28,29] Moreover, reductions in asthma exacerbations, symptoms, and rescue medication use with omalizumab were achieved despite the decrease in ICS use.[16,28]

The impact of omalizumab on asthma exacerbations also has been demonstrated in the recent EXTRA study, a large randomized, double-blind, placebo-controlled trial in which all the patients received high-dose ICS and LABAs at baseline.[35] The addition of omalizumab to maximal asthma therapy significantly reduced the risk of exacerbations over 48 weeks by 25% relative to placebo (the rate was 0.66 in the omalizumab group vs 0.88 in the placebo group; $P = .0006$) as well as increasing the time to first asthma exacerbation by 26% (hazard ratio 0.74 [95% CI, 0.60-0.93]; $P = 0.008$).[35] Other clinical benefits of omalizumab relative to placebo were a more marked improvement in quality of life, greater reductions in rescue medication use, and greater improvements in symptom score.[35] Subgroup analysis suggested a greater effect on the exacerbation rate in patients who received ICS and LABAs compared with those patients who received ICS plus LABA plus maintenance oral corticosteroids (OCS).[35]

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