Omalizumab in children with uncontrolled allergic asthma: Review of clinical trial and real-world experience

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Asthma is one of the most common chronic diseases of childhood. Allergen sensitization and high frequencies of comorbid allergic diseases are characteristic of severe asthma in children. Omalizumab, an anti-IgE mAb, is the first targeted biologic therapeutic approved for the treatment of moderate-to-severe persistent allergic asthma (AA) that remains uncontrolled despite high-dose inhaled corticosteroids plus other controller medications. Since its initial licensing for use in adults and adolescents 12 years of age and older, the clinical efficacy, safety, and tolerability of omalizumab have been demonstrated in several published clinical trials in children aged 6 to less than 12 years with moderate-to-severe AA. These studies supported the approval of the pediatric indication (use in children aged ≥6 years) by the European Medicines Agency in 2009 and the US Food and Drug Administration in 2016. After this most recent change in licensing, we review the outcomes from clinical trials in children with persistent AA receiving omalizumab therapy and observational studies from the past 7 years of clinical experience in Europe. Data sources were identified by using PubMed in 2016. Guidelines and management recommendations and materials from the recent US Food and Drug Administration's Pediatric Advisory Committee meeting are also reviewed. (J Allergy Clin Immunol 2017;139:1431-44.)

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In the United States asthma affects approximately 6 million children and poses a high burden measured by disability and premature death.[1-3] The disease is estimated to result in more than 10 million school days lost per year,[2] and the health care costs are substantial, with pediatric emergency department visits alone totaling approximately US$272 million in 2010.[4] Quality of life (QoL) can also be adversely affected; in a national health survey 5.5% of children aged 5 to 17 years with symptomatic asthma experienced limitation of activity caused by asthma.[2]

Control of symptoms can be achieved in many asthmatic children through avoidance of asthma triggers and/or with conventional medications, assuming adherence.[5,6] In a retrospective chart review of 142 children aged 5 to 17 years with uncontrolled asthma who were referred to a hospital-based pediatric asthma clinic over a 5-year period, by addressing remedial causes in the basics of asthma management (including poor adherence, ongoing exposure to environmental triggers, comorbidities, incorrect inhaler technique, and incorrect diagnosis), asthma control was achieved in 138 (97.2%) of 142 cases.[7] However, some children fulfill the criteria for true therapy-resistant asthma: 4 (2.8%) of 142 in the retrospective chart review[7] and 3 (4.5%) of 67 in a separate childhood asthma study in Oslo, Norway,[5] did

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Abbreviations used
AA: Allergic asthma
AE: Adverse event
EMA: European Medicines Agency
EXCELS: Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma
FDA: US Food and Drug Administration
FENO: Fraction of exhaled nitric oxide
ICAC: Inner-City Asthma Consortium
ICATA: Inner-City Anti-IgE Therapy for Asthma
ICS: Inhaled corticosteroid
LABA: Long-acting β_2-agonist
PROSE: Preventative Omalizumab or Step-up Therapy for Fall Exacerbations
OCS: Oral corticosteroid
QoL: Quality of life
RDBPCT: Randomized double-blind, placebo-controlled trial
SAE: Serious adverse event

not respond to standard therapy. These children are described as having uncontrolled severe persistent asthma, which was defined as any combination of chronic symptoms, severe exacerbations, and persistent airflow limitation despite receiving high-dose inhaled corticosteroid (ICS) plus a second controller medication.[6,8,9] Furthermore, conventional bronchodilatory and anti-inflammatory therapeutics do not modify the underlying disease mechanism, and debate continues regarding the safety of prolonged high-dose ICS use in children.[10,11] The safe and appropriate use of long-acting β_2-agonists (LABAs) has also been widely debated, although a recent randomized, double-blind trial showed that LABA given in combination with ICS did not result in a higher risk of severe asthma events among children versus those receiving ICS alone.[12] Consequently, a need remains for safe and efficacious targeted therapeutic options in children with uncontrolled severe asthma.

Approved by the US Food and Drug Administration (FDA) in 2003, omalizumab (Xolair; Genentech, San Francisco, Calif), a subcutaneously administered humanized anti-IgE mAb, is the first targeted biologic treatment licensed for use in adults and adolescents 12 years of age and older with moderate-to-severe persistent asthma who have a positive skin test response or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled by ICSs.[13] Omalizumab was subsequently approved in 2005 by the European Medicines Agency (EMA) as an add-on therapy for patients aged 12 years and older with uncontrolled severe persistent allergic asthma (AA) despite daily high-dose ICS plus inhaled LABA treatment.[14] The pediatric indication for omalizumab in asthmatic patients (use in children aged ≥6 years) was approved by the EMA and FDA in 2009 and 2016, respectively.[14-16]

AA is believed to result from polarization of naive airway T cells to a T_H2 phenotype. Allergens entering the airway are presented to T cells by antigen-presenting cells, leading to selective recruitment of mast cells, basophils, and eosinophils, along with induction of B-cell immunoglobulin class-switching to IgE, which in turn provides mechanisms for initiating and maintaining allergic inflammation in the airway.[17-19]

By attaching with high affinity to free (unbound) IgE, omalizumab blocks IgE-receptor binding on the surfaces of antigen-presenting cells, mast cells, and basophils.[20-22] This prevents subsequent inflammatory cell activation and causes IgE receptor downregulation by reducing levels of free IgE.[20,21] Additional evidence supports the role of omalizumab in preventing inflammatory responses to or long-term consequences of allergen exposure, including tissue remodeling, inflammatory cell recruitment, and T_H2-type inflammation (Fig 1).[8,17-26]

IgE sensitization and high frequencies of comorbid allergic diseases characterize severe asthma in children. In the Severe Asthma Research Program pediatric cohort, a cluster analysis revealed 4 defined phenotypic clusters, each featuring atopic characteristics with differing degrees of allergic sensitization,[27] and children with severe asthma had significantly higher serum IgE levels, increased aeroallergen sensitization, and higher concentrations of fraction of exhaled nitric oxide (FENO; a marker of airway inflammation) than children with mild-to-moderate asthma.[28] High IgE levels, allergen sensitization, high frequencies of allergic comorbidities, and high rates of health care and medication use were also characterizing features of severe or difficult-to-treat asthma in children and adolescents enrolled in the 3-year observational The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study.[29-31] An observational study of the Unbiased Biomarkers in Prediction of Respiratory Disease Outcome Project pediatric cohort documented that children with severe preschool wheeze or severe asthma were typically atopic and had impaired QoL that was associated with inadequate control and airflow limitation.[32] These observations differ from adult severe asthma, which is characterized by a broad spectrum of phenotypes; adult mild asthma has a more striking association with allergy than severe disease.[33]

With the pivotal role of IgE in patients with AA, including severe disease, there is a pathophysiologic rationale for the use of anti-IgE therapy in the management of children with uncontrolled AA. International asthma guidelines and position papers also recommend omalizumab as an add-on therapy for the treatment of severe, IgE-mediated AA in children whose asthma symptoms are uncontrolled despite optimal pharmacologic management and appropriate allergen avoidance.[8,34-37] Here we review the experience of children with persistent AA receiving omalizumab therapy by summarizing findings from clinical trials and real-world observational studies.

OVERVIEW OF OMALIZUMAB STUDIES

Efficacy outcomes

In 2001, Milgrom et al[38] evaluated omalizumab use in children aged 6 to 12 years with moderate-to-severe AA that was well controlled with ICSs who received placebo or omalizumab in a randomized double-blind, placebo-controlled trial (RDBPCT). The primary efficacy outcome was corticosteroid reduction. After 28 weeks of therapy, ICS dose reduction was significantly greater in the omalizumab versus placebo groups, and ICS use was withdrawn completely in a greater percentage of omalizumab-treated patients versus placebo-treated patients without compromising asthma control (Table I).[25,38-48] Additionally, a reduction in the incidence and frequency of asthma exacerbations was observed in the omalizumab versus placebo groups, and both investigator- and patient-rated Global Evaluation of Treatment Effectiveness results favored improvements in the omalizumab versus placebo groups (Table I). A follow-up study also demonstrated positive effects of omalizumab on asthma-related QoL (Table I).[39,40]