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Treatment of moderate to severe pediatric asthma Omalizumab and potential future use of monoclonal antibodies

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Introduction

Asthma is among the most common chronic illnesses of childhood. Asthma prevalence is increasing. Asthma morbidity and mortality remain high among children from low-income and minority backgrounds.¹ Historically, pediatric asthma has been described as largely atopic, with a T_H2 cytokine profile that includes interleukin (IL) 4, IL-5, and IL-13; however, more recently, there has been emerging evidence of more phenotypic diversity, including T_H1 phenotypes related to obesity (also an inflammatory condition).^{2–4} Thus, it is important to tailor pediatric asthma treatment. Inhaled corticosteroids (ICSs) have been the mainstay of treatment in pediatric asthma. However, when ICSs and other standard treatments are ineffective in treating poorly controlled moderate to severe asthma, targeting the T_H2 profile with monoclonal antibodies may be effective in select atopic pediatric populations, and omalizumab, anti-IgE therapy, provides the first example. In this review article, we present a case of an atopic urban child with poorly controlled severe asthma. We review the evidence for the use of omalizumab in pediatric asthma. Omalizumab was the first biologic approved for use in pediatric asthma; however, more recently mepolizumab has been approved for use, and there are other monoclonal antibodies that are under investigation, including reslizumab, lebrikizumab, and tralokinumab (which we will review briefly).

Clinical Vignette

Case Presentation

A 12-year-old African American boy with asthma is referred by his primary care physician to the allergy clinic for treatment of his poorly controlled severe asthma. At the age of 2 years, he was diagnosed as having reactive airway disease and subsequently asthma after an episode of bronchiolitis. He has a history of infant eczema, allergic rhinitis, and asthma. His asthma has been poorly controlled with high-dose ICSs, long-acting β -agonists (LABAs), and montelukast for the past few years. In the past month, he has used his albuterol rescue

inhaler daily for shortness of breath, and he has decreased physical activity. He has nighttime awakenings because cough more than twice a week. He has no known food or drug allergies.

Asthma and environmental history

He takes his asthma medications daily as prescribed, and his parents report strict adherence. He requires 2 to 3 bursts of oral glucocorticoids per year (mainly during the fall and winter). He has 2 to 3 emergency department visits a year for asthma. He had 1 hospitalization in the distant past for bronchiolitis at the age of 2 years. He has no history of prior intubations. His asthma triggers include upper respiratory tract infections, cold air exposure, and exercise. There is no environmental tobacco smoke exposure. He lives in an urban environment. There are no pets in the home, but there is rodent and cockroach infestation.

Family history

He has a strong family history of atopy. His mother has asthma and eczema. His father has asthma and hay fever. He has a 5-year-old sister with asthma, eczema, and food allergies.

Physical examination findings

He is a 12-year-old boy with normal vital signs and pulse oximetry. His body mass index (calculated as the weight in kilograms divided by height in meters squared) is in the 75th percentile. He does not appear to be in any respiratory distress. He has no use for accessory muscles for breathing. He has pale edematous bilateral nasal turbinates. There is normal chest excursion, and his lungs are clear to auscultation, with no audible wheezes, but he has poor air movement. There are no eczematous changes on his skin.

Test Results

On skin prick testing, he has sensitization to dust mite, mold, trees, grass, weeds, mouse, and cockroach. He has normal spirometry results and a clear chest radiograph. His laboratory findings are as follows: blood eosinophils, 15%; absolute eosinophil count, 1050 cells/ μ L; serum total IgE level, 700 IU/mL; and fraction of exhaled nitric oxide, 30 ppb.

Clinical Context of the Case

This case highlights the complexity and challenges physicians face when treating children with severe or poorly controlled asthma. There are multiple factors that contribute to the patient's asthma morbidity. He is African American and has a highly atopic background, with an elevated blood eosinophil count, total IgE level, and fraction of exhaled nitric oxide. He has multiple sensitizations and environmental exposures and lives in an urban environment with cockroach and mouse exposure.⁵ Cockroach was implicated as a major allergen that contributes to inner-city asthma morbidity with increased symptom-days, school absences, and health care use.⁶ More recently, in Baltimore, Ahluwalia et al⁷ conducted a study in the homes of 144 inner-city children with asthma, and there was a high prevalence of both mouse and cockroach allergen exposure and sensitization; however, mouse allergen exposure and sensitization contributed more to asthma morbidity.

This case is complex, and all potential factors that may contribute to asthma morbidity should be addressed before adding any additional treatment (eg, perform asthma education, review medication adherence and technique for inhaler use, counsel on environmental trigger avoidance strategies, and consider environmental remediation with integrated pest management).⁸ His asthma is persistent, severe, and poorly controlled with daily symptoms despite treatment with high-dose ICSs, LABAs, and montelukast. He has an elevated IgE level. He is in need of step-up therapy, and according to the National Asthma Education and Prevention Program Expert Panel Report 3 guidelines, omalizumab should be considered (at step 5 or 6).⁹ Although this case is complex, this review will have a narrow focus on the evidence that supports the use of omalizumab in moderate to severe pediatric asthma and other monoclonal antibodies that are currently being investigated in pediatric asthma.

Monoclonal Antibodies in Pediatric Asthma

Omalizumab use in urban pediatric asthma—Omalizumab is a humanized monoclonal anti-IgE antibody. It inhibits binding of IgE to mast cells and decreases serum levels of free IgE.¹⁰ As described earlier, our urban patient with severe asthma would likely benefit from treatment with omalizumab based on findings of the Inner-City Anti-IgE Asthma (ICATA) trial: he is highly atopic with cockroach sensitization and exposure and seasonal peaks in asthma. ICATA was a seminal (double-blind randomized controlled) trial of 419 individuals that evaluated the efficacy of omalizumab in inner-city individuals with poorly controlled moderate to severe asthma (6–20 years old).¹¹ The ICATA study population was highly atopic and had elevated serum IgE levels. Omalizumab was used as add-on therapy to ICSs and LABAs. In the treatment group, asthma symptom-days (in a 2-week period) were reduced by 24.5% compared with placebo (1.48 vs 1.96 days, $P < .001$).¹¹ In participants sensitized and exposed to cockroach, asthma symptom-days were reduced by 48.5%.¹¹ In addition, treatment with omalizumab was associated with a marked decline in peaks of seasonal asthma exacerbations and reduced the use of ICSs.¹¹ In post hoc analysis, the authors concluded that the onset of action of omalizumab was fast (<30 days). Predictors of omalizumab efficacy included elevated exhaled nitric oxide (>20 ppb), blood eosinophilia (>2%), and body mass index (>25), which are characteristics that our patient possesses.¹²

Omalizumab use in the general pediatric asthma—Omalizumab has efficacy in the general pediatric population. In early pediatric studies, omalizumab use was associated with reductions in the requirement for ICSs and oral corticosteroids in the treatment of asthma exacerbations.¹³ Omalizumab use was also associated with a reduction in unscheduled medical visits, missed school days, and hospitalizations.^{11,13} There is evidence to suggest that children 6 to 11 years of age with moderate to severe asthma benefit from omalizumab. In a study of 627 patients, omalizumab use was associated with a 31% reduction in asthma exacerbations compared with placebo ($P = .007$).¹⁴

There are limited data on long-term efficacy and safety on omalizumab use in the treatment of pediatric asthma. Because of the uncertainty of long-term safety profile of omalizumab, more studies are needed. This information may also provide insight for the future use of monoclonal antibodies in pediatric asthma.

Potential future use of monoclonal antibodies in pediatric asthma—Although omalizumab was the first monoclonal antibody approved for the treatment of asthma in children 12 years of age and older in the United States, mepolizumab was recently approved for use and there are other monoclonal antibodies in the pipeline that have been investigated in clinical trials for future use in pediatric asthma, including reslizumab, lebrikizumab, and tralokinumab (summarized in Table 1). Most published data available for monoclonal antibodies that include adolescents do not separately report pediatric outcomes from outcomes in adults; thus, this poses a challenge to interpretation of these findings in the pediatric populations. In this review, we briefly review key findings from the literature on monoclonal antibodies in the treatment of asthma. We have to caution applying adult literature to children because children have a different body composition and lung function; however, it is important to be familiar with the results in the adult literature. It is critical to conduct asthma clinical trials in children because they present unique challenges with phenotypic variation that has not been as well described as in adults.^{3,4}

Mepolizumab and reslizumab are 2 anti-IL-5 monoclonal antibodies that have been investigated in pediatric asthma. IL-5 is highly correlated with sputum eosinophilia and airway hyper-responsiveness in asthma.¹⁵ In the DREAM (Dose Ranging Efficacy And Safety with Mepolizumab in Severe Asthma) trial, mepolizumab reduced asthma exacerbations in patients with severe eosinophilic asthma (reductions ranged from 39% to 52% compared with placebo, $P < .001$).¹⁶ Similar results were found in a study by Ortega et al¹⁷ of patients with asthma and severe eosinophilia taking high-dose ICSs. In the mepolizumab treatment group, there was a 47% and 53% rate of reduction in asthma exacerbations in the intravenous and subcutaneous administration groups, respectively, compared with placebo ($P < .001$).¹⁷ These trials included adolescents; however, the mean age of participants was approximately 50 years of age, and there was no separate reporting of results in participants 12 to 17 years of age.^{16,17} Reslizumab has been associated with modest improvements in asthma quality-of-life scores and lung function.^{18,19} More recently, in a trial that included adolescents, reslizumab was associated with a reduced frequency of asthma exacerbations; however, pediatric outcomes for efficacy and safety in children 12 years and older with elevated blood eosinophil counts were not reported separately from adults.²⁰

Lebrikizumab and tralokinumab are 2 anti-IL-13 monoclonal antibodies under investigation in pediatric asthma. IL-13 promotes the secretion of periostin by bronchial epithelial cells, which results in airway remodeling.²¹ In adults with moderate to severe asthma, treatment with lebrikizumab was associated with improved lung function (5.5% improvement in forced expiratory volume in 1 second and 8.2% in those with elevated periostin levels) compared with placebo.²² Lebrikizumab is currently under investigation for the treatment of pediatric asthma in children 12 years and older (currently taking ICSs and a second controller medication and in corticosteroid-dependent patients with asthma) in 2 clinical trials (NCT01875003 and NCT01987492). Tralokinumab was associated with improved lung function in asthmatic patients with elevated levels of eosinophils.²³ The pharmacokinetics of tralokinumab were investigated in adolescents, and the drug had favorable tolerability (similar to the safety profile in adults).²⁴

Conclusion

Omalizumab has efficacy in select populations of children with asthma. In this review, we presented a complex case of an atopic African American pediatric patient with poorly controlled asthma in an urban environment where environmental exposures and sensitization are likely playing a critical role. Findings from the ICATA trial¹¹ revealed that omalizumab is an effective treatment for the inner-city patients with asthma, significantly reducing asthma symptom-days and exacerbations. Although omalizumab was the first biologic approved for use in children 12 years of age and older in the United States, there are other monoclonal antibodies under investigation in pediatric asthma, and mepolizumab was recently approved for use. We would not expect all monoclonal antibodies to be effective in treating pediatric asthma because of concerns about long-term efficacy, safety, and cost-effectiveness,²⁵ but monoclonal antibodies tailored to treating pediatric phenotypes may be of potential benefit in select pediatric populations when standard treatment is ineffective. However, we face unique challenges in pediatric asthma because (1) pediatric phenotypes are not as well characterized compared with adults and (2) clinical trials that include adult and pediatric populations often do not separately report findings in children, which may limit one's ability to effectively target biologic therapy. Thus, more studies need to be conducted to further elucidate pediatric phenotypes and to determine the long-term efficacy and safety of omalizumab and future monoclonal antibodies in pediatric asthma.

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Table 1**Monoclonal Antibodies in the Treatment of Pediatric Asthma**

Name	Therapeutic target	Asthma phenotype/endotype	Approved for use in children
Omalizumab	IgE	Atopic asthma/urban asthma	Yes (12 years of age)
Mepolizumab	IL-5	Eosinophilic asthma	Yes (12 years of age)
Reslizumab	IL-5	Eosinophilic asthma	Under investigation
Lebrikizumab	IL-13	Elevated periostin	Under investigation
Tralokinumab	IL-13	Eosinophilic asthma	Under investigation

Abbreviation: IL, interleukin