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Omalizumab in Asthma : Is the Therapeutic Window Too Small?

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an invalid easy-to-remember number is still invalid. Miller et al¹ add more data to what numerous committees and research reports have already emphasized³⁻¹¹: GOLD categorization underdetects airway obstruction in many younger individuals and overdetects airway obstruction in many older individuals. Their report also reemphasizes the folly of using 80% predicted as a threshold to separate normal from abnormal for other pulmonary function parameters. It has been pointed out that absolute values (eg, FVC, FEV₁, TLC) have moderate population variability, that ratios of volumes (eg, FEV₁/FVC, FEV₃/FVC, residual volume/TLC) have considerably lower population variability, and that flows divided by volumes (eg, forced expiratory flow, midexpiratory phase [FEF_{25%-75%}]) have very high population variability.¹² Although 80% predicted may be a somewhat defensible LLN value for FEV₁, FEV₆, and FVC for individuals between age 20 and 40, it is too high a value for older individuals. Eighty percent is also too high for FEV₁/FVC or FEV₃/FVC at any age and too low for FEF_{25%-75%} at any age.

It is our responsibility as pulmonologists to help reeducate physicians and other health professionals. We can begin by improving the reporting of data from our pulmonary function laboratories. One suggested method for reporting laboratory values is shown in Table 1, which displays (1) the mean predicted values based on the demographics of the patient; (2) either the SE of the estimate or the residual SD, or, preferably, 1.645 times of either as the LLN or upper limit of normal; (3) the actual values of the test; and (4) bronchodilator responsiveness values. There is no need to report percent-predicted values because they are both misleading and easy for anyone to calculate. It is acceptable to underline, color-code, or place an asterisk next to a value below the LLN, but it is not appropriate to do so simply because a value is <80% or >120% of the mean predicted value or for an FEV₁/FVC ratio <70%.

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Omalizumab in Asthma

Is the Therapeutic Window Too Small?

Asthma is an inflammatory disorder of the airways that affects approximately 300 million people worldwide. A significant number of these patients, estimated at 10% to 15%, have severe disease that is mechanistically heterogeneous and poorly controlled by conventional therapy. Patients with severe asthma are challenging for clinicians because of complex and arcane pathogenic mechanisms, frequent exacerbations, chronic impairment of lung function, and unpleasant medication side effects. This therapeutic gap has sparked the development of novel approaches to care.

The heterogeneous pathogenesis of asthma produces multiple incompletely characterized phenotypes. One such phenotype is the patient with atopic disease characterized by specific IgE-mediated reactions to one or more aeroallergens. In these patients, IgE on the cell

surface of inflammatory cells induces and perpetuates a cascade, resulting in characteristic airway hyperresponsiveness (AHR), inflammation, and remodeling.

IGE AND ASTHMA

The relationship of elevated total IgE levels and asthma expression, independent of specific atopy, has been repeatedly documented.¹⁻³ The production of IgE is initiated by complex interactions of the adaptive and innate immune systems. Activation of mast cells, basophils, and T helper (Th) 2 cells results in the production of cytokines, including IL-4 and IL-13, which coordinate and amplify the inflammatory cascade. Subsequently, B cells initiate the transcription and production of allergen-specific IgE.

The fraction (crystallizable) portion of free IgE molecules binds to the surface of mast cells, basophils, macrophages, and dendritic cells by high-affinity (FcεRI) and low-affinity (FcεRII) receptors. Allergens then bind to the variable region of the bound IgE molecule, inducing cell activation and the generation of proinflammatory mediators, including Th 2-type cytokines, chemokines, prostaglandin D₂, leukotriene C₄, and tumor necrosis factor-α. This process augments the recruitment of additional eosinophils, basophils, and Th 2 cells, ultimately resulting in mucosal inflammation, AHR, airflow limitation, and symptoms of asthma.

OMALIZUMAB AND IGE MECHANISMS IN ASTHMA

This critical involvement of IgE in allergic asthma was the biologic rationale for the development of omalizumab, a humanized monoclonal anti-IgE antibody. Omalizumab targets the interaction between IgE molecules and IgE receptors by binding the Fcε portion of free IgE molecules, reducing free-circulating IgE, and blocking its binding to inflammatory cells. Therapy with omalizumab results in a rapid reduction of free IgE levels and the prompt downregulation of FcεRI expression on circulating basophils⁴ and dendritic cells.⁵ Invasive studies using bronchial biopsy and immunohistochemical examination have shown decreased tissue binding of IgE, reduced FcεRI expression in airway mucosa, and blunted production of sputum and tissue eosinophilia.⁶ Subsequent large clinical trials have demonstrated the efficacy of omalizumab in patients with uncontrolled severe asthma, with reductions in asthma exacerbation rates, corticosteroid use, and symptoms, in both adults and children.^{6,7}

CLINICAL NOVELTY OF THIS CASE

In this issue of *CHEST* (see page 190), van den Berge and coauthors⁸ present a compelling case of

a woman with poorly controlled, severe, persistent, nonallergic asthma with elevated IgE levels whose asthma improved significantly with the initiation of omalizumab, recrudesced with its withdrawal, and improved again on restarting the medication. Omalizumab is currently approved in the United States for patients with moderate to severe atopic asthma who are ≥ 12 years of age and are not controlled by conventional therapy, including daily inhaled corticosteroids. Atopy is defined by a positive skin test result or in vitro IgE reactivity to a perennial aeroallergen. Similarly, in Europe, omalizumab is indicated as an adjunct to improve control in patients with severe persistent allergic asthma, convincing IgE-mediated asthma with frequent daytime/nighttime symptoms, FEV₁ < 80%, and several documented exacerbations despite the use of daily high-dose inhaled corticosteroids and long-acting inhaled β-2-agonist therapy.⁹ Of note, current guidelines for omalizumab therapy recommend both elevated IgE levels (within a specified window) and IgE immunoreactivity to a perennial allergen. Hence, the use of omalizumab in the United States and Europe is constrained by both quantitative IgE and qualitative atopic parameters.

Interestingly, the patient presented in this case had elevated total serum IgE levels but did not reveal sensitization to common aeroallergens by history or formal testing. Therefore, she would not have been a “guideline” candidate for omalizumab therapy in the United States or Europe.

POSSIBLE MECHANISMS OF EFFICACY OF OMALIZUMAB

Why was treatment with omalizumab successful in this case? The patient’s clinical course was consistent with the known pharmacokinetic and pharmacodynamic properties of omalizumab. Although this patient had elevated total IgE levels and peripheral eosinophilia, her skin-prick and specific serum IgE test results for common aeroallergens were negative. It is certainly possible, and perhaps most likely, that her specific allergic sensitivity was simply not identified. Previous studies identifying the association between elevated IgE levels and nonatopic asthma have suggested as much.¹ The range of potential allergenic agents is considerably larger than current diagnostic reagents can address, so “false-negative” allergen-skin-test results (in reality, failing to test for the allergen of biologic importance) are a real possibility. Alternatively, it is possible that IgE elevation occurs as a nonspecific reaction secondary to asthmatic Th 2 cell-like inflammation with IL-4 elaboration and that IgE triggers AHR independent of a specific allergen sensitization. This mechanism is supported by empirical evidence of increased AHR

in bronchial rings from patients who are nonatopic and who are incubated with the sera of patients with high IgE levels.¹⁰ Finally, it is important to consider that this particular patient case was not blinded, either for the patient or for her physicians, and so the contribution of placebo effects cannot be excluded. However, improvements were seen in objective parameters of lung function and inflammation, in addition to subjective symptom improvement, the magnitude of which were greater than that generally observed with placebo effects.

CLINICAL IMPLICATIONS

Whether we should consider the use of omalizumab as an adjunct medication in patients with nonatopic severe asthma who are poorly controlled on conventional therapy, on a case-by-case basis, is unclear. Certainly, in the paradigm of using best evidence to inform guidelines for clinical practice, this case cannot be used to justify the broad use of omalizumab in patients with nonallergic asthma. The use of omalizumab in patients with high IgE levels but no demonstrable allergic reactivity to perennial allergens has not been adequately studied in properly designed trials. IgE unquestionably plays a role in the inflammatory cascade contributing to AHR and remodeling in many patients with asthma, but the current understanding of the process includes both sensitization and exposure to specific allergens, findings not present in this case. It is clinically intriguing that certain patients, such as in this case, may benefit from this therapy but are not currently candidates for omalizumab. However, the broad use of this expensive therapy in patients not shown to have benefit cannot be recommended. At the present time, there are several active trials registered in ClinicalTrials.gov that are evaluating the use of omalizumab in allergic asthma, but only three involve the use of omalizumab in nonatopic asthma. Further studies of omalizumab targeting patients with nonallergic asthma who have elevations in baseline IgE levels would be helpful in determining whether the current indications for omalizumab are too restrictive. Accordingly, defining additional patient populations, such as patients with nonatopic asthma with elevated IgE levels or those with IgE values outside of the current therapeutic window, is of utmost importance. This information must come from properly designed and executed randomized clinical trials of sufficient magnitude and statistical power to provide definitive information on which appropriate evidence-based recommendations can proceed.

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