

Asthma Attacks in Children: Does Blocking IgE Reduce Rhinovirus Infections?

Asthma attacks lead to impaired quality of life and mortality, but the rates of hospital admission for acute asthma have changed little over the last 20 years (1). We know that a combination of allergen sensitization, allergen exposure, and viral infections triggers attacks (2). Although these factors usually work together, a large allergen load alone can also be sufficient to trigger an attack (thunderstorm), and although viruses contribute to increased symptoms, in the context of atopic asthma, they are not the only culprit. Although influenza viruses can be targeted by specific agents, including vaccines, we lack strategies to treat most of the common respiratory viruses that result in asthma attacks, especially rhinovirus (RV). IFN responses to RV are altered in individuals with asthma (3), but a recent study using nebulized IFN (4) failed to meet its primary end point, suggesting that interactions between allergic immunity and antiviral immunity are of key importance. Hence, investigators have turned their attention to modulating the allergic components of asthma attacks. Examples of this approach include reducing exposure to house dust mite allergens by using impermeable covers, which has shown promise in sensitized children (5), and modulating the response to allergens with omalizumab (6).

The annual surge in hospital admissions when children return to school in the fall is well documented in Western countries (7). This is likely multifactorial: children are reexposed to respiratory viral infections (RV in particular) (7), children may have forgotten to use their maintenance therapy during the summer holidays, and there may be high levels of allergens in the school environment (8). The cost of this surge, in terms of time lost from school and time off work for carers, is considerable. The PROSE (Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations) study undertaken by the Childhood Inner City Asthma Consortium showed that treatment with omalizumab in children before they returned to school in the fall resulted in fewer asthma attacks, especially in those who had recently experienced an attack (9). Interestingly, *ex vivo* stimulation of peripheral blood mononuclear cells by RV resulted in increased secretion of IFN- α in children who had been treated with omalizumab, suggesting an IgE-mediated mechanism by which protection from RV-induced exacerbations may be achieved.

In this issue of the *Journal*, Esquivel and colleagues (pp. 985–992) report a potential causal link among RV infection, IgE-mediated pathways, and asthma attacks based on results from the PROSE study (10). They determined RV subtypes isolated during asthma attacks (RV-A, RV-B, and RV-C), and the frequency and duration of attacks in patients receiving omalizumab compared with placebo. RV-A and RV-C were more strongly associated with

attacks than RV-B. A considerable strength of this study is the weekly nasal sampling for virus detection. Regardless of symptoms, 43% of children in the placebo group had detectable RV at any time during the 90-day intervention period, compared with 36% of children who received omalizumab. RV infection (regardless of symptoms) was defined as detection of virus in nasal mucus. Omalizumab had no impact on the number of RV infections, but it did reduce the average length of infection from 12.4 days to 11.2 days. Interestingly, the reduction was greater for RV-C (from 11.6 to 9.5 d), which in many studies is the serotype most associated with severe attacks (11). A respiratory illness was defined as an increase in a composite cold score and simultaneous detection of RV in nasal mucus. Omalizumab resulted in a significant reduction in RV-associated symptomatic illnesses. However, despite its importance, this must be considered a proof-of-concept study. The effect sizes are small, and although a reduction in the RV detection rate by 7%, the duration of RV detection by 1.2 days, and RV illnesses of 0.4 per patient with omalizumab treatment is a statistically clear signal, it is not of much clinical importance, particularly in the context of the high cost of omalizumab and the inconvenience of administration. Importantly, what this study does do is mandate a trial in children who are experiencing repeated severe asthma attacks to determine whether more relevant clinical end points, such as unscheduled healthcare visits, prednisolone therapy, and hospital admissions, are reduced by omalizumab.

As with all good studies, there are unanswered questions. RV infection is important, but failed treatment of acute asthma attacks is associated with multiple viruses and polyviral infection is common (12). What remains unknown is whether the effect of blocking IgE is RV specific or is applicable to all common respiratory viruses, and, importantly, the size of any effect in other viral infections. Bacterial infection is also associated with asthma attacks, and interactions between RV and common bacterial pathogens may result in completely opposite outcomes (13). Additional studies to assess the interactions between viruses and bacteria in the PROSE study samples are eagerly awaited. More work is also needed to delineate the molecular pathways underpinning the actions of omalizumab, which could lead to novel agents with greater specificity.

However, as the authors have stressed elsewhere (9), before using any “beyond guidelines” approaches, it is essential to get the basics of asthma therapy right, and in the PROSE study improvement was also seen during the run-in period. Low-dose inhaled corticosteroids if correctly and regularly administered reduce asthma attacks, and one should institute other environmental control measures, such as reducing exposures to allergens and tobacco smoke (14), before using an expensive and relatively invasive therapy.

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Finally, we must rise to the challenge of risk stratification. Not all children with asthma have attacks. In both the PROSE trial (9) and a previous omalizumab study (6), children with the highest levels of exhaled nitric oxide and peripheral blood eosinophils had the best response, and the peripheral blood eosinophil count is a promising marker in pediatrics (15). Personalizing treatment for asthma attacks must be the next goal, especially if omalizumab treatment is extended into the preschool years. ■

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Bringing Lung Function Prediction Equations to Diverse Populations

Guidelines published in 2005 by the American Thoracic Society and European Respiratory Society (1) recommend using reference equations derived in populations that match the age and anthropometric, racial/ethnic, socioeconomic, and environmental characteristics of patients being tested in the pulmonary function laboratory. Although no specific reference equation is recommended, most pulmonary function laboratories in the United States default to equations derived by Hankinson and colleagues from three populations (whites, African Americans, and Mexican Americans) participating in NHANES III (the

third National Health and Nutrition Examination Survey) (2) for adults, whereas outside the United States the 2012 multiethnic Global Lung Initiative (GLI) equations are commonly used (3). Unfortunately, although these equations are reasonably well matched to the patient populations from which they are drawn, the equations from Hankinson and colleagues may be poorly predictive for racial/ethnic groups outside of the three used. Globally, the GLI equations included a paucity of participants from South Asia, the islands of the Pacific, Africa, and Latin America. This leaves clinicians evaluating patients inadequately matched to reference equations in a quandary. They can apply a race adjustment factor, if known, which is not as accurate as using ethnic-specific equations, or they can apply the reference equation of the

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