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Does IgE Have a Role in Aspirin-exacerbated Respiratory Disease?

Aspirin-exacerbated respiratory disease (AERD) is a unique phenotype of asthma with nasal polyps and characterized by sensitivity to aspirin and nonsteroidal antiinflammatory drugs (NSAIDs) (1, 2). A hallmark feature of AERD is dysregulated function of the 5-lipoxygenase pathway, which leads to overproduction of cysteinyl leukotrienes (LTs) by mast cells (MCs) after exposure to cyclooxygenase inhibitors (3). Although the mechanisms of AERD are not fully established, Laidlaw and Boyce (1) and Boyce (3) have identified dysregulated MC activation as a pivotal component of NSAID-sensitive asthma. In AERD, NSAIDs inhibit cyclooxygenase, shifting 5-lipoxygenase metabolism to generate excessive cysteinyl LTs and large quantities of prostaglandin D2 (PGD2) from MCs, thereby causing acute airflow obstruction (4). A biomarker for dysregulated MC function in AERD is elevated urinary excretion of cysteinyl LT metabolites (i.e., LTE_4 and PGD-M).

Interest in regulating MC cysteinyl metabolism in AERD to NSAIDs began with studies of MC-stabilizing cromone drugs, which blocked both the aspirin-provoked asthma and parallel rise in urinary LTE_4 (5). Cromone drugs also rapidly improved FEV_1 values, suggesting a prompt suppression of chronic MC activation, LT generation, and consequential bronchospasm.

Omalizumab is a monoclonal antibody that binds and reduces circulating IgE to block MC activation and allergic airway reactions. Reducing free IgE also diminishes expression of high-affinity IgE receptors on MCs and MC activation (6). Consequently, and based on evidence of ongoing MC activation and existing eosinophil airway inflammation in AERD, Hayashi and colleagues (7) treated 21 patients with omalizumab, which significantly reduced urinary excretion of LTE_4 and PGD-M and, interestingly, peripheral blood eosinophils. In an open-label study, Lang and colleagues (8) investigated whether omalizumab attenuated airflow obstruction in patients with AERD undergoing aspirin desensitization. Five of the seven omalizumab-treated participants had neither a respiratory reaction nor an increase of urinary LTE_4 during aspirin desensitization. These preliminary findings of Hayashi and colleagues (7) and Lang and colleagues (8) are indirect evidence that MC biology and, possibly, IgE are components of AERD.

In this issue of the *Journal*, Hayashi and colleagues (pp. 1488–1498), from Sagamihara National Hospital in Nagoya, Japan, expanded and extended their earlier studies with omalizumab in a placebo-controlled, double-blind, crossover study in 16 highly selected and carefully managed patients with AERD (9). From 21 patients with AERD screened, 16 participants were randomized into their clinical trial. The subjects had a mean age of 53 years, required high-dose inhaled corticosteroids for asthma control (655 μg/d of fluticasone equivalent), and previously had a positive aspirin challenge reaction to confirm AERD. All enrolled subjects with AERD had asthma control with a mean Asthma Control Questionnaire 6 score of 0.8 (0.3–2.6) and FEV_1 of 104.4% predicted (92.7–112.0). Their mean peripheral blood eosinophil count was 370 cells/μl. These are not the typical clinical profiles of severe disease in patients with AERD but necessary criteria to safely conduct an aspirin challenge. The study design had two 3-month intervention phases, omalizumab or placebo, with an 18-week washout between the randomized treatment crossover. After each 3-month treatment phase, an oral aspirin challenge was conducted with escalating aspirin doses until either an AERD reaction occurred or the maximal challenge dose of aspirin, 930 mg, was reached. MC activation to the aspirin challenge was determined by measuring LTE_4 and PGD-M concentrations in 24-hour urine collections, which also served as the primary study outcome.

Aspirin challenge of the subjects with AERD after 3 months of omalizumab treatment did not cause a significant increase of LTE_4 and PGD-M in the 24-hour urine analysis compared with placebo (Hayashi and colleagues' Figure 2). Ten of the 16 subjects achieved the maximal aspirin dose of 930 mg without AERD; whereas, on placebo, an AERD response to aspirin was achieved at doses ranging from 30 mg to 530 mg (Hayashi and colleagues' Table 3). Furthermore, the mean percent fall in FEV_1 was significantly reduced by omalizumab treatment compared with placebo (−4.7 vs. −10.0; $P = 0.039$) (Hayashi and colleagues' Table E2).

Hayashi and colleagues (9) also evaluated the kinetics of omalizumab effects on urinary LTE_4 and PGD-M concentrations over the 3-month treatment (their Figure 4). Small but significant reductions in urinary excretion of LTE_4 and PGD-M began shortly after initiating omalizumab, reached maximal reductions at 1 month, and were sustained at the aspirin challenge (Table 4).

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Omalizumab treatment was also associated with gradual reduction in peripheral blood eosinophils, from a baseline mean value of 320 cells/μl to 220 cells/μl, an effect not usually seen in non-AERD asthma (10).

The authors cautiously, but justifiably, conclude that omalizumab "has inhibitory effects on ongoing MC activation." These omalizumab-associated MC inhibitory effects are convincing because both the respiratory reaction and expected increase in urinary excretion of LTE_4 and PGD-M to aspirin were inhibited. How do these findings explain mechanisms of AERD and MC function to also direct future treatment options for this asthma phenotype? Omalizumab is an effective treatment in selected patients with allergic asthma, presumably by preventing IgE-allergen activation of pulmonary MCs (10). Omalizumab is also effective in chronic spontaneous urticaria in which allergen-specific IgE responses are usually absent and, in this sense, parallels AERD in which the reaction to NSAIDs is not an IgE-antigen response (11). Omalizumab's mechanisms of action in chronic urticaria are not established, but the prompt reduction of hives suggests a suppression of MC function. Whether this benefit relates to diminished MC IgE receptor expression on MCs and/or a suppression of MC activation is not established but possible. The data from Hayashi and colleagues (9) showing both diminished baseline and post–aspirin challenge increases in urinary LTE and PGD-M generation strongly supports but does not prove the possibility of reduced MC activation.

There are limitations to the Hayashi and colleagues study (9). The number of subjects enrolled was small, 16, with a protective response to omalizumab found in only 10. The fall in FEV_1 to aspirin while on placebo treatment was modest, a mean drop of 10%; however, these aspirin-associated pulmonary reactions were associated with increased LT generation. These shortcomings aside, this study is the first double-blind, placebo-controlled, crossover trial in which both airway AERD reactions and measures of MC function were made. I believe these findings represent a major step forward to more fully understand mechanisms of AERD.

Important questions remain about the AERD puzzle, particularly identifying mechanisms underlying dysregulated reactions to NSAIDs and how omalizumab modified AERD. Intriguing and enlightening to me were new insights gained by using omalizumab to probe the roles of MCs and IgE in AERD. Hayashi and colleagues (9) have directed attention to IgE as a potential component of dysregulated MC function in AERD and as a possible therapeutic target in this high-risk asthma population, and have provided new clues to more definitively solve this complicated puzzle. ■

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