

Aspirin and nonsteroidal anti-inflammatory drug intolerance

Asthma is a respiratory condition of the lower respiratory tract that affects approximately 8% to 12% of the general population. It is characterized by symptoms of cough, wheeze, and shortness of breath associated with airway obstruction with reversibility or bronchial hyperreactivity.¹ Rhinitis is a condition of the upper nose characterized by symptoms of sneezing, nasal congestion, and nasal discharge. It affects 21% to 40% of the general population. Both conditions are relatively common, are related to inflammation, and are associated with nasal polyps and eosinophilia and other factors (allergic and nonallergic and genetic and environmental).²

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used drugs.² They have been reported to trigger respiratory symptoms but have not been studied completely, especially regarding ethnic group, geographic location, age, duration and severity. It is thought that approximately 15% of asthmatic patients who have not been challenged with aspirin and NSAIDs also probably have intolerance. It is, therefore, estimated that approximately 10% to 20% of individuals with asthma have aspirin and NSAID intolerance.^{1,2}

The role of aspirin and NSAIDs in asthma, rhinitis, nasal polyps, and eosinophilia is not well defined. It has been suggested that understanding the pathogenesis of aspirin sensitivity will help us understand these conditions. It has also been suggested that the pathogenesis of aspirin and NSAID intolerance involves augmentation of the production of cysteinyl leukotrienes (LTs) such as LTC₄, LTD₄, and LTE₄ or the overexpression of the cysLT receptor on inflammatory cells in the respiratory tract.^{1,3}

Genetic and environmental factors are involved in aspirin and NSAID intolerance. Potential genetic biomarkers include HLA-DPB1*301, LTC₄ synthase, ALOX5, cysLT, PGE2, TBXA2R, TBX21, MS4A2, IL10-1082A>G, ACE-262 A>T, and CRTH2-466^>C together with the 4-locus single nucleotide polymorphism (SNP) set B2ADR 46A>G, CCR3-520T>G, cysLTR1-634C >, and FCER1B-109T.C.³ A recent study⁴ has suggested an association of tumor necrosis factor α genetic polymorphism with HLA DPB1*0301, a combined effect of interleukin 10 and transforming growth

factor β 1 promoter polymorphism, as a risk factor for aspirin sensitivity in asthma and rhinosinusitis⁵ and that *IDO* and *IL1R2* represent sensitivity genes of aspirin intolerance.⁶ In the October issue of the *Annals*, Lee et al. noted that the *UBE3C* gene on chromosome 7 is a member of the enzyme known as E3 ligase and is implicated in the ubiquitin proteasome pathway. This pathway is involved in immune responses to inflammation, including asthma. They investigated whether the *UBE3C* polymorphisms are associated with the risk of aspirin-induced asthma (AIA). They looked at 24 genetic variants of *UBE3C* by means of genotyping in 163 patients with AIA and 429 ATA controls. They found that the polymorphic markers rs3802122 and rs6979947 were significantly associated with the risk of AIA.⁷

It is apparent that further studies to evaluate the genetics of aspirin and NSAID intolerance should include microarray studies and integrative genomic, comparative genomic, and genome-wide association studies. Genome-wide association studies have revolutionized the search for genetic influences on complicated traits such as aspirin-sensitive asthma. This involves using hundreds of thousands of SNPs, which are tested for association with a disease in hundreds or thousands of persons.⁸ Aspirin-sensitive asthma is probably caused by many genetic and environmental factors working together, each having a relatively small effect and few, if any, being absolutely required for the disease to occur. Few of the SNPs identified in genome-wide association studies have clear functional implications that are relevant to mechanism of disease. The finding of a locus to a single variant that directly causes susceptibility to disease by disrupting the expression or function of a protein has been elusive to date. The most reliable evidence of a true genetic association, short of defining the causal variant functionally, is replication of the association, especially if it appears in multiple populations. Nearly 600 genome-wide association studies covering 150 distinct diseases and traits have been published to date.⁸ Asthma has shown positive findings.^{9,10} None, to date, have found factors regarding aspirin sensitivity. Much more remains to be learned about how variations in intrinsic and interagency regions affect gene expression, protein coding, and disease phenotypes. In addition, continued efforts are needed to identify genetic variants that affect the response to drugs. Multiple factors, genetic and environmental, play a role in the ultimate clinical picture of AIA and ATA. Many more studies are needed to use this information on a clinical level.

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Guest editorial

Persistent severe asthma and aging: step-up therapy with omalizumab to improve control

As the number of deaths from asthma in the United States has declined from a peak of 5,627 in 1995 to 3,447 in 2007,¹ there is controversy about how to achieve and maintain effective control of this very complex disease.^{2–4} The management of some patients with asthma can require a high level of clinical acumen. Patients differ in their recognition of or lack of perception of underlying airway obstruction and dynamic hyperinflation. There are different phenotypes, changing levels of severity and extent of control across time, and variable responses to therapy.⁵ It is clear that many patients have not reached acceptable levels of control despite monotherapy with an inhaled corticosteroid or combination therapy with an inhaled corticosteroid/long-acting β_2 -adrenergic agonist with or without a leukotriene modifier.^{6,7} For the physician or health care professional managing a patient with persistent asthma, the most important goal is to prevent death, and next is to eliminate or reduce the number of severe exacerbations of asthma while recommending therapies that provide sufficient benefit and little or no harm to patients. The assessment of severity and control of asthma includes attention to current

impairment and risk.⁸ According to the National Asthma Education and Prevention Program Expert Panel Report 3,⁸ the dimension of risk includes (1) preventing or minimizing future exacerbations of asthma, emergency department visits, and hospitalizations; (2) preventing excessive loss of lung function, such as forced expiratory volume in 1 second or not achieving normal lung growth in children; and (3) trying to avoid adverse effects from medications.

In 2006 in the United States, there were approximately 444,000 hospitalizations for asthma (ICD code 493) or at least where asthma was listed first as a discharge diagnosis.⁹ The average length of hospital stay was 3.2 days for asthma, but this number increased with age, being 2.2 days in children 15 years or younger, 3.8 days in adults aged 45 to 64 years, and 4.5 days in adults 65 years and older.⁹ For comparison, the average length of stay for congestive heart failure was 5.1 days and for acute myocardial infarction was 6.1 days. Although the number of fatalities from asthma has declined, approximately 75% of the deceased were 45 years and older.^{1,9} Thus, prevention of severe exacerbations, hospitalizations, and deaths remains an important target for improved control of asthma.

In this issue of the *Annals*, in a 6-month observational study of adults with uncontrolled, persistent severe asthma, step-up therapy with omalizumab was evaluated with consideration of effectiveness (reduction in exacerbations), harm (adverse effects), and discontinuation of therapy to explore whether the benefit-harm relationship was favorable in patients 50 years and older.¹⁰ The data were generated from 2

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