

The HLA-DPB1*0301 marker might predict the requirement for leukotriene receptor antagonist in patients with aspirin-intolerant asthma

To the Editor:

Aspirin-intolerant asthma (AIA) affects 10% to 20% of adult asthmatic patients and is characterized by aspirin hypersensitivity, bronchial asthma, and chronic rhinosinusitis, often with nasal polyposis.¹ Patients with AIA ingesting aspirin or other cyclooxygenase inhibitors might experience life-threatening asthma exacerbations. The pathogenic mechanisms are not fully understood, but a possible involvement of the HLA genotype DPB1*0301 was suggested in small populations of white and Asian patients with AIA.^{2,3} It has been reported that leukotriene receptor antagonists (LTRAs) are effective for symptom control in patients with AIA, but clinical responses show marked interindividual variation.^{4,5} This study aimed to assess the association of the clinical requirement for LTRA therapy over 1 year in a large group of patients with HLA-DRB1, HLA-DQB1, and HLA-DPB1 genotypes analyzed by means of high-resolution genotyping.

Seventy-one South Korean patients (30 male patients) with mild-to-moderate persistent asthma (90% moderate persistent type) were enrolled with a clinical history of AIA and showing a positive response (decrease in FEV₁ of >20%) to a lysine-aspirin bronchoprovocation test, as previously described.² Twenty-eight (39.4%) patients were atopic. In accordance with the Global Initiative for Asthma guidelines (2002), the asthma control state was defined as "control of the disease with minimal asthmatic symptoms," with near-normal peak expiratory flow and less than 20% diurnal variability. The requirement for LTRA therapy to maintain the asthma control state was assessed as the mean aggregate dose of montelukast per month taken during the study period by each patient. The study protocol was as follows. All subjects received an inhaled glucocorticoid (budesonide, 800 µg/day) regularly with a short-acting β₂-agonist as required for 1 year. For the first 2 months, all subjects received oral montelukast (10 mg/day). If asthma symptom control was not achieved within this time, the patient stopped receiving montelukast, and other asthma medications were added to achieve control. Such subjects were defined as group III (montelukast requirement of <5 mg/month). The remaining patients with good control in the first 2 months continued receiving oral montelukast at the same dosage for the subsequent 4 months. At the end of this period, montelukast was withdrawn, and results were followed every week. Those patients whose asthma control decreased (worse asthmatic symptoms and changes in lung parameters: ≥20% peak expiratory flow rate variability or ≥10% decrease in FEV₁) within a month of withdrawal were again treated with oral montelukast at the same

TABLE I. Association between HLA-DPB1*0301 and LTRA requirement in 71 patients with AIA

HLA-DPB1*0301 status	LTRA requirement (mg/month)		
	≥200 (n = 28)	5-150 (n = 15)	<5 (n = 28)
Present	14 (50.0%)	2 (13.3%)	4 (14.3%)
Absent	14 (50.0%)	13 (86.7%)	24 (85.7%)

* $P = .004$ (χ^2 test).

TABLE II. Clinical characteristics of the 71 patients with AIA

	DPB1*0301 ⁺	DPB1*0301 ⁻	P value
No.	20	51	
Age (y)	44.9 ± 15.4	45.2 ± 13.3	NS
Sex (M/F)	7/13	23/28	NS
Atopy	8 (40.0%)	20 (40%)	NS
Asthma duration (y)	6.1 ± 6.6	6.9 ± 6.2	NS
FEV ₁ (%)	76.4 ± 18.9	84.0 ± 23.3	NS
PC ₂₀ (mg/mL)	6.2 ± 9.7	4.1 ± 8.0	NS
Blood eosinophil count (/µL)	413.1 ± 400.2	380.0 ± 337.8	NS
Rhinosinusitis	18 (90.0%)	43 (84.3%)	NS
Nasal polyposis	13 (65.0%)	22 (43.1%)	NS

dosage to achieve best asthma control until the end of the 1-year study (group I, montelukast requirement of ≥200 mg/month). The remainder, whose asthma control was maintained after montelukast withdrawal, were defined as group II (montelukast requirement of 5-150 mg/month). All the study subjects gave their informed consent to the study, which was approved by the ethical committee of Ajou University Hospital, Suwon, Korea. High-resolution genotyping for HLA markers was performed as previously described² by using the amplified gene product of locus-specific primers and direct sequencing with the ABI 3100 Genetic Analyzer (Applied Biosystems, Foster City, Calif). Genotype prevalence and clinical characteristics were compared between groups by using χ^2 and Student *t* tests. A *P* value of less than .05 was regarded as significant.

The HLA-DPB1*0301 genotype was present in 14 (prevalence, 50%) of 28 patients in group I but in only 2 (13.3%) of 15 in group II and only 4 (14.3%) of 28 in group III (Table I). This association between the presence of HLA-DPB1*0301 and LTRA requirement was highly significant ($P = .004$), whereas no associations were found with other HLA alleles or with sex or atopic status. When all 71 patients with AIA were stratified with respect to the DPB1*0301 genotype, the subgroup of 20 patients with positive results for DPB1*0301 tended to have lower

FEV₁ values (76% vs 84%), a lower proportion of male subjects (54% vs 82%), and a higher prevalence of rhinosinusitis and nasal polyposis than the 51 negative subjects, but these trends did not reach statistical significance ($P > .05$, Table II).

Previous studies have linked short-term clinical responsiveness to LTRA therapy in patients with mild-to-moderate asthma,^{6,7} with genetic polymorphism in the terminal enzyme for cysteinyl-leukotriene synthesis, leukotriene C₄ synthase (-444A/C), although other studies have showed negative results.⁸ To the best of our knowledge, our data are the first to demonstrate a significant association between LTRA responsiveness and an HLA allele in the long-term management of patients with AIA. The study was performed in a real-life setting of the chronic management of AIA within a Korean population. The lack of significant differences between the DPB1*0301-positive and DPB1*0301-negative groups in a range of characteristics, including age, sex, clinical history, duration of asthma, atopic status, spirometry, and methacholine responsiveness, reinforces the difficulty of identifying those patients with AIA most likely to benefit clinically from LTRA therapy. Our data might enable such predictions, as well as providing clues to the pathogenesis of AIA.

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Primary care physicians' approach to food-induced anaphylaxis: A survey

To the Editor:

Food-induced anaphylaxis is the most common cause of anaphylaxis outside of the hospital, and a trend for the increasing incidence of this cause of anaphylaxis has been recently reported. Severe anaphylaxis may occur without skin symptoms, and specific symptoms may mimic those observed in related allergic (asthma) and non-allergic (choking and myocardial infarction) disorders, making diagnosis challenging.¹⁻³ In addition, although there may be some debate on treatment approaches, it is recognized that prompt intervention with epinephrine is an important cornerstone of therapy for severe reactions. In regard to potential confusion in diagnosis and management, there is only 1 article describing the approach of physicians to anaphylaxis in the emergency room setting.⁴ Here we report the results of a survey regarding diagnosis and management of food-induced anaphylaxis that was administered to medical staff at Mount Sinai Medical Center, New York.

An anonymous survey, approved by the Mount Sinai Institutional Review Board, was distributed to participants at pediatric and internal medicine grand rounds conferences when the lecture topic was unrelated to allergy. The participants were presented with a case (adjusted for the pediatric or internal medicine audience) of a patient allergic to peanuts who was experiencing peanut-induced anaphylaxis. A total of 121 audience members completed the survey (response rate of 52%), but 8 medical students were excluded. Of the remaining 113 participants, 66 were attending physicians and 47 were residents and fellows; 61 participants were from pediatrics departments, and 52 participants were from internal medicine departments.

The questions and responses are shown in Table I. The majority (72%) of the participants recognized this case as food-induced anaphylaxis and recommended treatment with epinephrine; however, it is remarkable that half selected the incorrect concentration (1:10,000) and the subcutaneous route of administration less likely to result in optimal absorption.^{5,6} Residents and fellows were more likely than attending physicians to identify this case as