

Should HLA-B*5701 Screening Be Performed in Every Ethnic Group before Starting Abacavir?

Wan Beom Park,¹ Pyoeng Gyun Choe,¹ Kyoung-Ho Song,¹ Shinwon Lee,¹ Hee-Chang Jang,¹ Jae Hyun Jeon,¹ Sang-Won Park,¹ Myoung Hee Park,² Myoung-don Oh,¹ and Kang Won Choe¹

Departments of ¹Internal Medicine and ²Laboratory Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea

Human leukocyte antigen allele (HLA)-B*5701 is associated with abacavir hypersensitivity. However, the carriage rate of HLA-B*5701 has rarely been studied in Asians. In 534 Korean patients with human immunodeficiency virus infection, HLA-B*5701 status was determined by polymerase chain reaction with HLA-B*5701-specific primers. No patients had the HLA-B*5701 allele (95% confidence interval, 0%–0.7%). This explains the paucity of immunologically confirmed cases of abacavir hypersensitivity in Koreans.

Hypersensitivity reaction is a major adverse effect of the nucleoside reverse-transcriptase inhibitor abacavir, which has activity against HIV. Because screening for HLA-B*5701 is known to identify patients who are at risk of hypersensitivity to abacavir [1, 2], recent guidelines strongly recommend screening for HLA-B*5701 before starting patients on an abacavir-containing regimen [3]. However, the carriage rate of HLA-B*5701 has rarely been studied in Asians [4], although the prevalence of HLA-B*5701 differs in different ethnic groups [5]. We evaluated the frequency of the HLA-B*5701 allele and the effect of HLA-B*5701 screening on the prevalence of abacavir hypersensitivity in Korean patients with HIV infection.

Methods. In 534 Korean patients with HIV infection who had available blood samples, the presence of HLA-B*5701 was determined by multiplexed PCR with HLA-B*5701-specific primers described elsewhere [6]. In brief, genomic DNA samples were extracted from whole-blood specimens with use of

AccuPower Genomic DNA Extraction Kit (Bioneer). The sequence of HLA-B*5701 sequence-specific primers include primer 1F (5'-GTCTCACATCATCCAGGT-3'), primer 2R (5'-ATCCTTGCCGTCGTAGGCCG-3'), primer 3R (5'-ATCCTTGCCGTCGTAGGCCAG-3'), and primer 4R (5'-CGCCTCCCACT-TGCGCTGGG-3'). Housekeeping primer 5F HGH-I (5'-CAG-TGCCCTTCCCAACCATTCCCTTA-3') and primer 6R HGH-II (5'-ATCCACTCACGGATTTCTGTTGTGTTTC-3') were also included. DNA samples from donors who had HLA-B*5701 and HLA-B*5801 status confirmed to be positive by sequence-based typing were used as positive and negative controls, respectively. The PCR products that were amplified in touch-down amplification-cycling conditions were electrophoresed on a 2% agarose gel.

The prevalence of clinically suspected abacavir hypersensitivity was investigated in all Korean patients with HIV infection who received abacavir therapy at Seoul National University Hospital (Seoul, Republic of Korea) from September 2003 through April 2008. Because the routine screening test for HLA-B*5701 was not performed at Seoul National University Hospital until October 2007, HLA-B*5701 was tested after the beginning of abacavir therapy for the patients who had started receiving abacavir before October 2007.

Clinically suspected abacavir hypersensitivity was defined as occurrences of ≥ 2 of the following symptoms within 6 weeks after starting abacavir treatment: fever, rash, or gastrointestinal, constitutional, or respiratory symptoms that disappeared within 3 days after discontinuing abacavir treatment and that could not be explained by other causes. A skin patch test was performed, as described elsewhere [7], for patients with suspected cases of abacavir hypersensitivity, for which patients provided consent. All patches were taken off after 48 h, and reading was performed at 48 h and 72 h by 1 investigator who was unaware of HLA-B*5701 status.

The study was approved by the Seoul National University Hospital Institutional Review Board. Continuous variables were compared using the Student's *t* test, and categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. A *P* value $< .05$ was considered to be statistically significant. Statistical analyses were performed with SPSS software, version 12.0 (SPSS).

Results. Of 534 Korean patients with HIV infection for whom the HLA-B*5701 test was performed, none had an HLA-B*5701 allele (95% CI, 0%–0.69%). An abacavir-containing regimen was administered to 150 patients during the study period. Of these, 57 (38%) received abacavir without the HLA-

Received 23 August 2008; accepted 7 October 2008; electronically published 30 December 2008.

Reprints or correspondence: Dr. Myoung-don Oh, Dept. of Internal Medicine, Seoul National University College of Medicine, 28 Yeongeong-dong, Jongno-gu, Seoul, Republic of Korea 110-744 (mdohmd@snu.ac.kr).

Clinical Infectious Diseases 2009;48:365–7

© 2008 by the Infectious Diseases Society of America. All rights reserved.

1058-4838/2009/4803-0015\$15.00

DOI: 10.1086/595890

B*5701 screening test, and 93 (62%) received abacavir after the HLA-B*5701 screening test. The HLA-B*5701 allele was not found in any of these patients.

The median age of the 150 patients was 43 years (interquartile range, 35–51 years); 141 (94%) were male, and 17 (11%) were antiretroviral-naïve patients. When abacavir treatment was started, the median CD4 cell count was 441 cells/mm³ (interquartile range, 236–630 cells/mm³), and 79 (53%) had undetectable HIV titers. A new protease inhibitor was concurrently introduced in treatment of 41 patients (27%), a new nonnucleoside reverse-transcriptase inhibitor (NNRTI) was introduced in 8 patients (5%), and neither was introduced in 101 patients (67%). There were no statistically significant differences in age, sex, CD4 cell count, HIV suppression, and the introduction of a new NNRTI between patients who did or did not have screening, although introduction of a new protease inhibitor was more frequent in patients who were not screened than in those who were screened for HLA-B*5701 (44% vs. 17%; $P < .001$) (table 1).

Fifteen patients (10%) discontinued abacavir treatment within 6 weeks after starting therapy with the drug. Seven (5%) of 150 patients, including 3 (5%) of 57 patients who did not have HLA-B*5701 screening and 4 (4%) of 93 patients who did have HLA-B*5701 screening, met the criteria for clinically suspected abacavir hypersensitivity. There was no statistically significant difference in the prevalence of clinically suspected abacavir hypersensitivity between patients who had and had not been screened for HLA-B*5701 ($P > .999$).

The most common symptom in 7 patients with clinically

suspected abacavir hypersensitivity was fever (6 patients [86%]), followed by constitutional symptoms (4 [57%]), rash (3 [43%]), gastrointestinal symptoms (3 [43%]), and respiratory symptoms (2 [29%]). In all cases, time to onset of symptoms was <21 days after initiating abacavir therapy, and there was no patient with a severe presentation that required hospitalization. The skin patch test results were all negative in 7 patients with clinically suspected abacavir hypersensitivity. The median interval between a suspected hypersensitivity reaction and patch test was 4 months (range, 2–48 months). There were no cases with doubtful (i.e., faint erythema) or weak-positive reactions.

Discussion. The present study demonstrated that HLA-B*5701 was significantly less common (0%; 95% CI, 0%–0.7%) in HIV-infected Koreans than in US Caucasians (6%–8%) and African Americans (2.5%) [5]. The low frequency of HLA-B*5701 in HIV-infected Koreans is consistent with the results from healthy Koreans (gene frequency of HLA-B*5701, 0.2%–0.3%) [8, 9]. The previous studies reported that East Asians, including Taiwanese, Japanese, Chinese, and Koreans, have a similarly low prevalence of HLA-B*5701. Sun et al. [4] reported that only 1 (0.3%) of 320 Taiwanese patients with HIV infection expressed HLA-B*5701, and Saito et al. [10] showed that none of 371 Japanese expressed HLA-B*5701. The allele frequency of HLA-B*5701 in Chinese patients was reported to be 0%–2% in various ethnic groups [5]. It was 0.003% in Hong Kong Chinese patients (572 patients) and 0% in Singapore Chinese patients (149 patients) [11].

However, some Asians in selected areas other than East Asia

Table 1. Abacavir hypersensitivity in 150 Korean patients with HIV-1 infection, by availability of the HLA-B*5701 screening test.

Variable	HLA-B*5701 test		P
	Unavailable (n = 57)	Available (n = 93)	
Age, median years (IQR)	45 (40–52)	41 (35–51)	.144
Male sex	53 (93)	88 (95)	.731
CD4 cell count, median cells/mm ³ (IQR)	481 (214–710)	420 (245–602)	.483
Undetectable viral load	29 (51)	50 (54)	.731
Concurrent introduction			
New NNRTI	5 (9)	3 (3)	.260
New PI	25 (44)	16 (17)	<.001
HLA-B*5701 carrier ^a	0 (0)	0 (0)	ND
Abacavir discontinuation within 6 weeks	8 (14)	7 (8)	.197
Abacavir hypersensitivity reaction			
Clinically suspected ^b	3 (5)	4 (4)	>.999
Immunologically confirmed ^c	0 (0)	0 (0)	ND

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range; ND, not done; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

^a None of 534 Korean patients with HIV infection, including these 150 patients, had HLA-B*5701.

^b Occurrences of ≥ 2 of the following: fever, rash, or gastrointestinal, constitutional, or respiratory symptoms.

^c Determined by the skin patch test.

showed relatively high carriage rates of HLA-B*5701. For example, the prevalence of HLA-B*5701 is 5%–20% in selected Asian Indian populations and 4%–10% among Thais [5].

The prevalence of suspected abacavir hypersensitivity was 9%–10% in Caucasians not routinely screened for HLA-B*5701 [1, 12]. In Korean patients with HIV infection, clinically suspected abacavir hypersensitivity was relatively low (5%), even in patients not screened for HLA-B*5701, which was comparable to that in Caucasians (4%) who were prospectively screened for HLA-B*5701 [1]. In addition, because there was no patient with a positive skin patch test result in this study, true cases of abacavir hypersensitivity seem to be rare among Koreans, which is compatible with a very low frequency of HLA-B*5701 in this population [9].

HLA-B*5701 screening is supposed to be useful even in countries with a low prevalence of HLA-B*5701, because it may reduce clinical overdiagnosis of abacavir hypersensitivity reactions. However, in the present study, HLA-B*5701 screening did not significantly decrease the prevalence of clinical diagnosis of abacavir hypersensitivity. A negative HLA-B*5701 test result cannot absolutely rule out abacavir hypersensitivity, because an immunologically confirmed case of abacavir hypersensitivity in patients without HLA-B*5701 was reported [13]. A physician in clinical practice will decide to discontinue abacavir treatment if hypersensitivity is clinically suspected, even for patients who test negative for HLA-B*5701. This may be why the prevalence of clinically suspected abacavir hypersensitivity in this study did not decrease after HLA-B*5701 screening was introduced.

Our findings suggest that the HLA-B*5701 test may not be cost-effective as a screening test in regions like Korea, which has a low carriage rate of HLA-B*5701. Instead, clinical observation could replace the HLA-B*5701 screening test, especially in a resource-limited health care setting. In that case, the skin patch test could be used to retrospectively confirm abacavir hypersensitivity in patients who are clinically suspected of or whose symptoms are ambiguous with regard to abacavir hypersensitivity.

This study has some limitations. First, the patient population may not have been large enough to determine differences in the prevalence of abacavir hypersensitivity between patients who did and did not undergo HLA-B*5701 screening. Second, the concurrent introduction of other medications or medical conditions could influence the clinical diagnosis of abacavir hypersensitivity [1]. An NNRTI was concurrently administered with abacavir to 5 patients (9%) who did not undergo the HLA-B*5701 screening test and to 3 patients (3%) who did

undergo the HLA-B*5701 screening test. This infrequent use of NNRTIs might have contributed to the low incidence of clinically suspected hypersensitivity reaction in our study, especially NNRTI-associated skin rash.

In summary, HLA-B*5701 is very rare in Korean patients with HIV infection, and that explains the paucity of immunologically confirmed abacavir hypersensitivity in this study. These findings suggest that the HLA-B*5701 test may be less useful as a screening test for abacavir hypersensitivity in Asians, who have a low prevalence of HLA-B*5701.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

References

1. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med* **2008**; 358:568–79.
2. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-B*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis* **2008**; 46: 1111–8.
3. Panel on Antiretroviral Guidelines for Adult and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents, November 2008. Department of Health and Human Services. Available at: <http://www.aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>. Accessed 14 December 2008.
4. Sun HY, Hung CC, Lin PH, et al. Incidence of abacavir hypersensitivity and its relationship with HLA-B*5701 in HIV-infected patients in Taiwan. *J Antimicrob Chemother* **2007**; 60:599–604.
5. Phillips EJ. Genetic screening to prevent abacavir hypersensitivity reaction: are we there yet? *Clin Infect Dis* **2006**; 43:103–5.
6. Martin AM, Nolan D, Mallal S. HLA-B*5701 typing by sequence-specific amplification: validation and comparison with sequence-based typing. *Tissue Antigens* **2005**; 65:571–4.
7. Phillips EJ, Sullivan JR, Knowles SR, Shear NH. Utility of patch testing in patients with hypersensitivity syndromes associated with abacavir. *AIDS* **2002**; 16:2223–5.
8. Park MH, Kim HS, Kang SJ. HLA-A, -B, -DRB1 allele and haplotype frequencies in 510 Koreans. *Tissue Antigens* **1999**; 53:386–90.
9. Lee KW, Oh DH, Lee C, Yang SY. Allelic and haplotypic diversity of HLA-A, -B, -C, -DRB1, and -DQB1 genes in the Korean population. *Tissue Antigens* **2005**; 65:437–47.
10. Saito S, Ota S, Yamada E, Inoko H, Ota M. Allele frequencies and haplotypic associations defined by allelic DNA typing at HLA class I and class II loci in the Japanese population. *Tissue Antigens* **2000**; 56: 522–9.
11. Middleton D, Hawkins BR, Williams F, et al. HLA class I allele distribution of a Hong Kong Chinese population based on high-resolution PCR-SSOP typing. *Tissue Antigens* **2004**; 63:555–61.
12. Rauch A, Nolan D, Martin A, McKinnon E, Almeida C, Mallal S. Prospective genetic screening decreases the incidence of abacavir hypersensitivity reactions in the Western Australian HIV cohort study. *Clin Infect Dis* **2006**; 43:99–102.
13. Waters LJ, Mandalia S, Gazzard B, Nelson M. Prospective HLA-B*5701 screening and abacavir hypersensitivity: a single centre experience. *AIDS* **2007**; 21:2533–4.