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Prevalence of Human Leukocyte Antigen-B*5701 Among HIV-infected Children in Thailand and Cambodia: Implications for Abacavir Use

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Abstract

Human leukocyte antigen (HLA)-B*5701 allele is associated with abacavir hypersensitivity. Limited data among Asians showed lower rates of HLA-B*5701 compared with Caucasians. In 296 children with HIV in Thailand and Cambodia, the prevalence of HLA-B*5701 was 4.0% (95% confidence interval: 1.6–8.0%) among Thai and 3.4% (95% confidence interval: 0.9–8.5%) among Cambodian children. HLA-B*5701 carriage is not uncommon among Thai and Cambodian children; it is close to the prevalence found in European and higher than the prevalence found in East Asian and African studies.

Keywords

HIV; human leukocyte antigen-B*5701; abacavir hypersensitivity

Abacavir is a nucleoside reverse transcriptase inhibitor with activity against HIV. It has excellent efficacy and a favorable long-term toxicity profile.¹ There has been increasing demand for abacavir in first-line and second-line treatment of HIV-infected children in Asia. Abacavir may be preferred to stavudine or zidovudine as part of a nucleoside reverse transcriptase inhibitor backbone in first-line regimens due to its minimal mitochondrial toxicity and lipodystrophy.² It is also frequently recommended as part of second-line

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treatment regimens. A key adverse effect of abacavir that limits its use is an immunologically mediated hypersensitivity reaction affecting 5–8% of patients during the first 6 weeks of treatment.³ Abacavir hypersensitivity is strongly associated with the human leukocyte antigen (HLA)-B*5701 allele.^{4,5} HLA-B*5701 screening is recommended before initiating abacavir to reduce the risk of hypersensitivity reaction.⁶ A study among HIV-infected patients in the United Kingdom showed differences by race. Among Caucasians, the prevalence was 7.93% (95% confidence interval [CI]: 5.80–10.06%), whereas among Africans, the prevalence was only 0.26% (95% CI: 0.07–0.94%).⁷ The reported prevalence of HLA-B*5701 in East Asian populations was lower than 0.5% among Koreans⁸ and Taiwanese.⁹ We evaluated the frequency of the HLA-B*5701 allele and report the prevalence of abacavir hypersensitivity in HIV-infected Thai and Cambodian children.

MATERIAL AND METHODS

This is a substudy of the Pediatric Randomised Early versus Deferred Initiation in Cambodia and Thailand (PREDICT) study study, a randomized study of early versus deferred antiretroviral therapy initiation in children aged 1–12 years in Thailand and Cambodia (NCT 00234091).¹⁰ The first-line antiretroviral regimen was zidovudine, lamivudine and nevirapine. Abacavir was used in children with adverse events from zidovudine or used as part of second-line regimen. Clinically suspected abacavir hypersensitivity was defined as occurrences of >2 of the following 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.

HLA typing was performed retrospectively from the stored blood samples at the end of the study. High molecular weight genomic DNA was extracted from the peripheral mononuclear cell using QIAGEN kit (Qiagen, Valencia, CA). The concentration of extracted DNA samples was determined by spectrophotometry and stored at –20°C before HLA typing. The HLA-B with 4-digit specificities was determined using Hiseq single-end sequencing of the amplicon/high-resolution technique by Beijing Genomic Institute-Hong Kong Co., Limited, Shenzhen, China.

The study was approved by the Institutional Review Board of all participating sites. The proportion of children who carried HLA-B*5701 and 95% CI was calculated. Statistical analysis was performed using Stata version 11 (StataCorp, College Station, TX).

RESULTS

There were 296 HIV-infected children in this substudy. The median (interquartile range) age was 6 (4–8) years, 42% were male, 177 (60%) were Thai and 119 (40%) were Cambodian. HLA-B*5701 allele was present in 11 children (3.7%, 95% CI: 1.9–6.6%). The prevalence of HLA-B*5701 was 4.0% (95% CI: 1.6–8.0%) among Thai and 3.4% (95% CI: 0.9–8.5%) among Cambodian children.

An abacavir-containing regimen was administered to 30 patients during the study period. The HLA status was performed retrospectively after study had ended; therefore, HLA status was not known at the time of abacavir initiation. However, none of 30 children who received abacavir carried HLA-B*5701. One child (3.3%; 95% CI: 0.8–17.2%) developed clinically suspected abacavir hypersensitivity. Abacavir had been substituted for zidovudine in his antiretroviral regimen because he developed anemia after using a zidovudine-containing regimen for 7 weeks. On day 3 of abacavir administration, he developed high-grade fever, sore throat and cough (but no rash or no myalgia) leading to drug discontinuation due to

clinically suspected hypersensitivity. Symptoms resolved within 3 days. He was subsequently found to have HLA-B*5701 and HLA-B*1801, but not HLA-B*5701.

DISCUSSION

This is the first report of HLA-B*5701 frequency in HIV-infected children in Thailand and Cambodia. The prevalence of 3.4–4.0% is lower than that in Caucasians,⁷ but higher than that reported in East Asians (including Koreans, Taiwanese and Japanese). Park et al reported that none of 534 Korean patients carried HLA-B*5701.⁸ Sun et al found only 1 (0.3%) HLA-B*5701 carrier of 320 Taiwanese patients.⁹ Saito et al showed that none among 371 Japanese patients carried HLA-B*5701.¹¹ The previous report from 49 Thai adults showed that HLA-B*5701 allele was found in 3.1% of study population.¹²

The purpose of prospective HLA-B*5701 screening is to identify patients at greatest risk of abacavir hypersensitivity than to predict which patients will definitely develop a hypersensitivity reaction. A double-blinded study to determine the benefit of screening HLA-B*5701 before treatment with abacavir to reduce the incidence of hypersensitivity reaction found that 39% of patients who had HLA-B*5701 tolerated abacavir during the 6-week observation period without evidence of hypersensitivity reaction. However, the negative predictive value of HLA-B*5701 for patch test-positive abacavir hypersensitivity was found to be 100%.⁶ Screening for HLA-B*5701 has been found to be cost effective in developed countries.^{13,14} One of the obstacles for screening for HLA-B*5701 in developing countries is laboratory cost. Low cost techniques, such as polymerase chain reaction sequence-specific primer-based genotyping, may make screening feasible in resource-limited settings.¹⁵ Whether or not HLA-B*5701 screening has been performed, clinical training on early detection of the clinical symptoms of abacavir hypersensitivity, especially in the first 6 weeks of treatment, should be emphasized. Abacavir should be immediately discontinued in any patient who develops clinical signs and symptoms consistent with hypersensitivity and rechallenge is contraindicated.

This study has some limitations. First, there were only 30 patients who actually received abacavir, which is too small to determine the actual rate of clinically diagnosed abacavir hypersensitivity in Thai and Cambodian children. Furthermore, none of them carried HLA-B*5701. Second, we did not perform epicutaneous patch testing in the patient with clinically diagnosed abacavir hypersensitivity; therefore, we could not confirm whether he had immunologically confirmed hypersensitivity.

This study suggests that carriage of HLA-B*5701 is not uncommon among Thai and Cambodian children. Early detection of abacavir hypersensitivity reaction through close clinical monitoring remains important whether or not HLA-B*5701 screening has been performed.

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References

1. Green H, Gibb DM, Walker AS, et al. Paediatric European Network for the Treatment of AIDS (PENTA). Lamivudine/abacavir maintains virological superiority over zidovudine/lamivudine and zidovudine/abacavir beyond 5 years in children. *AIDS*. 2007; 21:947–955. [PubMed: 17457088]
2. Welch S, Sharland M, Lyall EG, et al. PENTA Steering Committee. PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. *HIV Med*. 2009; 10:591–613. [PubMed: 19878352]
3. Hetherington S, McGuirk S, Powell G, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. *Clin Ther*. 2001; 23:1603–1614. [PubMed: 11726000]
4. Phillips EJ, Wong GA, Kaul R, et al. Clinical and immunogenetic correlates of abacavir hypersensitivity. *AIDS*. 2005; 19:979–981. [PubMed: 15905681]
5. Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet*. 2002; 359:1121–1122. [PubMed: 11943262]
6. Mallal S, Phillips E, Carosi G, et al. PREDICT-1 Study Team. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008; 358:568–579. [PubMed: 18256392]
7. Orkin C, Sadiq ST, Rice L, et al. UK EPI team. Prospective epidemiological study of the prevalence of human leukocyte antigen (HLA)-B*5701 in HIV-1-infected UK subjects. *HIV Med*. 2010; 11:187–192. [PubMed: 19780860]
8. Park WB, Choe PG, Song KH, et al. Should HLA-B*5701 screening be performed in every ethnic group before starting abacavir? *Clin Infect Dis*. 2009; 48:365–367. [PubMed: 19115972]
9. 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. [PubMed: 17631508]
10. Puthanakit T, Vonthanak S, Ananworanich J, et al. on behalf of the PREDICT Study Group. Early versus deferred antiretroviral therapy for HIV-infected children older than one year of age: PREDICT--a randomised study. *Lancet Infect Dis*. 2012 Oct 8. Epub ahead of print.
11. Saito S, Ota S, Yamada E, et al. 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; 56:522–529. [PubMed: 11169242]
12. Pimthanotai N, Charoenwongse P, Mutirangura A, et al. Distribution of HLA-B alleles in nasopharyngeal carcinoma patients and normal controls in Thailand. *Tissue Antigens*. 2002; 59:223–225. [PubMed: 12074714]
13. Kauf TL, Farkouh RA, Earnshaw SR, et al. Economic efficiency of genetic screening to inform the use of abacavir sulfate in the treatment of HIV. *Pharmacoeconomics*. 2010; 28:1025–1039. [PubMed: 20575592]
14. Wolf E, Blankenburg M, Bogner JR, et al. Cost impact of prospective HLA-B*5701-screening prior to abacavir/lamivudine fixed dose combination use in Germany. *Eur J Med Res*. 2010; 15:145–151. [PubMed: 20554495]
15. Dello Russo C, Lisi L, Lofaro A, et al. Novel sensitive, specific and rapid pharmacogenomic test for the prediction of abacavir hypersensitivity reaction: HLA-B*57:01 detection by real-time PCR. *Pharmacogenomics*. 2011; 12:567–576. [PubMed: 21521028]