

HLA- B*5701 Allele in HIV-infected Indian Children and its Association with Abacavir Hypersensitivity

MAMTA V MANGLANI, YASHWANT R GABHALE, MAMATHA M LALA, ROHINI SEKHAH AND DIPTI MORE

From Pediatric Centre of Excellence for HIV Care (PCoE), Department of Pediatrics, Lokmanya Tilak Municipal Medical College and General Hospital, Sion, Mumbai, India.

Correspondence to: Dr. Yashwant R. Gabhale, Deputy Program Director, Pediatric Centre of Excellence for HIV Care (PCoE), Lokmanya Tilak Municipal Medical College and General Hospital, Sion, Mumbai-22, India. dryashg@rediffmail.com
Received: August 08, 2016;
Initial review: November 30, 2016;
Accepted: November 06, 2017.

Objective: To determine the prevalence of HLA-B*5701 allele in HIV-infected children, and to find its association with Abacavir hypersensitivity. **Methods:** Children (2 to 18 y) already on, or to be initiated on Abacavir were included for PCR sequencing to detect HLA-B*5701. Outcome measures were: proportion with HLA B*5701 allele and hypersensitivity with Abacavir. Abacavir was stopped if patient tested positive for HLA-B*5701 allele. **Results:** 100 children (median age 11 y) were enrolled; 10 were already on Abacavir. HLA-B*5701 positivity was observed in 11 (11%) children. Two of these 11 children developed hypersensitivity after initiation of Abacavir. Abacavir was thereafter stopped in all who tested HLA-B*5701 positive, irrespective of the development of hypersensitivity reaction. **Conclusion:** HLA-B*5701 allele was present in 11 (11%) of HIV-infected children, of which two developed Abacavir hypersensitivity. None of the patients without the allele developed hypersensitivity.

Keywords: Antiretroviral drugs, Adverse effects, Genetics, HIV, Treatment.

Published online: December 14, 2017. PII:S097475591600099

Abacavir (ABC) is a potent nucleoside reverse transcriptase inhibitor, and is an integral part of antiretroviral therapy (ART). It has good efficacy, fewer drug interactions and a favorable long term toxicity profile. However, hypersensitivity is a recognized treatment-limiting toxicity with its prevalence of approximately 3.7% [1]. A significant association between ABC hypersensitivity and the presence of HLA-B*5701 allele has been established [2,3]. It is thought that a derivative of the Abacavir prodrug binds to an antigen-presenting cleft unique to HLA-B*5701, which explains why the drug does not cause a similar hypersensitivity syndrome in carriers of other HLA-B alleles [4,5]. The prevalence of HLA-B*5701 allele varies in different races, ranging from 2% to 20% [6,7]. Abacavir hypersensitivity and its association with the HLA-B*5701 allele has hardly been studied in the Indian population. The present study was conducted with the objective of determining the prevalence of HLA-B*5701 allele in HIV-infected children, and to find out any association with Abacavir hypersensitivity.

METHODS

This prospective study was conducted from June 2013 to May 2014 at the Pediatric Centre of Excellence (PCoE) for HIV Care, Lokmanya Tilak Municipal Medical College and General Hospital, Sion, Mumbai. Institutional Ethics Committee approval was obtained. The inclusion criteria

were HIV-infected children between 2 years to 18 years of age, already on Abacavir-based regimen or soon to be initiated on an Abacavir-based regimen. Children with a past history of skin allergy were excluded. A written informed consent of parents for children up to 12 years of age, and consent of parents as well as an assent for adolescents (>12 years) was obtained. History and examination findings were documented in a pre-designed case-record form. All children were subjected to HLA-B*5701-associated HCP5rs2395029 genotyping by PCR sequencing at a NABL accredited laboratory (Metropolis Labs) [8,9]. Patients were evaluated on a weekly basis for hypersensitivity reactions (fever, rash, nausea and vomiting). Reports were obtained within 1 to 2 weeks of collection of the sample. Abacavir was stopped in all cases of HLA-B*5701 allele positivity. The proportions were compared using chi square test or Fisher's exact test for expected cell counts. We used t-test for parametric data and Mann-Whitney test for non-parametric data.

RESULTS

A total of 100 children were enrolled during the study period. The median age was 11 years (range 2 to 18 y; 61 males). HLA-B*5701 was positive in 11/100 patients (11%). Abacavir was stopped in these children as soon as reports were available. Of these 11 children, 9 had received ABC for less than 6 weeks, and two for more than 6 weeks. Two of these 11 children developed hypersensitivity (one on 7th

WHAT THIS STUDY ADDS?

- HLA-B*5701 positivity prevalence of 11% was seen in HIV-infected children in our setting.

day and one on day 45 of ABC). The symptoms of reactions were fever and gastrointestinal intolerance in both, and respiratory distress in one child. Symptoms resolved in both these children after discontinuation of Abacavir. Abacavir was taken for a median (range) duration of 7 (3 - 15) days in those who were to be initiated on ABC and 88 (16 - 774) days in those who were already on ABC. Age ($P=0.25$), gender ($P=0.52$), baseline CD4 ($P=0.29$) and CD4 at enrolment ($P=0.912$) did not impact the presence of the allele, or hypersensitivity to ABC ($P=0.88$, 1.0, 0.48 and 0.81 for age, gender, baseline CD4 and CD4 at enrolment, respectively).

DISCUSSION

The present study demonstrated 11% prevalence of HLA B*5701 positivity among HIV-infected children at our center. Hypersensitivity to Abacavir, irrespective of the HLA-B*5701 allele, was found to be 2%. Those two out of eleven children positive for the allele had a hypersensitivity, whereas none of the children negative for the allele showed hypersensitivity reactions.

The presence of HLA-B*5701 allele and its impact on hypersensitivity to Abacavir has been well established in studies reported in literature [2,3,10-12]. However, a wide variation has been found in different ethnic groups with prevalence of the allele ranging from 2% to 3% in African-Americans to 20% in Asian population, with 5 to 8% in Caucasians, 4% among Thais and 3.4% in Cambodia [6,7]. Prevalence in our population is much higher than that of the African-Americans and Caucasians, and is more closer to data from the Asian population [6].

The limitation of our study was a small sample size and a short follow-up period of treatment with ABC (for less than 6 weeks) in 9 of the 11 children, who were positive for the allele, making it difficult to arrive at a true prevalence of hypersensitivity.

We conclude that HLA-B*5701 allele may be present in about one out of every ten Indian children and is associated with higher frequency of hypersensitivity. Larger studies from different settings with a longer duration of follow-up are required before recommendations about its routine screening are made.

Contributors: MM: conceptualized the study and critically revised the manuscript for intellectual content; YG, MML: supervised the management of patients, edited the manuscript, helped in clinical care of the patients, and performed the data analysis; DM, RS: managed the patient enrollment and follow-up,

and also helped in writing the manuscript. All authors approved the final version.

Funding: National AIDS Control Organization (NACO), Ministry of Health and Family Welfare, Government of India.

Competing interests: None stated.

REFERENCES

1. Hewitt RG. Abacavir hypersensitivity reaction. *Clin Infect Dis.* 2002;34:1137-42.
2. Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, *et al.* Association between presence of HLA-B*5701, HLA-DR7, HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet.* 2002;359:727-32.
3. Saag M, Balu R, Phillips E, Brachman P, Martorell C, Burman W, *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.
4. Chessman D, Kostenko L, Lethborg T, Purcell AW, Williamson NA, Chen Z, *et al.* Human leukocyte antigen class I restricted activation of CD8+ T cells provides the immunogenetic basis of systemic drug hypersensitivity. *Immunity.* 2008;28:822-32.
5. Kiepiela P, Leslie AJ, Honeyborne I, Ramduth D, Thobakqale C, Chetty S, *et al.* Dominant influence of HLA-B in mediating the potential co-evolution of HIV and HLA. *Nature.* 2004;432:769-75.
6. Nolan D, Gaudieri S, Mallal S. Pharmacogenetics: a practical role in predicting antiretroviral drug toxicity? *J HIV Therapy.* 2003;8:36-41.
7. Puthanakit T, Bunupuradah T, Kosalaraksa P, Vibol U, Hansudewchakul R, Ubolyam S, *et al.* Prevalence of human leukocyte antigen-B*5701 among HIV-infected children in Thailand and Cambodia: Implications for abacavir use. *Pediatr Infect Dis J.* 2013;32:252-3.
8. Rodriguez-Novoa S, Cuenca L, Morello J, Cordoba M, Blanco F, Jimenez-Nacher I, *et al.* Use of the HCP5 single nucleotide polymorphism to predict hypersensitivity reactions to abacavir: Correlation with HLA-B*5701. *J Antimicrob Chemother.* 2010;65:1567-9.
9. Colombo S, Rauch A, Rotger M, Fellay J, Martinez R, Fux C, *et al.* The HCP5 single-nucleotide polymorphism: A simple screening tool for prediction of hypersensitivity reaction to abacavir. *J Infect Dis.* 2008;198:864-7.
10. Martin AM, Nolan D, Gaudieri S, Almeida CA, Nolan R, James I, *et al.* Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and a haplotypic Hsp70-Hom variant. *Proc Natl Acad Sci USA.* 2004;101:4180-5.
11. Ma JD, Lee KC, Kuo GM. HLA-B*5701 testing to predict abacavir hypersensitivity. *PLoS Curr.* 2010;2:RRN1203.
12. Lucas A, Nolan D, Mallal S. HLA-B*5701 screening for susceptibility to abacavir hypersensitivity. *J Antimicrob Chemother.* 2007;59:591-3.