

HLA – B 17 Prevalence in HIV-1 Infected Patients under Antiretroviral Treatment

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KEYWORDS Abacavir. HLA B17. Western India

ABSTRACT Abacavir hypersensitivity reaction is a multi-organ systemic illness that occurs in approximately 5-8% of HIV-infected patients who initiate therapy with abacavir — associated strongly with HLA B*5701. Population studies have reported frequency of serologically defined HLA B17 splits B57 and B58 antigens, with molecular subtypes 31 for (B*5701-B*5731) and 28 for B*5801-B*5828) as of April 2010. HLA B57 frequency is 5 -20% in India. The incidence of abacavir hypersensitivity reported from Caucasian clinical trials is approximately 8% (range 2-9%). We analysed the B17 incidence among HLA association of 205 HIV-1 patients on anti-retroviral treatment. Ethnically age and sex matched 200 normal individuals served as controls. The ARV treated patients were evaluated for their CD4 counts by flowcytometry, and viral load monitoring by Taqman real time PCR method. HLA typing was done using conventional microlymphocytotoxicity assay. The prevalence of HLA B17 was found to be 13.17% in 205 patients compared to 7.75% in controls (OR=1.805; P value 0.011) which indicates that this particular HLA B17 and its subtype HLA B57 has to be considered when the antiretroviral treatment cocktail contains abacavir though costly in resource limited countries like India.

INTRODUCTION

Abacavir is a commonly used nucleoside analog with potent antiviral activity against HIV-1. Approximately 5 to 9% of patients treated with abacavir develop a hypersensitivity reaction characterized by multisystem involvement that can be fatal in rare cases (Mallal et al. 2002; Hetherington et al. 2002). Symptoms usually appear within the first 6 weeks of treatment which include fever, rash, gastrointestinal problems, and malaise. The symptoms worsen with continued therapy but improve within 72 hours of discontinuation of abacavir. Rechallenge with it after a hypersensitivity reaction typically results in recurrence of symptoms within hours. Genetic predisposition for this idiosyncratic hypersensitivity syndrome was suggested when it occurred in a small percentage of abacavir recipients for a short period and familial occurrence and decreased incidence in

individuals of African American origin (Symonds et al. 2002). In concurrence to these clinical observations, a strong predictive association of HLA-B*5701 was demonstrated. In serologically defined broad group of HLA B 17 there are two splits HLA B57 and HLA B58 with B*5701-B*5731 and B*5801-B*5828 molecular subtypes as of April 2010 respectively which could be genetic determinants for the hypersensitivity. It was more evident by recombinant haplotype mapping found the susceptibility locus or loci reside specifically in the 57.1 ancestral haplotype with the haplospecific alleles HLA-B*5701, C4A6 and, the HLA-DRB1*0701, HLA-DQ3 combination (Mallal et al. 2002). Martin et al. (2004) reported that the combination of HLA-B*5701 and a haplotypic M493T polymorphism of HSP70-HOM is highly predictive of abacavir hypersensitivity. Earlier studies have reported incidence of HLA B*5701 as 5-20% in India.

MATERIALS AND METHODS

In a prospective case-controlled association present study 205 HIV- 1 positive patients of more than 18 years of age and on primary line of antiretroviral treatment were recruited for the study. Patients fulfilling the inclusion criteria were enrolled after written informed consent and

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proper counselling. Then patients were evaluated for their HLA antigens by serology using microlymphocytotoxicity assay, CD4 counts using Tritest CD3/CD4/CD8 (BD Diagnostics) by Flow cytometry and plasma HIV-1 viral load using COBAS Taqman HIV-1 kit (Roche Diagnostics) by Real-time PCR method.

RESULTS

The prevalence of HLA-B 17 was found to be 26.34% in 205 HIV-1 positive patients on primary line antiretroviral treatment (Table 1). There was no clear correlation of the risk of abacavir hypersensitivity with the CD4 cell count or HIV-1 RNA level. We have found HLA B17 prevalence as 26.34% in 205 AIDS cases on primary line. Earlier we have reported HLA B*57 and B*58 frequencies (Table 2) in HIV-1 infected naïve patients (Umapathy et al. 2007). HLA B*5701 a molecular subtype of HLA B*57 is reported to be associated very strongly with hypersensitivity reaction to abacavir.

DISCUSSION

HLA plays a crucial role in immunopathophysiology of infections, for which, knowing frequencies of HLA alleles in a particular population is of paramount importance. Kiepiela et al. (2004) have found a significantly greater number of HLA-B CD8+ T cell responses compared to HLA-A (2.5-fold; $P = 0.0033$). He has shown that variation in viral set point, in absolute CD4 count and, by inference, in rate of disease progression

in the cohort, was strongly associated with particular HLA-B but not HLA-A allele expression. Moreover, substantially greater selection pressure was imposed on HIV-1 by HLA-B alleles than by HLA-A. The principal focus of HIV-specific activity is found at the HLA-B locus cause B alleles to evolve more rapidly than A alleles and thereby, influence gene frequencies in the population by HIV disease.

Association with class I HLA alleles and infectious disease has been demonstrated mainly with HLA-B: B8 with susceptibility to pulmonary tuberculosis, B35 with susceptibility to AIDS, B53 with resistance to severe malaria, and B57 with resistance to AIDS (Cooke and Hill 2001). Martin et al. (2002) reported that the activating KIR allele KIR3DS1, in combination with HLA-B alleles that encode molecules with isoleucine at position 80 (HLA-B Bw4-80Ile), is associated with delayed progression to AIDS in individuals infected with HIV-1. In the absence of KIR3DS1, the HLA-B Bw4-80Ile allele was not associated with any of the AIDS outcomes measured. By contrast, in the absence of HLA-B Bw4-80Ile alleles, KIR3DS1 is significantly associated with more rapid progression to AIDS. These observations strongly suggest a model involving an epistatic interaction between the two loci. The strongest synergistic effect of these loci is seen on progression to depletion of CD4+ T cells, which suggested that a protective response of NK cells involving KIR3DS1 and its HLA class I ligands begins soon after HIV-1 infection. By testing the effects on HIV disease progression and viral load of inhibitory KIR3DL1 subtypes in combination

Table 1: HLA distribution among HAART - treated HIV-1 infected individuals and controls from Mumbai

| HLA | Patients (N=205) | | Controls (N=200) | | OR | Ki2 | EF | PF | 95% CI | P value |
|-----|------------------|-------|------------------|------|-------|-------|-------|----|-----------|---------|
| | N + | % AF | N + | % AF | | | | | | |
| B17 | 54 | 13.17 | 31 | 7.75 | 1.805 | 5.770 | 0.057 | | 1.13-2.87 | 0.011 |

N+ -Number Positive OR - Odds Ratio PF- preventive fraction** significant P value

%AF -allele frequency percentage Ki2 -Chi-square with Yates Correction

EF -etiologial fraction 95% CI- 95% confidence Interval

Table 2: Comparative HLA B*17 subtype allele distribution among the west Indian AIDS patients with the world*

| HLA | Western India* N =75 AF (%) | Caucasian N=11 AF (%) | West Indies N = 17 AF (%) | Hispanic N = 33 AF (%) | African American N = 38 AF (%) |
|------|-----------------------------------|-----------------------------|---------------------------------|------------------------------|--------------------------------------|
| B*57 | 5.33 | 9.09 | 14.7 | | 6.57 |
| B*58 | 6 | 4.54 | 14.7 | 4.54 | 6.57 |

* Ref . Umapathy et al. 2007

with HLA-B allelic groups, Martin et al. (2007) have determined that highly expressed, highly inhibitory KIR3DL1**h* alleles strongly enhance protection conferred by HLA-Bw4-80Ile alleles, including HLA-B*57. He has proposed that greater dependency on the expression of specific KIR3DL1-Bw4 receptor-ligand pairs for NK cell inhibition in the resting state results in more pronounced NK cell responses when the inhibition is abrogated in the face of infection.

Gao et al. (2005) proposed that the presence of the various HLA-B alleles may lead to different scenarios for viral escape from cytotoxic T-lymphocyte pressure and virus subtypes with different immunity. He has found that HLA-B alleles interfere at distinct intervals after HIV infection. HLA-B35-Px and HLA-B57 are associated with rate of progression leading to four outcomes: (1) progression to CD4+ T cells less than 200 (CD4 less than 200), (2) CD4 less than 200 and/or an AIDS-defining illness, (3) an AIDS-defining illness, and (4) death. HLA-B27, on the other hand, has only been associated with the last 3 outcomes. Protection mediated by HLA-B57 is seen early after infection, whereas HLA-B27-mediated protection has delayed progression to an AIDS-defining illness after the decline in CD4 counts. HLA-B35-Px show has rendered an early susceptibility effect associated resulting in rapid progression from seroconversion to CD4 less than 200.

All Amerindian groups have show limited HLA polymorphism which probably reflects the small founder populations that colonized America by overland migration from Asia 11,000 to 40,000 years ago. Belich et al. (1992) have found that the nucleotide sequences of HLA-B alleles from two culturally and linguistically distinct tribes of Southern Brazil are distinct from those in Caucasian, Oriental, and other populations. New alleles are formed through recombination between pre-existing alleles, not by point mutation, giving rise to distinctive diversification of HLA-B in different South American Indian tribes. Segmental exchanges of this type, even if they occur at a lower frequency than point mutations, could be useful in the development of resistance to infectious disease, for example, in as much as the probability of an adaptively useful variant is much higher when there is segmental exchange of already structurally valid coding sequence rather than random point mutation. The findings in literature support the

hypothesis that the extraordinary polymorphism of major histocompatibility complex genes has evolved primarily through natural selection by infectious pathogens. Although most of the human MHC loci are relatively stable, the HLA-B locus appears to be capable of rapid changes, especially in isolated populations. McAdam et al. (1994) compared the sequences of 19 HLA-B homologs from chimpanzees (*Pan troglodytes*) and (*Pan paniscus*) to 65 HLA-B human sequences. Despite obvious similarities between chimpanzee and human alleles in exon 2, little conservation of exon 3 between human and the 2 chimpanzee species is shown suggesting characterization of the HLA-B locus and its homologs for over 5 million years by recombination unlike all other HLA Loci.

CONCLUSION

Thus, our study demonstrates that HLA B17 frequency in Indian HIV antiretroviral treated patients is due to the different composite ethnic groups studied. The testing for HLA B17 (57) antigen along with HLA B*5701 allele subtype can be used as pharmacogenetic testing to prevent abacavir hypersensitivity reaction among Indian patients.

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