UPDATED EXPERIENCE OF ABACAVIR HYPERSENSITIVITY GENETIC TESTING WITHIN THE MAJOR HISTOCOMPATIBILITY COMPLEX: ADDRESSING DIAGNOSTIC PRECISION AND PREDICTIVE VALUE

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OBJECTIVES: To assess the predictive value (PV) of genetic testing for abacavir hypersensitivity syndrome (HSR) in the Western Australian HIV Cohort Study, and to extend genetic mapping of genetic susceptibility locus/loci. Abacavir-specific immunological responses were assessed to improve precision of the HSR diagnostic classification, and to provide insights into possible underlying mechanisms.

METHODS: The abacavir-exposed cohort comprised prospectively tested patients (n=48) and retrospectively analysed abacavir-exposed individuals (n=200). Diagnostic precision was assessed using epicutaneous patch testing, and immunological response to ex vivo abacavir exposure measured by peripheral blood mononuclear cell tumour necrosis factor alpha (TNF-α) expression (three-colour flow cytometry) or whole blood extracellular TNF-α (chemiluminescence). Depletion of CD4 and CD8 cells was undertaken to determine the characteristics of the major histocompatibility complex (MHC)-restricted immune response. MHC typing utilized standard molecular techniques, and genetic mapping within the MHC Class III region analysed single nucleotide polymorphisms (SNP) to identify recombinant MHC haplotypes.

RESULTS: Application of revised diagnostic criteria (including a positive ex vivo test) identified abacavir HSR 18 cases out of 248 abacavir-exposed patients (2/48 prospectively tested). HLA-B*5701 was present in 94% of cases and 1.7% of controls
Based on these data, prospective testing for HLA-B*5701 carriage would be predicted to reduce abacavir HSR incidence from 7.3% to 0.4%, while inappropriately denying 1.6% of the population access to abacavir. Presence of HLA-B*5701 and a central MHC polymorphism (hspA1L rs2227956C) was found in 94% of cases and 0.43% of controls (OR 3910, PV+ 94%, PV– 99.5%). Depletion of CD8 cells resulted in marked attenuation of abacavir-stimulated TNF-α expression ex vivo, consistent with a Class I-restricted immune response. Recombinant mapping in patients carrying markers of the 57.1 ancestral/extended haplotype suggest a susceptibility locus within the highly conserved heat shock protein 70 (hsp70) gene cluster, although these data suggest that the HLA-B*5701 may provide specificity to the abacavir-induced immune response.

**CONCLUSIONS:** Presence of HLA-B*5701 is highly predictive of abacavir HSR in the Western Australian HIV Cohort, with evidence that an abacavir-specific Class I-restricted immune response may involve the concurrence of HLA-B*5701 and a second locus within the central MHC that is carried on the 57.1 extended haplotype.

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