

GENETIC SCREENING FOR ABACAVIR HYPERSENSITIVITY (ABC-HSR) IN THE WESTERN AUSTRALIAN COHORT: PROSPECTIVE DATA AND NOVEL DIAGNOSTIC APPROACHES

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Background: Abacavir treatment is associated with drug hypersensitivity reactions in ~8% of Caucasians, and is highly predicted by the presence of *HLA-B*5701* allele.

Objective: To determine the incidence of ABC-HSR after introduction of prospective *HLA-B*5701* screening, and to develop new tests to rapidly screen and identify susceptible individuals.

Methods: Prospective study. All individuals prescribed abacavir after January 2002 were examined (n=138). ABC-HSR was diagnosed utilising standardised criteria. HLA results were obtained by sequence-based typing (SBT).

Diagnostic assay development. A multiplexed sequence specific primer (SSP) assay to identify *HLA-B*5701* alleles, and a serological flow cytometry assay for HLA-B57 phenotyping using commercial B17 monoclonal antibodies and gating on the CD45+ lymphocyte population, were developed and validated.

Results: Prospective study. Three *HLA-B*5701*+ individuals developed classical ABC-HSR symptoms. In two cases HLA results were not reviewed, while one patient with limited treatment options made an informed choice based on the absence of other markers of the 57.1 ancestral haplotype. No definite cases of ABC-HSR were identified among the 135 *HLA-B*5701*-negative individuals, with no symptoms in 96% (n=131). Abacavir was discontinued within 6 weeks due to minor symptoms in one case (diarrhoea) or symptoms likely to be associated with an alternative drug in three cases (nevirapine = 2, zidovudine = 1).

Diagnostic assay development. The PCR-SSP assay amplified all *HLA-B*5701* alleles and was able to distinguish between *HLA-B*5701* (n=10) and related alleles *B*5702* (n=2), *B*5703* (n=1), *B*5704* (n=1); and non-*HLA-B*57* alleles (n=61). Flow cytometry testing of whole blood samples from *HLA-B57*+ individuals were positive (n=7), while all *HLA-B57*-negative individuals (n=77) tested negative.

Conclusion: Testing and excluding individuals carrying the susceptibility locus *HLA-B*5701* has decreased the incidence of abacavir HSR in the WA HIV cohort to 0% (95% CI 0-0.03) in *HLA-B*5701*⁻ individuals. The SSP diagnostic test for *HLA-B*5701* detection is a rapid and accurate typing method with high specificity, sensitivity and reproducibility. The B17/CD45 dual staining was sufficient to discriminate between individuals carrying B57/B58 antigens and could be used as a rapid screen to identify and possibly exclude individuals with potential genetic susceptibility to abacavir. Confirmation of the *HLA-B57* subtypes must be done using molecular methods.