Pharmacogenetic (PG) Investigation of Hypersensitivity to Abacavir

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Abstract
Abacavir (ABC) is an effective antiretroviral drug. In the totality of ABC clinical studies, the overall rate of suspected ABC hypersensitivity reaction (HSR) was 5.4%. In rare cases, HSR has proven fatal. A clinical risk management program has successfully reduced the rate of serious outcomes. Pharmacogenetic (PG) research, involving over 500 clinically suspected ABC HSR cases and over 700 ABC tolerant controls has been completed. In Caucasian subjects, the HLA-B*5701 allele was confirmed as the most predictive individual genetic marker and no marker pairs or combinations had superior performance characteristics. In non-Caucasians, the sensitivity of HLA-B*5701 as a predictor of clinically suspected HSR ranged from 8% in Blacks to 37% in Thai Asians. GSK has initiated two clinical studies in which skin patch testing will be used to augment the clinical diagnosis of ABC HSR. PREDICT-1 will evaluate the impact of HLA-B*5701 screening on the incidence of ABC HSR. SHAPE will estimate the sensitivity of HLA-B*5701 in Caucasian Americans and in African Americans. Clinical management must remain the basis for the diagnosis and management of ABC HSR. Over-reliance on prognostic markers could lead to reduced clinical vigilance and more serious outcomes.

Introduction
- Abacavir (ABC) is an effective antiretroviral drug.
- In clinical studies to date, 5.4% of patients have experienced a suspected HSR.
- A clinical risk management program has successfully reduced the incidence of serious outcomes.
- A highly predictive genetic marker could improve the benefit to risk ratio of ABC.
- HLA-B*5701, has been shown to be highly associated with ABC HSR in multiple studies of Caucasian patients.

Methods
- Subjects
  - From 5 clinical studies
  - 595 “Cases” – RETROSPECTIVELY identified subjects with clinically suspected ABC HSR
  - 744 “Controls” – ABC treated subjects with no evidence of ABC HSR
  - Self-reported racial affiliation: Caucasian (71%), Black (9%), Hispanic (10%), and Asian (8%, from Study EPV40001, conducted in Thailand)
  - Average Age: 40.9, Gender: 24% were Female
- Genetic Markers
  - Candidate genes: Drug metabolism, immune response
  - Genome-wide genetic markers: >1.5 million
- Statistical Methods
  - Hardy-Weinberg Equilibrium testing
  - Genotypic association with HSR (Fisher’s Exact Test)
- Per-marker performance characteristics: sensitivity and specificity
- Per-marker positive and negative predictive values
- Marker pair performance characteristics
- Racial groups analyzed separately

Results
- Significant associations with suspected ABC HSR were found for markers located throughout the genome.
- The strongest associations were for markers located on chromosome 6 in the region surrounding HLA-B.

Discussion
- Retrospective assessment of ABC HSR is difficult
- Skin patch testing, a research tool not clinically validated, might improve diagnostic accuracy of ABC HSR.
- Two GSK studies that incorporate skin patch testing have commenced.
  - The PREDICT-1 Study: A prospective study that will compare the ABC HSR rate between a standard-of-care ABC treatment group and a cohort of patients who do not carry the HLA-B*5701 allele.
  - The SHAPE Study: A retrospective case-control study to evaluate the performance characteristics of HLA-B*5701 in Caucasian and African Americans.
- Symptoms of HSR may overlap with other syndromes; thus, diagnosis can be complicated by concurrent diseases or adverse events from concomitant drugs.
- Clinical management must remain the basis for diagnosis and management of ABC HSR.
- Over-reliance on prognostic markers could lead to reduced clinical vigilance and more serious outcomes.

Conclusions
- A strong association between clinically suspected ABC HSR and HLA-B*5701 carriage in Caucasians was confirmed.
- No other single marker and no marker pair featured a sensitivity and specificity greater than those for HLA-B*5701.
- Results in non-Caucasians are considered exploratory due to reduced sample sizes
- HLA-B*5701 was the marker mostly highly associated with clinically suspected HSR in Hispanics and Thai Asians.
- Evidence for association of HLA-B*5701 and clinically suspected HSR among Black subjects was limited.
- Further research is warranted to investigate variation in performance characteristics of HLA-B*5701 observed among different Caucasian study sets and among patient groups of different racial affiliation.

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References