Extensive Population Pharmacokinetic-Pharmacogenetic Study of nevirapine in HIV-Infected Cambodian Patients

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CONTEXT
• Importance of nevirapine
  - backbone of HAART in resource limited countries
• No pharmacokinetic studies in the Cambodian population
• Pharmacokinetics of nevirapine
  - metabolized by CYP2B6 and CYP3A which are regulated by the Pregnane X receptor (PXR)
  - weak substrate of the P-glycoprotein (P-gP) efflux transporter
• Pharmacogenetics of nevirapine
  - effect of five polymorphisms investigated on nevirapine apparent clearance in the Cambodian population investigated using nonlinear mixed effect models (1)
  - CYP2B6 516G/T associated with steady-state NVP clearance (CIF) in HIV-infected Cambodians
  - Sequenom assay previously designed for the pharmacogenetics of efavirenz and nevirapine (2)

RESULTS
• PK sampling
  - before morning dose intake
  - 18 months (M18) and 36 months (M36) after antiretroviral drug regimen onset
  - additional samples at 1, 2, 4 and 8h post intake in 10 patients
• Population pharmacokinetic model
  - built on the 170 patients of the PECAAN study
  - one compartment model parameterized in first order absorption (ka), apparent clearance (CIF) and apparent volume of distribution (V/F)
  - exponential model for the between and within subject random effects on CIF only
  - constant error model for the residuals
  - estimation using the SAEM algorithm implemented in Monolix 2.4
• Phenotype
  - derivation of the Empirical Bayes Estimates of the individual CI/F at each occasion
  - computation of the average individual CI/F across the occasions
• Genetic Analyses
  - 196 single nucleotide polymorphisms (SNPs) across 3 chromosomes
  - 126 polymorphic SNPs
  - Chromosome 3: 49 SNPs on NR1I2 (PXR)
  - Chromosome 7: 7 on ABCB1 (P-gp), 1 on CYP3A5 and 36 on CYP3A4
  - Chromosome 19: 1 on CYP2A6 and 47 on CYP2B6
• Haplotypes definition
  - blocks defined with the D’ confidence intervals method in Haploview
• Pharmacogenetic Analyses
  - Median (range) average individual CI/F: 2.6 (1-7.8) L/h
  - Univariate associations with CIF (P=0.03 to 4.6x10^-4)
  - 17 SNPs in CYP2B6
  - 1 in CYP3A4
  - 6 haplotypes in CYP2B6
  - No other SNP independently associated to CI/F once conditioning on CYP2B6 516G>T status (as shown on the figure below)

DISCUSSION
• Quantification of low between and within subject variability of NVP CI/F in this HIV-infected Cambodian population using nonlinear mixed effect models
• Flexible design to ensure a satisfactory number of patients of each genotype for most SNPs under study to meet the requirements of the medical authorities
• Low precision on volume of distribution and absorption constant rate parameters

REFERENCES

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