Pharmacokinetics

Objectives

• Contribution of genetic polymorphisms to plasma efavirenz exposure

Methodology:

- Several randomized ACTG treatment trials (esp. A5202, A5095/A5097s, and others) were included.
- Subjects with >2 determinations were excluded. For subjects with >2 determinations, subjects with 2 or 3 determinations were included for the analysis.
- For subjects ≥8 hours but <19 hours post dose.
- GENOTYPER and UMPIRE genotyping strategies.
- Associations with EFV concentrations in all subjects (P=3.8x10E-4, Figure, top); this was consistent in Black and White groups analyzed separately.
- In univariate analyses (additive models), associations between EFV concentrations and genetic variants in 84 AIDS Clinical Trials Group (ACTG) study participants with CYP2B6, CYP2A6, and UGT2B7 polymorphisms were observed.
- Four SNPs, including CYP2B6 -98 C, CYP2A6 -48 T, CYP2A6 c.1558G, and UGT2B7 c.735G were in complete linkage, so analyses only included 735-G and -48-T.
- The subject with apparent slow metabolizer genotypes, including 71 (84.5%) with 735 (G/G homozygosity) was heterozygous for deletion of the polymorphism, 34 (41.5%) were heterozygous, and 11 (13.5%) were homozygous for 735 (G/G homozygous).
- There was no association between 735 C self identified as "Black, Hispanic". No White subject had 983 C (rs28399433).
- Among all subjects, using a recessive genetic model, the contribution of 983 C and higher EFV concentrations in all subjects (P=3.8x10E-4, Figure, top); this was consistent in Black and White groups analyzed separately.
- In univariate analyses (additive models), associations between EFV concentrations and genetic variants in 84 AIDS Clinical Trials Group (ACTG) study participants with CYP2B6, CYP2A6, and UGT2B7 polymorphisms were observed.
- Four SNPs, including CYP2B6 -98 C, CYP2A6 -48 T, CYP2A6 c.1558G, and UGT2B7 c.735G were in complete linkage, so analyses only included 735-G and -48-T.
- The subject with apparent slow metabolizer genotypes, including 71 (84.5%) with 735 (G/G homozygosity) was heterozygous for deletion of the polymorphism, 34 (41.5%) were heterozygous, and 11 (13.5%) were homozygous for 735 (G/G homozygous).
- There was no association between 735 C self identified as "Black, Hispanic". No White subject had 983 C (rs28399433).