Optimization of HIV therapy in patients co-infected with tuberculosis

A pharmacogenetic and pharmacokinetic study of efavirenz in Rwandan adult patients undergoing HIV and tuberculosis co-treatment

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by

Emile Bienvenu

Faculty opponent:
Professor David Back
University of Liverpool, Liverpool, UK

This thesis is based on the following papers:

I.   **Bienvenu E**, Hoffmann KJ, Ashton M, Kayumba PC. A rapid and selective HPLC-UV method for the quantification of efavirenz in plasma from patients on concurrent HIV/AIDS and tuberculosis treatments. *Biomed. Chromatogr*. 2013; 27(11): 1554–1559.

II.   **Bienvenu E**, Swart M, Dandara C, Ekman A, Äbelö A, Wonkam A, Ashton M. Frequencies of Single Nucleotide Polymorphisms in Cytochrome P450 Genes (CYP1A2, 2A6, 2B6, 3A4 and 3A5) in a Rwandan Population: Difference to Other African Populations. *Curr Pharmacogenomics Person Med.* 2013, 11(3): 237 – 246.

III.   **Bienvenu E**, Swart M, Dandara C, Ashton M. The role of genetic polymorphisms in cytochrome P450 and effects of tuberculosis co-treatment on the predictive value of CYP2B6 SNPs and on efavirenz plasma levels in adult HIV patients. (*Submitted*)

IV.   **Bienvenu E**, Ashton M, Äbelö A. Population pharmacokinetic modeling of efavirenz in Rwandan adult patients on concomitant HIV and tuberculosis treatments. (*In manuscript*)

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Emile Bienvenu

Department of Pharmacology, Institute of Neuroscience and Physiology
Sahlgrenska Academy at University of Gothenburg, Sweden 2013

ABSTRACT

Tuberculosis (TB) is the most common opportunistic infection among people infected with human immunodeficiency virus (HIV). The co-management of HIV/TB co-infection is prone to multiple drug-drug interactions. In addition, the recommended HIV drug efavirenz (EFV) has a narrow therapeutic window which compromises its clinical safety and exhibits a highly variable pharmacokinetics (PK) between subjects due to genetic factors. A lack of genomic data on many African populations limits attempts aiming at optimizing therapies in general, HIV therapy in particular. This thesis specifically aimed to obtain genomic data in an African population and to investigate the pharmacokinetic and pharmacogenetic aspects of EFV exposure in the presence of TB therapy.

A clinical study was conducted in Rwandan HIV patients co-infected with TB. EFV plasma concentrations, CD4 cell counts and HIV-RNA copies were monitored. Genotyping for 13 single nucleotide polymorphisms (SNPs) with respect to five cytochrome P450 enzymes was conducted. A rapid and selective high performance liquid chromatography analytical method was developed for the quantification of EFV in plasma containing HIV and TB drugs.

Genetic variation was observed in 11 out of the 13 analyzed SNPs with minor allele frequencies for 12 SNPs. There was a significant difference between CYP1A2 -739T/G and T/T genotypes only in the presence of rifampicin-based TB treatment (RBT). In the presence and in the absence of RBT, CYP2B6 516T/T genotype was found to be associated with higher EFV plasma levels. CYP2A6 1093G>A, CYP2B6 516G>T and CYP2B6 983T>C SNPs were found to be independent predictors of EFV plasma levels accounting for 27%, 43%, and 29%, respectively, of the total variance in EFV plasma levels. There was a high positive predictive value for CYP2B6 516T/T and 983T/T genotypes in predicting supra-therapeutic EFV plasma levels. RBT was shown to significantly lower EFV plasma levels but did not affect HIV-treatment response. There were higher clearance (CL/F) values in patients with previous exposure to HIV therapy than in patients who were administered RBT prior to HIV therapy. Expectedly, carriers of CYP2B6 516G/G and T/T genotypes exhibited higher and lower CL/F, respectively, regardless of the previous treatment received by the patients.

In conclusion, CYP enzymes of the accessory metabolic pathways of EFV (CYP1A2 and CYP2A6) could explain variability in EFV exposure, in addition to CYP2B6 which proved to be the main pharmacogenetic determinant of EFV exposure in the patient population studied. As proven by the observed high positive predictive value, predictive genotyping in CYP2B6 SNPs may be useful in optimizing EFV-based HIV therapy. Not only should the patient genotype status with respect to CYP2B6 be taken into account, but also each individual patient treatment history, with caution to previous exposure to HAART. Even though it is clear from this thesis that specific CYP genotypes and co-medications do have a definite effect on EFV plasma levels causing its variation, this however does not seem to influence the efficacy of the EFV-based regimens in general.