Quantitative Clinical Pharmacological Studies on Efavirenz and Atazanavir in The Treatment of HIV-1 Infection

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs Universitet kommer att offentligen försvaras i hörsal Björn Folkow, Medicinargatan 11, Göteborg, fredagen den 14 december 2012 kl 13:00

av

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Avhandlingen baseras på följande delarbete:

I. **Rekić D**, Röshammar D, Mukonzo J, Ashton M. In silico prediction of efavirenz and rifampicin drug–drug interaction considering weight and CYP2B6 phenotype. *British Journal of Clinical Pharmacology.* 2011; 71 (4):536–43.

II. Mukonzo JK[1], Nanzigu S[1], **Rekić D**, Waako Paul, Rösham-mar D, Ashton M, Ogwal-Okeng J, Gustafsson LL, Aklillu E. HIV/AIDS patients display lower relative bioavailability of efavirenz than healthy subjects. *Clinical Pharmacokinetics*. 2011; 50 (8):531–40.

III. **Rekić D**, Clewe O, Röshammar D, Flamholc L, Sönnerborg A, Ormaasen V, Gisslén M, Äbelö A, Ashton M. Bilirubin-a potential marker of drug exposure in atazanavir-based antiretroviral therapy. *The AAPS journal*. 2011 Sep 13; 13 (4):598–605.

IV. **Rekić D**, Röshammar D, Bergstrand M, Tarning J, Calcagno A, D'Avolio A, Ormaasen V, Vigan M, Barrail-Tran A, Ashton M, Gisslén M, Äbelö A. External validation of the bilirubin-atazanavir nomogram for assessment of atazanavir plasma exposure in HIV-1 infected patients. *Submitted*

V. **Rekić D**, Röshammar D, Simonsson USH. Model based design and analysis of phase II HIV-1 trials. *Submitted*

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ABSTRACT

There are 34 million people infected with the HIV-1 virus in the world today. Due to increased access to antiretroviral therapy, AIDS related death has dropped by 30% since 2005. Optimizing the pharmacotherapy of the HIV-1 infection is of great importance to reduce adverse effects, reduce viral resistance development and increase the patients' survival as well as quality of life. This thesis presents pharmacometric applications to optimize pharmacotherapy of the HIV-1 infection as well as to expedite the clinical drug development of new drugs.

Methods to extrapolate *in vitro* data to *in vivo* settings have been applied to predict the level of the drug-drug interaction between efavirenz and rifampicin as well as to evaluate the current dosage recommendations. Nonlinear mixed effects (NLME) models, as implemented in the software NONMEM, have been fitted to data from clinical studies to investigate the disease effect of HIV-1 on efavirenz pharmacokinetics. Further, NLME modeling and simulation was used to evaluate and validate bilirubin as a marker of exposure and adherence in HIV-1 infected patients. Simulation of a mechanistic viral dynamics model, describing the interplay between virus and CD4 cells, was used to optimize the design and analysis of clinical trials in antiretroviral drug development. Model based techniques for hypothesis testing were shown to be superior in terms of power compared to traditional statistical hypothesis testing.

In conclusion, model based drug development techniques can be used to optimize HIV-1 therapy as well as expedite drug development of novel compounds.

Keywords: HIV, Pharmacokinetics, Pharmacodynamics
ISBN: 978-91-628-8590-8