Physiologically Based Pharmacokinetic Modeling using Simcyp™ to Predict Drug-Drug Interactions between HAART Drugs and Anticancer Drug, Dasatinib in Healthy Subjects

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**Purpose**
Dasatinib is approved for the treatment of chronic myelogenous leukemia, and is metabolized by CYP3A4. Inducers and inhibitors of CYP3A enzymes such as efavirenz, ritonavir, atazanavir and darunavir may be used as part of the HAART drugs to treat patients with HIV. When HIV patients with a malignancy need treatment with dasatinib, there is a potential, as yet undefined drug-drug interaction (DDI). Our objective is to predict the DDI between HAART drugs and anticancer drug, dasatinib using physiologically based pharmacokinetic (PBPK) modeling approach.

**Methods**
Mechanistic full PBPK modeling and simulations were implemented using Simcyp (version 12.1, Simcyp Limited, UK) for the pharmacokinetic and DDI simulations. In vitro data defining the physicochemical properties, and absorption, distribution, metabolism and elimination (ADME) properties for various HIV drugs and dasatinib were obtained from published literature or generated by Simcyp based predictions. DDIs were evaluated on 50 virtual subjects at steady state using once daily oral dose of 100 mg ritonavir or 600 mg efavirenz or 300 mg atazanavir or 800 mg darunavir for 14 days followed by 8 days of coadministration of once daily oral dose of 100 mg dasatinib. Additionally, combination of once daily oral dose of 100 mg ritonavir plus 300 mg atazanavir, and 100 mg ritonavir plus 800 mg darunavir were also tested.

**Results**
Mechanistic models adequately described dasatinib pharmacokinetics, and successfully predicted DDIs with various HIV drugs. The mean AUC, Cmax (ng/ml) and oral clearance (L/hr) values of dasatinib were 410±240 ng/ml*hr, 320±120 ng/ml and 336±217 L/hr, respectively. These values were comparable with clinical data. Treatment with ritonavir, atazanavir, ritonavir plus atazanavir, ritonavir plus darunavir showed increase in clearance of dasatinib by 4.5, 2.3, 4.2 and 3.4-fold, respectively (**P<0.001; unpaired t test, two sided). Whereas darunavir reduced the clearance of dasatinib by 1.4-fold (*P<0.01; unpaired student t test, two sided) and efavirenz did not affect the clearance of dasatinib.

**Conclusion**
In this study quantitatively predicted several HAART drugs and dasatinib DDIs. The dose of dasatinib may be increased by 4 and 3-fold, respectively when ritonavir plus atazanavir or ritonavir plus darunavir is co-administered. Whereas the dose adjustment of dasatinib may not be necessary when darunavir or efavirenz is co-administered.