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Clinical Exposure Boost Predictions by Integrating Cytochrome P450 3A4—Humanized Mouse Studies With PBPK Modeling

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ABSTRACT

NVS123 is a poorly water-soluble protease 56 inhibitor in clinical development. Data from *in vitro* hepatocyte studies suggested that NVS123 is mainly metabolized by CYP3A4. As a consequence of limited solubility, NVS123 therapeutic plasma exposures could not be achieved even with high doses and optimized formulations. One approach to overcome NVS123 developability issues was to increase plasma exposure by coadministrating it with an inhibitor of CYP3A4 such as ritonavir. A clinical boost effect was predicted by using physiologically based pharmacokinetic (PBPK) modeling. However, initial boost predictions lacked sufficient confidence because a key parameter, fraction of drug metabolized by CYP3A4 (f_mCYP3A4), could not be estimated with accuracy on account of disconnects between *in vitro* and *in vivo* preclinical data. To accurately estimate f_mCYP3A4 in human, an *in vivo* boost effect study was conducted using CYP3A4-humanized mouse model which showed a 33- to 56-fold exposure boost effect. Using a top-down approach, human f_mCYP3A4 for NVS123 was estimated to be very high and included in the human PBPK modeling to support subsequent clinical study design. The combined use of the *in vivo* boost study in CYP3A4-humanized mouse model mice along with PBPK modeling accurately predicted the clinical outcome and identified a significant NVS123 exposure boost (~42-fold increase) with ritonavir.

Introduction

Protease inhibitors often require high-systemic exposure levels for efficacy. Exposure “boosts” can be achieved for compounds that are highly metabolized by CYP3A4.[1] Coadministration with a strong CYP3A4 inhibitor such as ritonavir (RTV) can significantly increase the exposure of several CYP3A4 substrates by inhibiting their CYP3A4-mediated metabolic clearance.[1,2] RTV has been shown to increase the exposure of a coadministered drug, such as Danoprevir's, thus leading to a reduction in dose, dosing frequency, and alleviating food restrictions.[3] Moreover, overall high exposure variability (CV ~ 60%) can be reduced with RTV, likely by inhibiting intestinal CYP3A4.[1,2]

NVS123 is an anti-HCV drug in early drug development. It had been anticipated that the NVS123 human plasma exposures could be below the efficacious concentrations due to poor solubility and dissolution along with high CYP3A4-mediated clearance. A RTV-mediated exposure boost strategy to support further clinical development of NVS123 was pursued.

To predict the clinical RTV boost effect on NVS123, a human physiologically based pharmacokinetic (PBPK) model was established *a priori* based on *in vitro* and *in vivo* preclinical pharmacokinetic (PK) data using Simcyp (Simcyp Ltd, Sheffield, UK, version 13 and Release 1), a population-based clinical trial simulator for pharmacokinetics and drug-drug interaction (DDI) predictions. The predictions provided a wide range of boost effect (2- to 40-fold increase) as a key *in vitro* input parameter, fraction of drug metabolized by CYP3A4 (f_mCYP3A4), could not be estimated with confidence on account of the disconnect between *in vitro* human liver microsomal data and *in vivo* rat absorption, distribution, metabolism, and excretion (ADME) data.

Given the uncertainty in exposure boost, using conventional *in vitro* and *in vivo* data, emerging alternative approaches were used. *In vivo* boost effects or DDIs can be evaluated in humanized

Abbreviations: AUC, area under the plasma concentration-time curve; Cmax, maximum plasma concentration; CYP/Cyp, cytochrome P450; DDI, drug-drug interaction; f_mCYP3A4, fraction of drug metabolized by CYP3A4; hCYP3A4, CYP3A4 humanized mice; HLM, human liver microsomal; PBPK, physiologically based pharmacokinetic; PI, protease inhibitor; PK, pharmacokinetics; RTV, ritonavir.

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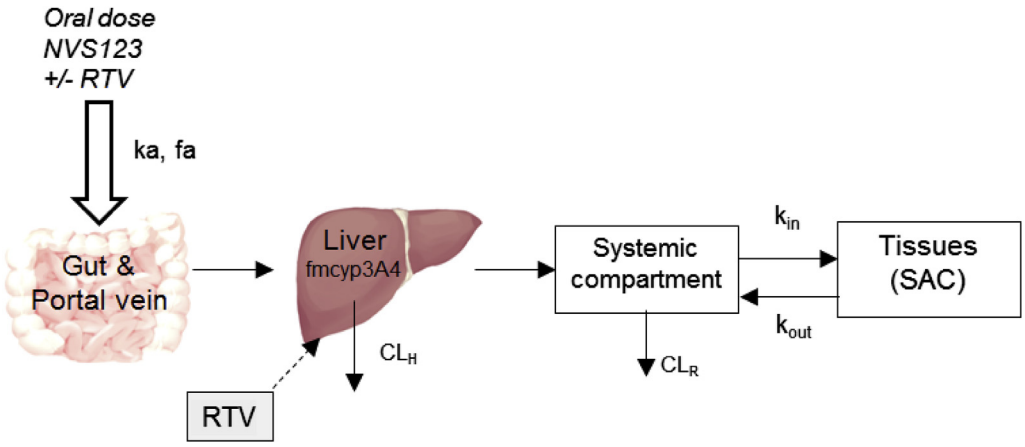

Figure 1. Minimal PBPK model scheme. Dosing of NVS123 was conducted with or without RTV in humanized mice or humans. SAC representing a lump of tissues excluding the liver and portal vein; k_{in} and k_{out}: first-order rate constants between systemic compartment and SAC. SAC, single adjusting compartment.

mouse models, generated either by a replacement of particular mouse genes involved in drug metabolism and disposition with their corresponding human counterparts[4,5] or by transplantation of human hepatocytes into immune-deficient mice to obtain chimeric liver-humanized mice.[6–8] Despite numerous examples demonstrating the utility of such models to overcome species differences, data showing how these humanized mice can be used to quantitatively predict DDIs in humans are still sparse.[9,10] Moreover, although previous studies focused on standard compounds with known clinical outcome, the utility of these models to prospectively predict the extent of DDIs in humans still needs to be demonstrated.

Here, we describe a case example of the combined use of a genetically humanized CYP3A4 mouse model and PBPK modeling to prospectively estimate the increase in human exposure of a CYP3A4 substrate, NVS123, due to coadministration with the established strong CYP3A4 inhibitor RTV. We show that this approach accurately predicted the clinical DDI or boost effect *a priori*, as subsequently confirmed in a clinical study.

Materials and Methods

PBPK Model NVS123

The PBPK model for NVS123 was built by using Simcyp simulator (Simcyp Population-based Simulator, version 13.1, Certara, Princeton, NJ). Figure 1 depicts the minimal PBPK model, which consists mainly of the liver, the portal vein, the systemic compartment, and the tissue sac (single adjusting compartment). Gut absorption is captured via an absorption rate constant.

Physicochemical Properties

Key NVS123 physicochemical and biopharmaceutic properties, which provide a fundamental input to the PBPK model in determining drug absorption and distribution, are listed in Table 1.

Table 1
Physicochemical and Biopharmaceutic Properties of NVS123

Parameters	Measured
LogP	5.0
pKa	5.8 (acidic), 8.36 (basic)
Solubility (mg/mL)	0.09 (buffer, pH 7.4)
Caco-2 permeability with inhibitor	3.7 e−6 cm/s
B/P	0.62

Key PBPK Model Input Parameters

A first-order absorption model was used to estimate drug absorption in human based on Caco-2 permeability data. A minimal PBPK model described drug distribution. Enzyme kinetics and CL_{int} for CYP3A4 were estimated using the retrograde model. Key pharmacokinetic parameters in the model have been listed in Table 2. Using a "top-down" approach, the PBPK model was verified with human PK data by comparing observed human PK profiles at 2 dose levels with simulated profiles (Figs. 2a and 2b). The simulated PK profiles could reasonably describe observed human PK profiles in healthy volunteers after a single 100-mg or 300-mg NVS123 dose.

PBPK Model for Ritonavir "Boost"

The default PBPK model for RTV in Simcyp, version 13.1, was slightly modified by incorporating published mechanism-based

Table 2
Key Pharmacokinetic Parameters of NVS123

Parameter	Initial Value	Refined Value	Comment
Absorption (model used: first-order model)			
$P_{eff,man}$ (10^{-4} cm/s)	1.52		Estimated from Caco-2 data
Caco-2 (10^{-6} cm/s)	3.7		Measured
Q_{gut} (L/h)	7.77		Scaled from Caco-2 data
fu_{gut}	0.5		Based on study of Yang et al.[11]
Distribution (model used: minimal PBPK)			
Vss (L/kg)	0.4		From human PK data
K_{in} (1/h)	0.511		From human PK data
K_{out} (1/h)	0.381		From human PK data
Vsac (L/kg)	0.23		From human PK data
Elimination			
CL_{po} (L/h)	600	300	From human PK data
f_m_CYP3A4	0.04-1.0	1.0	Rat ADME, HLM, hepatocyte, human oral CL
CL_R (L/h)_human	0.77		From human ADME data
CL_{int} (μL/min/pmol cyp)	0.16-4.0		Retrograde model