07M0130

Development of a Physiologically Based Pharmacokinetic Model for Raltegravir and Prediction of its Interactions with Rifampicin

Joyce S. Macwan, Michael B. Bolger, Viera Lukacova, Grazyna Fraczkiewicz, Walter S. Woltosz

Simulations Plus, Inc., 42505 10th Street West, Lancaster, California 93534, USA

2016 AAPS ANNUAL MEETING AND EXPOSITION
NOVEMBER 13 –17, 2016
COLORADO CONVENTION CENTER, DENVER
aaps

PURPOSE

Raltegravir (MK-0518; Isentress™), the HIV-1 integrase strand transfer inhibitor is approved for HIV-1 therapy in combination with other antiretroviral agents. The primary route for raltegravir ("RAL") elimination is glucuronidation, mainly catalyzed by the isoenzyme UGT1A1 with minor contributions from UGT1A3 and UGT1A9. Rifampicin ("RIF") is included in the preferred regimen for the treatment of tuberculosis (TB) infections, which are common in the HIV patient population. RIF has been shown to induce several drug metabolizing enzymes and transporters and hence is likely to affect the pharmacokinetics (PK) of RAL. The goal of this work was to develop a physiologically based pharmacokinetic (PBPK) model of RAL accounting for all relevant mechanisms for its disposition following oral administration. The effect of RIF administration on RAL PK was predicted and compared with observed drug interactions. The model can be used for quantitative prediction of drug interactions with co-administration of UGT1A1 inducers and inhibitors.

METHOD

The GastroPlus™ 9.0 (Simulations Plus, Inc.) Advanced Compartmental Absorption and Transit™ (ACAT™) model with its PBPKPlus™ and Metabolism and Transporter modules was used to build a mechanistic absorption/PBPK model for RAL. Tissue volumes, weights, and blood perfusion rates were generated by the program's internal Population Estimates for Age-Related (PEAR™) Physiology™ module. The drug's physicochemical and biopharmaceutical inputs were either obtained from literature or predicted by ADMET Predictor™ 7.2 (Simulations Plus, Inc.). Individual tissues were modeled as perfusion-limited tissues and the Poulin and Theil homogeneous method was used for tissue/plasma partition coefficient (Kp) estimation. The UGT1A1-mediated metabolism of RAL was modeled by Michaelis-Menten kinetics with enzyme kinetic parameters, along with the GastroPlus built-in expression levels of UGT1A1 in gut, liver, and kidney. The *in vitro* Km value for UGT1A1 metabolism was obtained from literature [1]. V_{max} values were fitted against *in vivo* data. Renal clearance of parent and metabolite was estimated as a fraction of kidney blood flow. The fraction for parent (0.055) and metabolite (0.7) was fitted to match *in vivo* renal elimination of each compound. Biliary excretion of glucuronide metabolite was modeled using permeability-surface area product (Pstc) at the apical side of liver hepatocytes. Enterohepatic circulation of RAL, derived from biliary excretion followed by deconjugation of RAL glucuronide metabolite in gut, was incorporated in the model (**Figure 1**). Particle size was adjusted to account for the formulation effect. The model was validated by comparing simulated and observed plasma concentration-time profiles of RAL across several different dose levels following both single and multiple oral administrations [2].

RIF is eliminated primarily by CYP3A4 metabolism. Intestinal passive absorption and CYP3A4-mediated metabolic clearance in gut and liver were included in the RIF PBPK model. Drug-drug interactions mediated by UGT1A1 were predicted with the GastroPlus DDI module through dynamic simulations using the validated RIF PBPK model. The EC_{50} (0.39 µM) value for UGT1A1 induction by RIF was from literature [3]. The E_{max} (1.2) was fitted from *in vivo* data [4] and was used to predict DDI for intermittent RIF dosing study [5]. Experimental data were obtained from the literature [4-5].

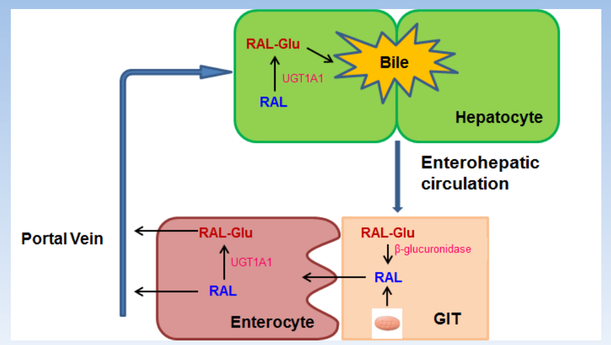

Figure 1. Overview of the major processes governing the disposition of RAL in gut and liver.

RESULTS

The developed PBPK model accurately described the PK of RAL. The prolonged terminal elimination phase of RAL was more accurately predicted when enterohepatic circulation of parent was included in the model. The simulated RAL plasma concentration-time profiles following both single and multiple oral administrations in healthy subjects were in excellent agreement with clinically observed data (**Figure 2**).

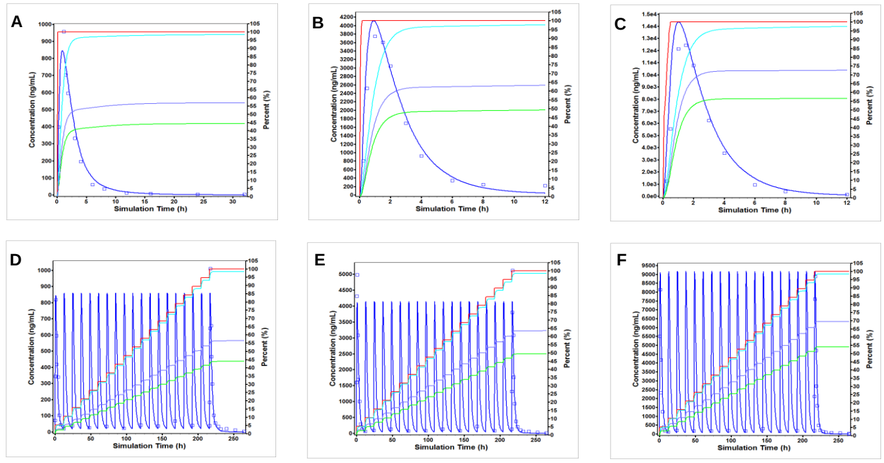

Figure 2. Observed (points) and simulated (lines) mean plasma concentration-time profiles of RAL after a single oral dose of 100 mg (A), 400 mg (B), 1200 mg (C) and multiple bid oral doses of 100 mg (D), 400 mg (E), and 800 mg (F) on day 10 in healthy volunteers [2]. Cumulative amount dissolved (red), absorbed (cyan), entered portal vein (blue), and entered systemic circulation (green), all shown as percent of the administered dose (Y-axis on the right).

Dynamic simulations adequately predicted the effect of UGT1A1 induction by RIF with daily and intermittent dosing on RAL PK in healthy volunteers (**Figure 3**). The predicted AUC, $C_{max,}$ and C_{12} ratios of RAL in the presence of RIF was in close agreement with observed values (**Table 1**). Significant reduction in C_{12} level which might relate to efficacy of RAL may raise concern for dose adjustment with daily RIF dosing due to PK differences in patient populations.

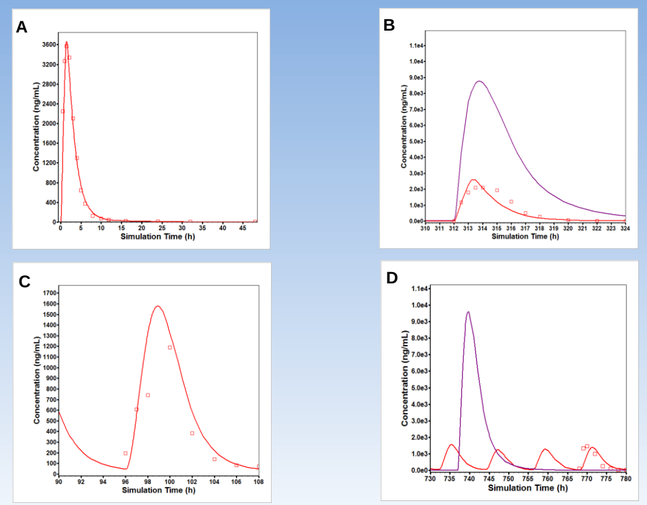

Figure 3. Observed (points) and simulated (lines) mean plasma concentration-time profiles of RAL following a single oral dose of 100 mg without RIF (A) and after multiple oral doses of RIF (600 mg qd for 14 days) (B) [4]; multiple oral doses (400 mg bid for 5 days) without RIF (C), followed by multiple oral doses of RIF (600 mg 3 times a week for 28 days) (D) [5]. The simulated RIF plasma concentration-time profiles are shown in purple.

Table 1. Summary of observed and predicted DDI of RAL with RIF.

Ratio	C_{max}		$AUC_{0\text{-}inf}$		C_{12}	
	Ref [4]	Ref [5]	Ref [4]	Ref [5]	Ref [4]	Ref [5]
Observed	0.62	1.16	0.60	1.08*	0.39	0.60
Predicted	0.72	1.00	0.62	0.75*	0.39	0.66

* $AUC_{0\text{-}12}$

CONCLUSION

The mechanistic absorption and PK of RAL were adequately predicted using physiological and drug-specific parameters. The model successfully predicted the drug-drug interactions related to induction of UGT1A1-mediated RAL metabolism by RIF. This model can also be extended to predict DDI between RAL and RIF in HIV/TB co-infected population by accounting for physiological changes caused by the diseases. This model can be successfully utilized for quantitative prediction of drug-drug interactions mediated by UGT1A1 inducers and inhibitors.

REFERENCES

1. Kassahun *et al* . Drug Metab Dispos. 2007; 35(9) 1657-63
2. Iwamoto *et al.* Clin Pharmacol Ther. 2008; 83(2) 293-99
3. Smith *et al.* J Biochem Mol Toxicol. 2005;19(2) 96-108
4. Wenning *et al.* Antimicrob Agents Chemother. 2009; 53(7) 2852-56
5. Reynolds *et al.* J Antimicrob Chemother. 2015; 70(2) 550-54

SimulationsPlus
SCIENCE + SOFTWARE = SUCCESS