PBPK MODELLING OF LONG-ACTING INJECTABLE CABOTEGRAVIR IN PREGNANCY

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BACKGROUND

Long-acting injectable (LAI) formulations promise improved patient adherence, sustained pharmacokinetics (PK) and good therapy outcomes. Cabotegravir (CAB) is an HIV integrase-strand inhibitor that is co-packaged with rilpivirine as a long-acting injectable formulation for combined administration.

LAI CAB has recently been approved for the treatment of HIV in adults, however, there are currently no adequate data to inform its administration during pregnancy. Physiologically-based pharmacokinetic (PBPK) modelling may help inform knowledge gaps on the PK of LAI CAB in pregnancy.

The aim of this study was to apply PBPK modelling to predict the PK of LAI CAB in pregnancy.

METHODS

A whole-body adult (non-pregnant) PBPK model was developed in SimBiology (MATLAB R2019a) and used to simulate 100 healthy individuals. Drug-specific parameter values for CAB and raltegravir (RAL) were obtained from literature.

The PBPK models were qualified against clinical PK data in adults for single doses of: 30 mg PO, 400 mg and 800 mg intramuscular (IM) CAB, and 400 mg PO RAL. In addition, the adult PBPK models were qualified against clinical PK data of 3 repeated dosing regimens of IM CAB in adults: 800 mg induction dose followed by a 200mg monthly, 400 mg monthly or 800 mg quarterly maintenance doses.

The models were considered qualified if the simulated values were within 2-fold of the reported clinical PK data using the absolute average-fold error (AAFE) approach.

Following successful validation, the PBPK models were modified to represent a pregnant population with the incorporation of pregnancy-induced anatomical, physiological, and metabolic changes (e.g., organ blood-flow rates, plasma protein levels, progesterone concentrations etc.) known to influence drug PK.

Progesterone-mediated induction of UGT1A1 was incorporated in the pregnancy PBPK model. Clinical PK data for probe substrate RAL in pregnant women was used to validate the activity of key enzyme UGT1A1 during pregnancy.

The qualified pregnancy model was used to predict the PK of single (approved) doses of CAB (30 mg oral, LAI 400 mg & 600 mg IM) across different trimesters in pregnancy.

RESULTS

AAFE of the mean PK parameters for oral RAL and CAB in adults were between 1.0-1.9 fold, and <1.5 fold, respectively (Table 1). IM CAB simulations in non-pregnant adults successfully passed model qualification criteria with AAFEs between 1.0-1.9 fold (Table 1 & 3). In the second and third trimester of pregnancy, AAFE values of oral RAL were within the 2-fold acceptance criteria (Table 2), providing confidence in model simulations for CAB. Predicted elimination kinetics of CAB were closely related to observed data. The predicted geometric mean of plasma exposures in pregnant and non-pregnant patients were comparable for each of the single doses of CAB that were examined in this study (Fig 1).

Table 1: Predicted and reported PK of cabotegravir and raltegravir in adults.

PK Variable*	Observed$^{\alpha}$ / Simulated CAB 30 mg PO	Observed$^{\beta}$ / Simulated RAL 400 mg PO
C_{12} (µg/mL)	- / -	0.036 / 0.036
C_{max} (µg/mL)	3.61 / 3.07	1.279 / 1.997
$AUC_{0-\infty}$ (µg.hr/mL)	146 / 98.2	4.884 / 9.281
	Observed$^{\gamma}$ / Simulated CAB 400 mg IM	Observed$^{\gamma}$ / Simulated CAB 800 mg IM
C_{Week4} (µg/mL)	0.40 / 0.74	2.0 / 2.6
C_{max} (µg/mL)	0.70 / 0.89	3.3 / 3.1
$AUC_{Week0-4}$ (µg.hr/mL)	290 / 534	1497 / 1856

Table 2: Predicted and reported PK of oral 400 mg raltegravir during pregnancy.

PK Variable**	Observed$^{\theta}$ / Simulated in 2nd Trimester	Observed$^{\theta}$ / Simulated in 3rd Trimester
C_{12} (ng/mL)	62.1 / 52.8	64.0 / 48.0
C_{max} (ng/mL)	2250 / 1985	1770 / 1970
AUC_{0-12} (ng.hr/mL)	6600 / 9781	5400 / 9581

Table 3: Predicted and reported PK of repeated intramuscular doses of long-acting injectable cabotegravir in adults.

PK Variable*	Observed$^{\phi}$ / Simulated CAB 800mg IM InD; 200 mg IM monthly	Observed$^{\phi}$ / Simulated CAB 800mg IM InD; 400 mg IM monthly	Observed$^{\phi}$ / Simulated CAB 800mg IM quarterly
C_{τ} (µg/mL)	1.61 / 1.64	3.27 / 2.42	1.1 / 1.4
C_{max} (µg/mL)	2.2 / 2.0	4.4 / 3.3	3.3 / 2.6
$AUC_{0-\tau}$ (µg.hr/mL)	1242 / 1254	2473 / 2019	4467 / 3947

*Data shown represent Geometric mean values. **Data shown represent Median values. PO – per oral, IM – intramuscular, InD – Induction dose, CAB – Cabotegravir, RAL – Raltegravir, C_{12} – Plasma concentration after 12 hours, Cτ – Plasma concentration after the end of the second dosing interval, C_{max} – Maximum plasma concentration, C_{Week4} – Plasma concentration at 4 weeks, $AUC_{Week0-4}$ - Area under the plasma concentration-time curve till 4 weeks, $AUC_{0-\tau}$ - Area under the plasma concentration-time curve till the end of the second dosing interval, $AUC_{0-\infty}$ - Area under the plasma concentration-time curve till infinity, α – Ford et al., 2017, β – Iwamoto et al., 2009, γ – Spreen et al., 2014a, θ – Watts et al., 2014, ϕ – Spreen et al., 2014b.

Pregnancy is predicted to have ***minimal influence*** on the PK of LAI CAB.

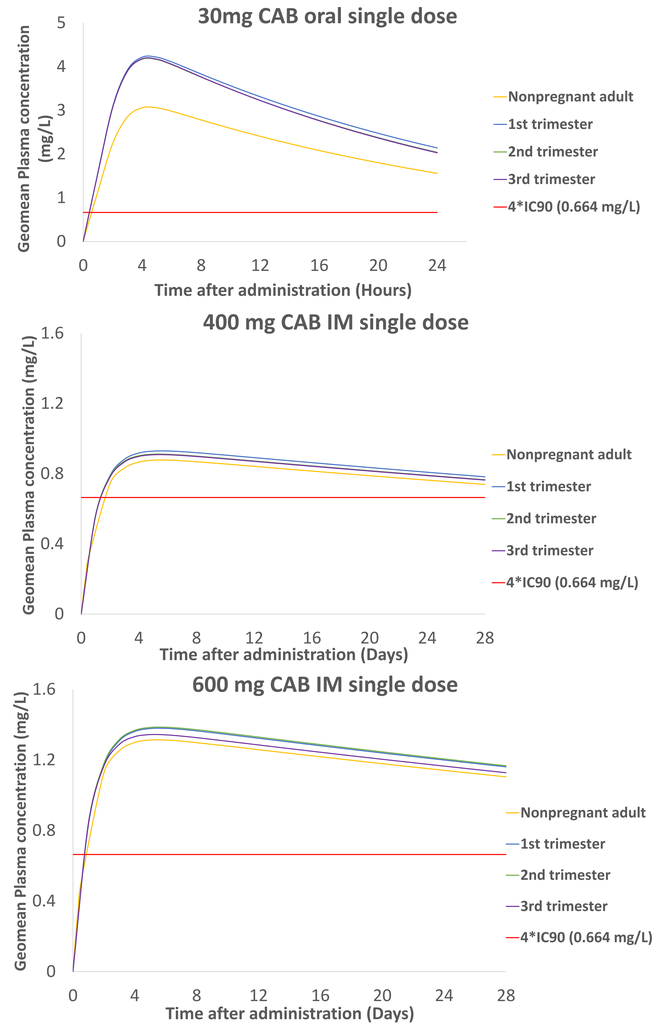

Figure 1: Predicted PK of single doses of oral 30 mg CAB and IM of 400 mg & 600 mg LAI CAB in non-pregnant and pregnant adults.

CONCLUSIONS

There was insufficient clinical PK data for model qualification in the first trimester. The predicted PK data suggest dosage adjustments are not necessary for IM LA CAB to maintain therapeutic concentrations and clinical efficacy during pregnancy. This approach could be utilised to predict the risk related to altered PK during pregnancy for IM LA therapy and support the design of future clinical trials in pregnant women.

REFERENCES

- Rajoli et al (2015)
- Rajoli et al (2018)
- Ford et al (2017)
- Watts et al (2014)
- Iwamoto et al (2009)
- Spreen et al (2014a)
- Spreen et al (2014b)

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