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CASE REPORT

Physiologically-based pharmacokinetic modeling of remdesivir and its metabolites in pregnant women with COVID-19

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Abstract

Pregnant individuals are at high risk for severe illness from COVID-19, and there is an urgent need to identify safe and effective therapeutics for this population. Remdesivir (RDV) is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor. Limited RDV pharmacokinetic (PK) and safety data are available for pregnant women receiving RDV. The aims of this study were to translate a previously published nonpregnant adult physiologically based PK (PBPK) model for RDV to pregnancy and evaluate model performance with emerging clinical PK data in pregnant women with COVID-19. The pregnancy model was built in the Open Systems Pharmacology software suite (Version 10) including PK-Sim® and MoBi® with pregnancy-related changes of relevant enzymes applied. PK were predicted in a virtual population of 1000 pregnant subjects, and prediction results were compared with in vivo PK data from the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network 2032 study. The developed PBPK model successfully captured RDV and its metabolites' plasma concentrations during pregnancy. The ratios of prediction versus observation for RDV area under the curve from time 0 to infinity ($AUC_{0-\infty}$) and maximum concentration (C_{max}) were 1.61 and 1.17, respectively. For GS-704277, the ratios of predicted versus observed were 0.94 for $AUC_{0-\infty}$ and 1.20 for C_{max}. For GS-441524, the ratios of predicted versus observed were 1.03 for AUC_{0-24}, 1.05 for C_{max}, and 1.07 for concentrations at 24 h. All predictions of AUC and C_{max} for RDV and its metabolites were within a twofold error range, and about 60% of predictions were within a 10% error range. These findings demonstrate the feasibility of translating PBPK models to pregnant women to potentially guide trial design, clinical decision making, and drug development.

INTRODUCTION

Pregnant individuals are at high risk for severe illness from COVID-19, including adverse pregnancy and maternal health outcomes.[1,2] Pregnant individuals have historically been excluded from participation in research protocols for drug development programs,[3,4] and this trend has continued during the COVID-19 pandemic despite the urgent need to identify safe and effective therapeutics during pregnancy.[5]

Remdesivir (RDV), a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleotide analog RNA polymerase inhibitor, is the first drug approved to treat COVID-19, the disease caused by the SARS-CoV-2 virus. RDV is administered intravenously due to high first-pass metabolism and is highly protein bound. RDV is a prodrug that is rapidly converted by plasma and liver hydrolases to an alanine intermediate (GS-704277) and then to a nucleoside analog monophosphate (GS-441524-MP) by phosphoramidase.[6,7] The nucleoside analog monophosphate is rapidly converted by intracellular kinases to the active triphosphate form (GS-443902), which competes with natural adenosine triphosphate to selectively inhibit RNA-dependent RNA polymerase. GS-441524-MP can also be dephosphorylated to GS-441524, the parent nucleoside form, which is the main metabolite and primary form that circulates in the blood throughout the dosing interval. GS-441524 can also be rephosphorylated and converted to the active triphosphate form, which has antiviral activity. Although physiological changes associated with pregnancy can have a large impact on drug disposition, limited pharmacokinetic (PK) data are available from pregnant individuals treated with RDV.[8]

Physiologically based PK (PBPK) modeling and simulation is a "bottom-up" approach that combines drug-specific characteristics and physiological information in a mechanistic framework to predict drug exposure. PBPK is well suited for pregnancy as it can integrate time-varying, pregnancy-related physiologic parameters that are relevant to PK processes, including maternal body weight, organ volumes/blood flows, cardiac output, transporter and enzyme expression/activities, and renal function.

The objectives of this study were to translate a previously published nonpregnant PBPK model for RDV[9] to pregnancy and evaluate the model performance with publicly available clinical PK data in pregnant women with COVID-19.[8]

METHODS

PBPK modeling

The Open Systems Pharmacology software suite (Version 10) including PK-Sim® and MoBi® was used for PBPK modeling. Here, a recently published PBPK model for nonpregnant adults[9] was translated to pregnancy following a previously described workflow.[10] The general adult model was transferred to MoBi®, where the standard model structure was replaced by the pregnancy model structure. The differences between the nonpregnant and pregnant model structure were described in detail previously.[11] After these adjustments, the model was exported to PK-Sim® for population simulations.

The pregnancy-related enzyme changes and renal elimination changes were applied to the model. Specifically, glomerular filtration was increased, on average, by ~30%[12] and tubular secretion by ~50%.[13] As suggested previously,[14] a 1.6-fold induction of cytochrome P450 3A4 (CYP3A4), which is a minor elimination pathway for RDV, was applied in the model. These changes were fixed during pregnancy across all gestational ages. The remaining enzymes involved in the metabolism of RDV, namely, carboxylesterase 1 (CES1) and cathepsin A (CatA), were assumed to be unaffected by pregnancy. The fraction unbound used in the nonpregnant PBPK model for RDV, GS-441524, and GS-704277 (0.12, 0.98, and 0.99, respectively) was scaled to pregnancy assuming that these compounds bind to albumin as described previously.[12] This resulted in values of 0.15, 0.98, and 0.99 for RDV, GS-441524, and GS-704277, respectively. GS-441524-MP and GS-443902 each have a fraction unbound of 1.0 in the nonpregnant PBPK model[9]; these values were kept unchanged in the pregnancy PBPK model. Model input parameters for RDV, GS-704277, and GS-441524 are included in Tables S1–S3. PK were predicted in a virtual population of 1000 pregnant subjects. The age, gestational age, and body weight ranges of this virtual population corresponded to those of the clinical study group described later. Model performance was assessed by visually and numerically comparing predicted with observed plasma concentrations and PK parameters. For RDV and GS-704277, the ratios of predicted versus observed values were determined for area under the curve from time 0 to infinity ($AUC_{0-\infty}$) and maximum concentration (C_{max}). For GS-441524, the ratios of predicted versus observed values were determined for AUC_{0-24}, C_{max}, and concentrations at 24 h post-dose (C_{24h}). Model performance was considered acceptable if prediction errors for $AUC_{0-\infty}$, AUC_{0-24}, C_{max}, and C_{24} did not exceed the twofold error range.

Clinical data used for model evaluation

The model was evaluated with emerging in vivo PK data from the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network 2032 Study, an ongoing phase IV, prospective, open-label, nonrandomized opportunistic study of pregnant and nonpregnant

women prescribed RDV for COVID-19.[8] Publicly available data were from 12 pregnant women who received RDV as a 1-h intravenous infusion (200 mg on Day 1 and 100 mg on Days 2–5). The median (range) gestational age at entry was 26.6 (21.9–32.7) weeks. The median (interquartile range) weight was 77 (71.1–93.4) kg, body mass index was 30.2 (27.9–37.2) kg/m^2, and estimated glomerular filtration rate was 129 (119–134) ml/min/1.73 m^2. Additional information on the clinical and demographic characteristics of the study population are found in Table S4.

RESULTS

Model prediction of RDV plasma concentration versus time profiles were in good agreement with the observed clinical data (Figure 1). The predicted RDV area under the curve from time 0 to infinity ($AUC_{0-\infty}$) was 1430 ng * h/ml, and C_{max} was 1143 ng/ml. The predicted GS-704277 $AUC_{0-\infty}$ and C_{max} were 401.1 ng * h/ml and 252 ng/ml, respectively. The predicted GS-441524 AUC_{0-24}, C_{max}, and C_{24} were 1857 ng * h/ml, 113.7 ng/ml, and 55.1 ng/ml, respectively. For RDV, the ratios of predicted versus observed were 1.61 for $AUC_{0-\infty}$ and 1.17 for C_{max}. For GS-704277, the ratios of predicted versus observed were 0.94 for $AUC_{0-\infty}$ and 1.20 for C_{max}. For GS-441524, the ratios of predicted versus observed were 1.03 for AUC_{0-24}, 1.05 for C_{max}, and 1.07 for C_{24h}. All predictions of AUC, C_{max}, and C_{24h} were within a twofold error range, and 57.1% were within a 10% error range (Table 1).

DISCUSSION

This is the first reported PBPK model of RDV and its metabolites in pregnancy. The model successfully predicted

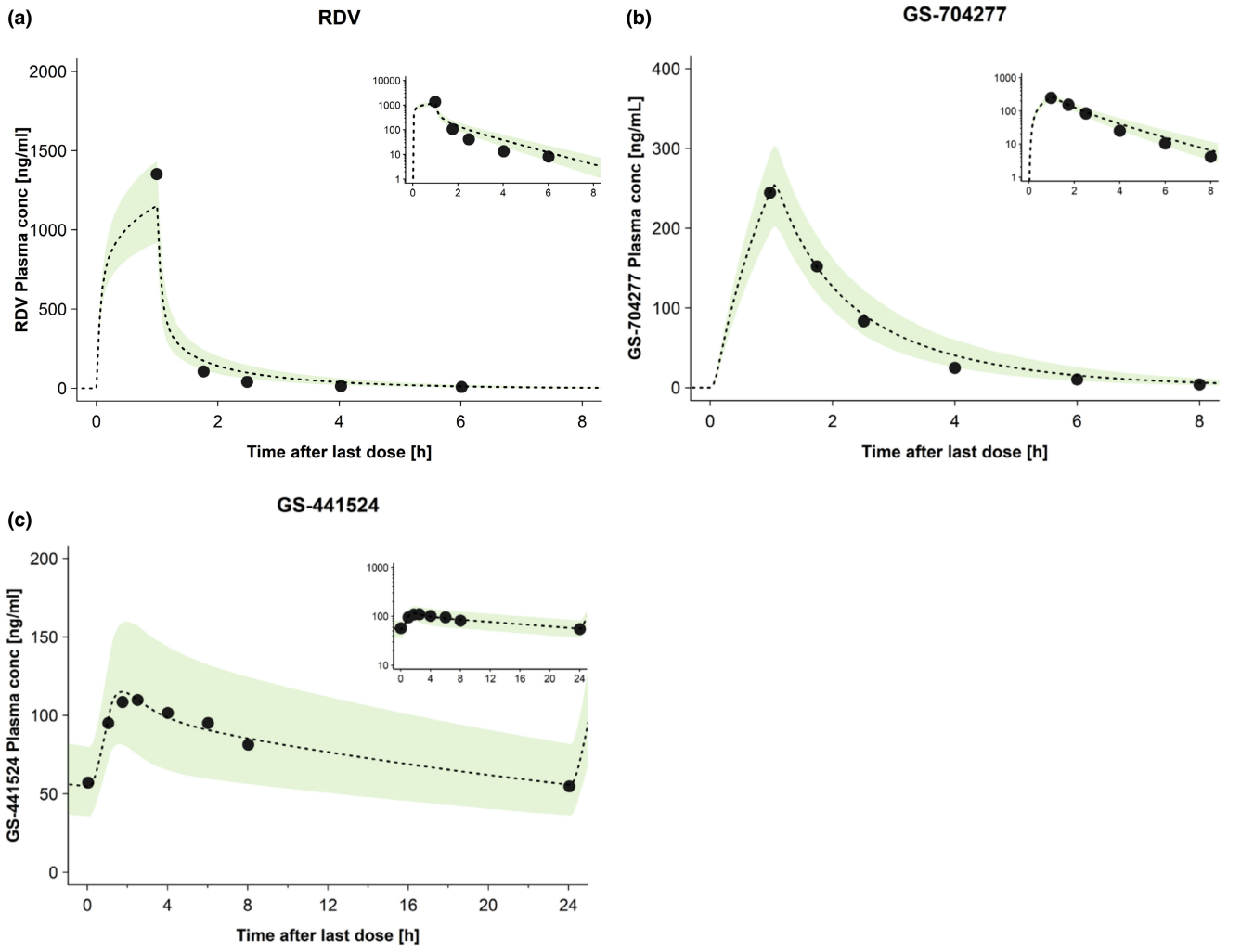

FIGURE 1 Plasma concentration–time profiles of (a) RDV, (b) GS-704277, and (c) GS-441524 following a 1-h intravenous infusion of 200 mg on Day 1 and then 100 mg once a day for Days 2–5 in pregnant women with an average gestational age of 26.6 weeks. Semilog scale figures are shown as inset figures. Observed steady-state in vivo data shown as dark circles were from the IMPAACT 2032 study.[8] The dotted line represents the predicted median concentration, and the shaded area shows the predicted 5th–5th percentile range. RDV, remdesivir

TABLE 1 Physiologically based pharmacokinetic model predictions versus observations of RDV, GS-704277, and GS-441524 in pregnant women

	Prediction/observation (geometric mean)	Ratio
RDV $AUC_{0-\infty}$ (ng * h/ml)	1430.3/888.1	1.61
RDV C_{max} (ng/ml)	1143/973	1.17
GS-704277 $AUC_{0-\infty}$ (ng * h/ml)	401.1/424.6	0.94
GS-704277 C_{max} (ng/ml)	252/210	1.20
GS-441524 AUC_{0-24} (ng * h/ml)	1857/1804	1.03
GS-441524 C_{max} (ng/ml)	113.7/108.7	1.05
GS-441524 C_{24h} (ng/ml)	55.1/51.7	1.07

Abbreviations: AUC_{0-24}, area under the curve over 24 h; $AUC_{0-\infty}$, area under the curve from time 0 to infinity; C_{24h}, concentration at 24 h post-dose; C_{max}, maximum concentration; RDV, remdesivir.

plasma exposures of RDV, GS-704277, and GS-441524 in pregnant women, with the majority of predictions within a 10% error range. PBPK model-predicted values for RDV and its metabolites during pregnancy did not significantly differ in comparison with observed data in nonpregnant women.[8] These findings are in good agreement with emerging clinical data where RDV $AUC_{0-\infty}$ and C_{max} during pregnancy were reduced by 18.9% and 10.9%, respectively; GS-704277 $AUC_{0-\infty}$ and C_{max} were similar between pregnant and nonpregnant women; and GS-441524 AUC_{0-24}, C_{max}, and C_{24} were reduced by 15.1%, 12.3%, and 10.4% during pregnancy.[8] Although the simulated plasma exposures of RDV and its metabolites in pregnant women did not significantly differ in comparison with nonpregnant women,[8] intracellular peripheral blood mononuclear cell (PBMC) concentrations may differ during pregnancy, and it is unclear whether this has implications for dosing.[8] Because the active drug's target is located intracellularly,[7] further studies could investigate the intracellular concentration of the active drug of RDV and potential pharmacodynamic changes in pregnancy.

RDV has a complicated metabolic pathway involving CES1, CatA, and CYP3A4. CES1 and CatA are involved with hydrolyzing RDV to an alanine intermediate while CYP3A4 plays a minor role through oxidative metabolism. The approximate contributions of CES1, CatA, and CYP3A4 to RDV metabolism are 80%, 10%, and 10%, respectively.[15,16] Further metabolism is facilitated via phosphoramidase, nucleotidase, and adenosine kinase enzymes. Pregnancy-related physiological changes may increase or decrease the expression and activity of individual enzyme systems. Changes in CYP3A4 activity have been well studied in pregnancy. However, there are limited data on the activity of CES1 and CatA activity during pregnancy.[17] Thus, the enzyme activity changes during pregnancy in the developed PBPK model included only CYP3A4 changes (1.6-fold induction). As CES1 accounts for 80% of RDV metabolism, the developed PBPK model suggests that CES1 activity is not significantly altered during pregnancy, at least not at the gestational age studied here (median [range]: 26.6 [21.9–32.7] gestational weeks). However, this finding is somewhat weakened by the fact that RDV plasma concentrations were only measured until 6 h post dose. Although the half-life of RDV is very short (~1 h in nonpregnant subjects), blood samples at later times might provide further insights into the elimination phase of RDV and corroborate the hypothesis of unchanged CES1 activity in the late second trimester of pregnancy. Additional studies with other CES1 substrates are needed to confirm this finding. GS-441524 is renally eliminated, and pregnancy-associated increases in glomerular filtration rate (on average ~ 30%) were incorporated in the PBPK model.

The current study has some limitations. The pregnancy PBPK model was parameterized based on physiological data from healthy pregnant women; COVID-19 was not assumed to have an influence on physiological model parameters, as has also been done in some previous nonpregnant PBPK models applied to COVID-19 patients.[18–20] However, other PBPK models for COVID-19 patients, including the model published by Fan et al.,[9] did consider organ dysfunction. Furthermore, the developed PBPK model did not include transporters, although RDV has been reported to be a substrate of P-glycoprotein (P-gp) and organic anion transporting polypeptide (OATP) 1B1.[7] A previous study investigating the PK of digoxin, a P-gp substrate, during pregnancy (28–32 weeks gestation) and postpartum (6–10 weeks) found that the unbound tubular secretion clearance was ~1.9-fold higher in pregnancy, suggesting increased renal P-gp activities during pregnancy.[21] As described elsewhere,[13] the pregnancy PBPK model scales tubular secretion via pregnancy-related changes in kidney size; here, this resulted in an increase in tubular secretion of, on average, ~50%, hence underestimating the P-gp–mediated tubular secretion of RDV. Plasma concentrations of RDV were only measured until 6 h post dose, making it difficult to assess whether the model truly underestimates RDV clearance. On the other hand, COVID-19 patients often present with kidney failure, which may outweigh pregnancy-related increases in (healthy) pregnant individuals. Clinical studies examining the activity of OATP1B1 during pregnancy by means of probe drugs are lacking; however, quantification of OATP1B1 protein abundance in liver-derived small extracellular vesicles prepared from the sera of pregnant women (liquid biopsies) did not suggest changes in OATP1B1 expression throughout pregnancy.[22] Finally,

clinical PK data from a relatively small number ($n = 21$) of pregnant women with a 10-week span of estimated gestational ages across second and third trimesters receiving RDV for COVID-19 were available for model evaluation.

The developed PBPK model successfully predicted plasma exposures of RDV and its metabolites in pregnant women. Although plasma exposures of RDV, GS-704277, and GS-441524 were not significantly altered during pregnancy, a prior report indicates that intracellular PBMC concentrations may be lower, which needs to be further explored in relation to RDV dosing in pregnancy.[8] However, PBMCs may not be important target cells and only approximate intracellular levels in other cells. Other target cells also may need to be defined, and metabolite concentrations in those cells may need to be explored. In addition, further research on fetal exposure to RDV and its metabolites as well as fetal safety is needed.

This study illustrates the utility of PBPK modeling as a bottom-up approach to predict the disposition of new drugs in pregnant women. PBPK modeling can potentially be used as a tool to stratify when pregnancy PK studies with intensive sampling are necessary or when PK changes are predicted to be minimal without the need for dosing adjustments. In the latter case, opportunistic pregnancy PK studies with sparse sampling could be used to validate PBPK pregnancy models.

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CONFLICT OF INTEREST

Drs. Brooks, Best, Clarke, Mirochnick, Capparelli, and Momper have received support from Gilead Sciences, Inc. Dr. Dallmann is an employee of Bayer AG and uses Open Systems Pharmacology software, tools, and models in his professional role. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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