ARTICLE

Semimechanistic Modeling to Guide Venetoclax Coadministration with Ritonavir and Digoxin

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Venetoclax is a cytochrome P450, family 3, subfamily A (CYP3A) substrate and was shown to inhibit P-gp efflux transporters in vitro. To quantify the impact of CYP3A inhibition by ritonavir on venetoclax disposition and P-gp inhibition by venetoclax on digoxin pharmacokinetics, two semimechanistic drug-drug interaction (DDI) models of venetoclax were developed using clinical data from healthy volunteers who received subtherapeutic doses of venetoclax with ritonavir 50–100 mg or digoxin 0.5 mg. These models were then used to assess the magnitude of interaction at therapeutic venetoclax doses and to explore various clinical dosing strategies that maintain venetoclax and digoxin concentrations within their respective therapeutic windows. Simulations demonstrated that venetoclax dose reductions of at least 75% are needed when venetoclax is coadministered with ritonavir and administering digoxin at least 2 hours before venetoclax would minimize DDI. Semimechanistic modeling leveraging clinical data is a plausible approach to predict DDI and propose dose adjustments, and administration time of interacting drugs.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✔ The metabolic profile of subtherapeutic doses of venetoclax with respect to cytochrome P450, family 3, subfamily A (CYP3A) metabolism and P-gp inhibition has been well-characterized in preclinical and clinical studies.

WHAT QUESTION DID THIS STUDY ADDRESS?

✔ What are the predicted magnitudes of drug interactions between therapeutic doses of venetoclax and CYP3A inhibitors or P-gp substrates in patients with chronic lymphocytic leukemia? How to modify venetoclax dosing regimen to allow co-administration?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✔ This study provides a semimechanistic modeling framework for the characterization of CYP3A-mediated and P-gp-mediated drug interactions for venetoclax.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

✔ Semimechanistic models can be leveraged to assess the impact of drug-drug interactions without the complexity of physiologically-based pharmacokinetic models.

Venetoclax (ABT-199, GDC-0199) is a selective inhibitor of the anti-apoptotic B cell lymphoma-2 (BCL-2) protein. It is currently approved for the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma, with or without 17p deletion, who have received at least one prior therapy, and patients with acute myeloid leukemia who have comorbidities which prevent the use of chemotherapy.1–4 Venetoclax has also shown efficacy in a variety of hematological malignancies in which BCL-2 is overexpressed, including non-Hodgkin’s lymphoma and multiple myeloma.5–7

The clinical pharmacokinetics (PK) of venetoclax has been characterized in patients with cancer and healthy volunteers.8–12 Under fed conditions, peak concentrations are observed between 5 and 8 hours after dosing and the half-life is ~15 hours.13 Venetoclax and its major metabolite, M27, are metabolized primarily by cytochrome P450, family 3, subfamily A (CYP3A) enzyme.14–16 Venetoclax is also a substrate and an inhibitor of the efflux transporter P-gp.17,18

Drug-drug interactions (DDIs) between venetoclax and medications that modulate CYP3A and/or are transported by P-gp have been previously characterized at subtherapeutic doses of venetoclax.19–21 The aim of the present work was to develop two integrated semimechanistic models of DDIs using the clinical data in order to predict changes in drug exposures at clinical doses of venetoclax and to guide dosing recommendations. The first model is for ritonavir, an inhibitor and inducer of CYP3A, with venetoclax (RTV-VEN model); and the second model is for venetoclax with digoxin, a P-gp substrate (VEN-DIG model).

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METHODS
Studies
PK data from two clinical studies in healthy female volunteers were included in the semimechanistic models. The studies were conducted in accordance with Good Clinical Practice guidelines and the ethical principles first originated from the Declaration of Helsinki. The study protocols were approved by the institutional review board and participants provided written informed consent before any study-related procedures were performed.

The details of the study designs have been described previously and are illustrated in Figure S1. For the evaluation of the effects of ritonavir on venetoclax, 20 subjects received a single dose of venetoclax 10 mg alone or with ritonavir (single dose of 50 or 100 mg or multiple doses of 50 mg q.d.) in a parallel-study design. For the evaluation of the effects of venetoclax on digoxin, 10 subjects received a single dose of digoxin 0.5 mg alone or with a single dose of venetoclax 100 mg in a two-sequence crossover study design. All drugs were administered orally. Serial blood samples were obtained to determine drug plasma concentrations, and urine samples were obtained only for digoxin to measure urine concentrations. Drug concentrations were measured using validated methods. The lower limits of quantitation were 2.11 ng/mL for venetoclax, 9.73 ng/mL for ritonavir, 0.01 ng/mL for digoxin in plasma, and 2.00 ng/mL for digoxin in urine. The accuracy of the assays (% bias) ranged from −4.7% to 7.1% and the precision (percentage of coefficient of variation) ranged from 1.6% to 9.6%.

![Figure 1](https://example.com/figure1.png)

**Figure 1** Final model for (a) venetoclax-ritonavir interaction and (b) digoxin-venetoclax interaction. CL, total body clearance (L/hour); Fe, fractional renal clearance (%); F1, relative bioavailability of digoxin when given with venetoclax; IC50, VC50 that achieves 50% inhibition; ICmax, maximal inhibition (%); Ka, absorption rate constant (1/hour); Ka eff, effect absorption rate constant (1/hour); Q, intercompartmental clearance (L/hour); VCg, venetoclax gut concentration.
Semimechanistic models

Model development and evaluation. The RTV-VEN and VEN-DIG semimechanistic PK models were developed using NONMEM version 7.3. For the RTV-VEN semimechanistic model, one-compartment and two-compartment PK models were fitted to ritonavir and venetoclax plasma concentration data, respectively. The decrease in the clearance of both drugs (ritonavir and venetoclax) was described by multiplicative maximal inhibition ($I_{\text{max}}$) functions of ritonavir plasma concentrations to account for the nonlinearity of ritonavir PK and the decrease in venetoclax clearance due to the net inhibitory effect of CYP3A. Separate parameters of the $I_{\text{max}}$ model were estimated for each drug to allow for the possibility of other metabolic pathways and different tissue distributions of ritonavir and venetoclax. For the VEN-DIG semimechanistic model, two-compartment PK models were fitted to both venetoclax and digoxin plasma concentrations with an additional compartment for digoxin urine concentrations. The increase in the digoxin absorption rate constant was described by a multiplicative $I_{\text{max}}$ function of venetoclax gastrointestinal concentrations, and a relative bioavailability was estimated in the presence of venetoclax. The model was fit under the following key assumptions: P-gp is only directly inhibited in the gastrointestinal tract by venetoclax, digoxin renal clearance remains unchanged (as supported by clinical data), and venetoclax inhibitory effect lasts only 13 hours, which is the total physiological transit time of the stomach and small intestine in humans. Different venetoclax absorption models were developed for the RTV-VEN and VEN-DIG semimechanistic models based on the extent of the data and ability to estimate parameters.

Model validation and simulations. Internal validation of the models was performed using visual predictive checks and numerical predictive checks of the maximum concentration ($C_{\text{max}}$) and area under the curve (AUC) ratios.

Figure 2. Visual predictive checks of (a) venetoclax and ritonavir plasma concentrations and (b) venetoclax plasma concentrations, digoxin plasma concentrations, and digoxin urine concentrations after the first dose.
of venetoclax with and without ritonavir; and digoxin with and without venetoclax. Upon validation, simulations were conducted to (i) evaluate different venetoclax dose reduction recommendations for concomitant use of strong CYP3A inhibitors (ritonavir), (ii) predict the effect of venetoclax clinical dose (400 mg q.d.) on digoxin PK, and (iii) predict the effect of different digoxin administration times relative to venetoclax dose on the PK of digoxin.

**RESULTS**

A total of 828 concentrations from the 20 female subjects in the ritonavir study (327 ritonavir plasma concentrations and 501 venetoclax plasma concentrations) and 562 concentrations from the 10 female subjects in the digoxin study (341 digoxin plasma concentrations, 130 digoxin urine concentrations, and 91 venetoclax plasma concentrations) were included in the analysis data sets.

**Figure 1a,b** display schematics of the two structural semimechanistic models that were fit to the clinical data. There was good agreement between the observed and model-predicted drug concentrations, as shown by the visual predictive checks (**Figure 2a,b**) and numerical predictive checks (**Table 1**) for each model.

**Ritonavir**

A ritonavir proportional residual error model with first-order absorption and a venetoclax proportional residual error model with time-dependent absorption best described the data. The \( I_{\text{max}} \) of ritonavir clearance was fixed at 1 (i.e., 100% inhibition) and the ritonavir concentration to achieve the 50% \( I_{\text{max}} \) (half-maximal inhibitory concentration (IC\(_{50}\)) was estimated at 0.056 µg/mL, whereas the estimates (\( I_{\text{max}} \) and IC\(_{50}\)) for venetoclax were 0.892 and 0.0008 µg/mL, respectively (**Table 2**). The decrease in ritonavir clearance due to CYP3A inhibition had to be incorporated in the model to account for ritonavir nonlinear PKs with increases in dose. Comparisons of models with and without time-dependent CYP3A inhibition and induction indicated that competitive inhibition was sufficient to explain the observed data for ritonavir and venetoclax.

**Figure 3** shows that a fourfold to eightfold reduction in venetoclax dose (from 400 mg) with ritonavir 100 mg q.d. is predicted to result in venetoclax exposures within the range of the therapeutic window of 400–1,200 mg q.d. with mono-therapy in CLL.15

**Digoxin**

For the VEN-DIG model, venetoclax data were best fit by a combined residual error model with first-order absorption plus a lag time, and the digoxin data by a proportional residual error model with first-order absorption plus a lag time at which \( Ka \) is 50% of \( Ka_{\text{max}} \); \( V2 \), volume of central compartment; \( V3 \), volume of peripheral compartment; \( V_{/RIC_{50}} \), concentration to achieve 50% \( I_{\text{max}} \) for venetoclax and ritonavir; respectively.

**Table 2** Final parameter estimates for the ritonavir-venetoclax drug interaction semimechanistic model

| Parameter | Estimate | RSE% |
|-----------|----------|------|
| Venetoclax pharmacokinetics |          |      |
| CL, L/day | 304      | 9    |
| V2, L     | 26.8     | 35   |
| Q, L/day  | 124      | 15   |
| V3, L     | 83.5     | 7    |
| Ka\(_{\text{max}}\), 1/day | 4.76     | 16   |
| T\(_{50}\), day | 0.13     | 7    |
| γ | 5 (fixed*) | –    |
| \( I_{\text{max}} \), % | 0.892    | 2    |
| V\(_{RIC_{50}}\), mg/L | 0.00008 | 36   |
| F1, %     | 1.19     | 13   |
| CL BSV, %CV | 32.6 | 18   |
| V2 BSV, %CV | 64      | 25   |
| T\(_{50}\) BSV, %CV | 26.1    | 21   |
| Ritonavir pharmacokinetics |          |      |
| CL, L/day | 1560     | 12   |
| V2, L     | 30.7     | 17   |
| Ka, 1/day | 1.17     | 5    |
| R\(_{RIC_{50}}\), mg/L | 0.056   | 16   |
| CL BSV, %CV | 17.9   | 15   |
| V2 BSV, %CV | 54.7    | 19   |

\( BSV \), between subject variability; CL, clearance; F1, bioavailability; γ, shape factor; \( I_{\text{max}} \), maximal inhibition; Ka\(_{\text{max}}\), maximum absorption rate constant (Ka); Q, intercompartmental clearance; RSE, relative standard error T\(_{50}\), time at which Ka is 50% of Ka\(_{\text{max}}\); V2, volume of central compartment; V3, volume of peripheral compartment; V\(_{/RIC_{50}}\), concentration to achieve 50% \( I_{\text{max}} \) for venetoclax and ritonavir; respectively.

*Estimated value from venetoclax combined data. When estimated, it was 5.29, but covariance step failed.

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**Table 1** Numerical predictive checks for the effect of ritonavir on venetoclax plasma pharmacokinetics and the effect of venetoclax on digoxin plasma pharmacokinetics

| Effect of single-dose ritonavir on venetoclax (period 1 day 1 vs. period 2 day 1) | Observed | Predicted |
|---------------------------------|----------|-----------|
|                                 | Central value | 5th | Median | 95th |
| Cohort 1 C\(_{\text{max}}\) ratio | 2.4 | 2.1 | 2.7 | 3.1 |
| AUC\(_{\text{inf}}\) ratio | 6.1 | 4.8 | 5.4 | 6.1 |
| Cohort 2 C\(_{\text{max}}\) ratio | 2.3 | 2.2 | 2.6 | 3.3 |
| AUC\(_{\text{inf}}\) ratio | 8.1 | 5.5 | 6.2 | 6.9 |
| Cohort 3 C\(_{\text{max}}\) ratio | 2.3 | 2.2 | 2.5 | 3.0 |
| AUC\(_{\text{inf}}\) ratio | 7.2 | 5.4 | 6.5 | 7.6 |

| Effect of multiple-dose ritonavir on venetoclax (period 1 day 1 vs. period 2 day 11) | Observed | Predicted |
|---------------------------------|----------|-----------|
|                                 | Central value | 5th | Median | 95th |
| Cohort 3 C\(_{\text{max}}\) ratio | 2.4 | 2.3 | 2.6 | 3.2 |
| AUC\(_{\text{inf}}\) ratio | 7.9 | 5.5 | 6.7 | 7.9 |

| Effect of venetoclax on digoxin | Observed | Predicted |
|---------------------------------|----------|-----------|
|                                 | Central value | 5th | Median | 95th |
| – C\(_{\text{max}}\) ratio | 1.4 | 1.2 | 1.4 | 1.5 |
| AUC\(_{\text{inf}}\) ratio | 1.1 | 1.0 | 1.1 | 1.1 |

AUC of venetoclax area under plasma concentration-time curve from zero until 96 hours postdose; AUC of area under the curve from zero until infinity; \( C_{\text{max}} \), maximum concentration. Ratios refer to \( C_{\text{max}} \) or AUC values observed during co-administration compared with those observed alone. Cohort 1: venetoclax 10 mg with a single dose of ritonavir 50 mg vs. venetoclax alone; Cohort 2: venetoclax 10 mg with a single dose of ritonavir 100 mg vs. venetoclax alone; Cohort 3: venetoclax 10 mg with ritonavir 50 mg q.d. for 11 days vs. venetoclax alone. Digoxin study: digoxin 0.5 mg with a single dose of venetoclax 100 mg vs. digoxin alone. See Figure S1 for additional details.
time. The estimated venetoclax $I_{\text{max}}$ and the gastrointestinal concentration to achieve $IC_{50}$ were 2.96 and 0.327 µg/mL, respectively (Table 3). The predicted median (95% confidence interval) increases in digoxin $C_{\text{max}}$ and $AUC_{\infty}$ when venetoclax 400 mg q.d. was administered at the same time as digoxin were 34% (23–53%) and 8% (3.4–12.5%), respectively. The numerical predictive checks showed that the predicted values are similar to the observed increases in digoxin $C_{\text{max}}$ and $AUC$ when a single dose of venetoclax 100 mg was administered at the same time as digoxin in the drug interaction study (Table 1). Based on the simulations, administration of digoxin ≥ 2 hours before venetoclax would result in negligible changes in digoxin $C_{\text{max}}$ and $AUC$, whereas administration of digoxin 2–8 hours after administration of venetoclax would result in a larger increase in digoxin $C_{\text{max}}$ than that observed with simultaneous dosing (Figure 4).

DISCUSSION

Venetoclax is a potent, selective, BCL-2 inhibitor that is approved for the treatment of certain hematological malignancies. Venetoclax is metabolized by CYP3A enzymes and is an inhibitor of P-gp transporters; thus, administration of concomitant medications whose disposition involves these pathways may result in drug interactions in patients being treated with venetoclax. This study presents integrated semimechanistic models of drug interactions for ritonavir with venetoclax, and venetoclax with digoxin, used to predict changes in drug exposures at therapeutic doses of venetoclax that had not been directly studied. The semimechanistic models adequately characterized interactions observed in two clinical studies. Results from simulations based on these models indicated venetoclax dose reduction of at least 75% is needed when venetoclax is co-administered with ritonavir 100 mg q.d., and administration of digoxin at least 2 hours before venetoclax can minimize DDI.

Ritonavir was shown to have competitive and time-dependent inhibition and induction of CYP3A with an overall net inhibition. An attempt was made to incorporate all effects; however, our limited data precluded building a full mechanistic model. Further, model comparisons confirmed the adequacy of a simple model with competitive inhibition component only. Because the currently available physiologically-based pharmacokinetic model of ritonavir did not predict observed ritonavir data well, we used clinical data to develop a semimechanistic model that better describes ritonavir nonlinear PK attributed to CYP3A automodulation, which was then linked to the venetoclax PK model to estimate the magnitude of DDI. The RTV-VEN model predicted fourfold to eightfold dose adjustments of venetoclax when combined with ritonavir to be adequate based on venetoclax exposure-response relationships assessed in subjects with CLL, acute myeloid leukemia, non-Hodgkin’s lymphoma, or multiple myeloma. To avoid the risk of lymphopenia, an on-target effect of venetoclax, a single subtherapeutic dose (100 mg) of venetoclax was studied in female healthy volunteers in the digoxin drug-interaction study. In that study, digoxin $C_{\text{max}}$ and $AUC$ were increased by 35% and 9%, respectively, with no changes in half-life or renal clearance. These clinical results form the basis for our assumption that the increases in digoxin exposures were due to venetoclax inhibition of CYP3A enzymes.
intestinal P-gp only, whereas renal P-gp remains unaffected.
We also assumed the effect of venetoclax inhibition lasts 13 hours because it is the total physiological transit time of
the stomach and small intestines in humans. The transit time
of the remaining gastrointestinal tract regions was ignored
as minimum drug absorption is expected, especially for di-

goxin that is absorbed quickly.

The simulation results from the VEN-DIG model pre-
predicted similar changes in digoxin exposures (34% and
8% increases in Cmax and AUCinf, respectively) with a
venetoclax therapeutic dose (400 mg q.d.). The estimated
venetoclax IC50 for P-gp inhibition and the high oral bio-
availability of digoxin are in line with these predictions.
Assuming a gastrointestinal volume of 250 mL and 33.63%
absolute bioavailability of venetoclax,31 the intestinal con-
centration of venetoclax following a single dose of 100 mg
is expected to be 400-fold greater than the P-gp IC50 value
of 0.32 mg/L; therefore, the increase in digoxin Cmax with
400 mg q.d. dosing of venetoclax is not expected to ex-
cede what was observed with the single 100 mg dose. In
addition, the PK sampling scheme did not allow estimating
interindividual variability for some parameters, such as the
absorption rate constant, which might limit the applications
of the model.

In addition, the high absolute bioavailability of digoxin ex-
plains the greater effect of venetoclax on digoxin Cmax than
AUCinf when digoxin is administered with or after veneto-
clax. This is because the increase of digoxin bioavailability
(8%) is small relative to its absolute bioavailability (~ 80%)32
as shown in Figure 4. For drugs with low oral bioavailabil-
ity, the increase in AUC is expected to be larger because
the ratio of increase to the absolute bioavailability will be
larger. Assuming the magnitude and duration of intestinal
P-gp inhibition by venetoclax are consistent, the co-admin-
ístration of other P-gp substrates with or after venetoclax
will also likely result in an increase in Cmax and AUC where
the magnitude will depend on the drug rate of absorption
and absolute bioavailability, respectively. Because complete
venetoclax inhibition of P-gp is not achieved until 2 hours,
a lower increase in Cmax is expected with the simultaneous

### Table 3 Final parameter estimates for the venetoclax-digoxin drug interaction semimechanistic model

| Parameter          | Digoxin pharmacokinetics | Venetoclax pharmacokinetics |
|--------------------|--------------------------|-----------------------------|
|                    | Estimate | RSE% |                | Estimate | RSE% |
| CL, L/hour         | 15.7     | 4    | CL, L/hour     | 4.47      | 8    |
| V2, L              | 150      | 18   | V2, L          | 19.1      | 30   |
| Q, L/hour          | 87.8     | 9    | Q, L/hour      | 1.28      | 24   |
| V3, L              | 592      | 5    | V3, L          | 25.4      | 16   |
| Ka, 1/hour         | 0.777    | 19   | Ka, 1/hour     | 0.209     | 21   |
| D, ALAG h          | 0.536    | 19   | V_ALAG, h      | 1.72      | 4    |
| Fe, %              | 0.438    | 2    |                | 0.3363 (fixed) | -    |
| F1, %              | 1.08     | 2    | CL BSV, %CV    | 22         | 27   |
| CL BSV, %CV        | 12.3     | 25   | I_max          | 2.96      | 51   |
| V2 BSV, %CV        | 28.9     | 31   | IC50, mg/L     | 0.327     | 44   |

ALAG, absorption lag time (hour); BSV, between subject variability; CL, clearance; F1, bioavailability; Fe, fraction of administered drug excreted into the urine; Ka, first-order absorption rate constant; Q, intercompartmental clearance; RSE, relative standard error; V2, volume of central compartment; V3, volume of peripheral compartment.

*Based on bioavailability in monkeys and moderate fat diet effect on bioavailability in humans.

Figure 4 The effect of digoxin administration time relative to venetoclax dose on digoxin exposures. AUCinf area under the curve from zero to infinity; Cmax, maximum concentration.
administration and with drugs that are absorbed in < 2 hours. Similarly, the recommended 2-hour window of digoxin administration before venetoclax is dependent on rate of absorption of concomitant P-gp substrate drug. The window would be longer for slowly absorbed drugs and shorter for quickly absorbed medications. Thus, our finding is specific to digoxin and cannot be generalized to other P-gp substrate drugs.

CONCLUSION

The recommended venetoclax dose reduction of at least 75% during co-administration with ritonavir and the recommended digoxin administration of at least 2 hours before venetoclax 400 mg q.d. are expected to be optimal in patients with CLL. Semimechanistic models can accurately predict the effect of drug interactions without the need for complex physiologically-based pharmacokinetic modeling.

Supporting Information. Supplementary information accompanies this paper on the Clinical and Translational Science website (www.cts-journal.com).

Figure S1. Study designs.
Figure S2. Goodness of fit plots for the final RTV-VEN model.
Figure S3. Goodness of fit plots for the VEN-DIX model.

NONMEM Control Stream for RTV-VEN interaction semi-mechanistic model.
NONMEM Control Stream for VEN-DIX interaction semi-mechanistic model.

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Conflict of Interest. A.H.S. and K.J.F. are AbbVie employees and may own stock. A.A.A. declared no competing interests for this work.

Author Contributions. A.A.A., A.H.S., and K.J.F. wrote the manuscript. A.A.A., A.H.S., and K.J.F. designed the research. A.A.A., A.H.S., and K.J.F. performed the research. A.A.A., A.H.S., and K.J.F. analyzed the data.

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