



An Integrated Pharmacokinetic/Viral Dynamic Model for Daclatasvir/Asunaprevir in Patients with Genotype 1 Chronic Hepatitis C



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Objective:

To develop an integrated pharmacokinetic/viral dynamic model to predict long-term virological response rates of daclatasvir (DCV) and asunaprevir (ASV) combination therapy in patients infected with genotype 1 (GT 1) chronic hepatitis C virus (HCV).

Methods:

A systematic publication search was conducted for DCV or ASV monotherapy or combination therapy in healthy volunteers or patients infected with GT 1 HCV. A meta-database consisting of 635 study-level aggregate concentrations and 952 individual-level viral load data were captured from 13 clinical studies. An integrated pharmacokinetic/viral dynamic model was sequentially developed to characterize the effect of DCV and ASV on decline of HCV viral RNA. The viral dynamic model was linked to the pharmacokinetic models via an effect compartment to account for the possible time delay observed between plasma drug concentrations and antiviral activity. A sigmoid E_{MAX} function was applied to describe the antiviral effect of DCV and ASV depending on the drug concentrations in the effect compartment. To capture the rebound of viral load observed in the MAD studies due to the rapid emergence of viral resistance, an empirical exponential function with a rate coefficient $K_{r,ik}$ to model the change of $IC_{50,ijk}$ over time during therapy :

$$IC_{50,ijk} = IC_{50,t=0,ik} \cdot e^{-K_{r,ik} \cdot t}$$

where $IC_{50,ijk}$ is the j^{th} concentration of i^{th} subject of drug k (k represents DCV or ASV, the same hereinafter) in the effect compartment. The combined antiviral efficacy $E_{COMB,ij}$ of DCV and ASV was assumed to take an additive form:

$$E_{COMB,ij}/(1 - E_{COMB,ij}) = E_{DCV,ij}/(1 - E_{DCV,ij}) + E_{ASV,ij}/(1 - E_{ASV,ij})$$

The pharmacokinetic/viral dynamic model was evaluated externally by comparing the predicted and observed virological response rates.

Results:

A total of 13 clinical trials, representing 43 treatment arms with 148 healthy volunteers and 809 HCV infected patients were included in this analysis. Of these, 10 trials provided aggregate concentration data for pharmacokinetic models, 4 trials provided individual viral load data for viral dynamic models and 3 trials provided virological response information for model evaluation.

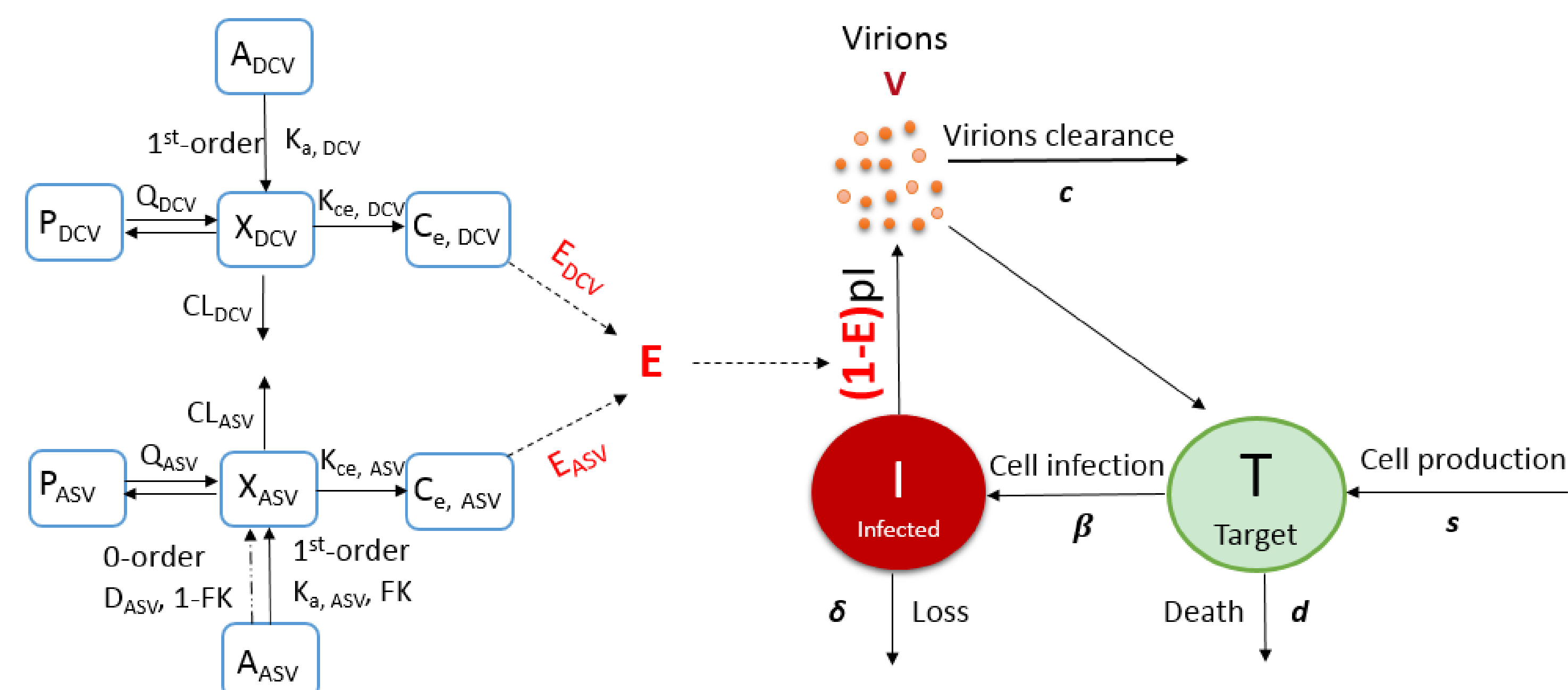


Figure 1: Structure of the integrated pharmacokinetic/viral dynamic model.

All pharmacokinetic parameters were estimated with reasonable precision (relative standard errors < 30%). Dose and subject type were the only two significant covariates. The effect of dose on CL of DCV or FK of ASV was characterized with a linear model after $\log_{10}$ -transformation of dose:

$$\theta_{mk} = (\hat{\theta}_k + \beta_{k,Dose} \cdot (\log_{10}(Dose_{mk}) - \log_{10}(Dose_{k,median}))) \cdot \exp(\eta_{\theta_{mk}})$$

where θ_{mk} is the pharmacokinetic parameter of drug k in m^{th} arm, $\hat{\theta}_k$ is the typical value of θ_{mk} at median dose, $\beta_{k,Dose}$ is the coefficient of the dose effect. A separate DCV V_2 of 59.5 L estimated for subjects with impaired hepatic function. Subjects with normal hepatic function, no matter whether infected with hepatitis C, had an estimated DCV V_2 of 34.8 L. No influence of age, sex, BMI, race or HCV status was found on the pharmacokinetic model parameters.

Table 1: Population parameters estimates for the pharmacokinetics model of DCV and ASV.

Parameters	Description	DCV		ASV	
		Estimate (%RSE)	IAV CV%	Estimate (%RSE)	IAV CV%
CL (L/h)	Elimination clearance	4.87 (5.00)	15.5	448 (11.8)	49.9
V_2 (L)	Volume of central compartment	34.8 (20.0)	15.6	1840 (21.9)	75.3
K_a (h ⁻¹)	First-order absorption rate constant	0.882 (26.8)	19.7	0.0339 (10.0)	-
Q (L/hr)	Inter-compartment clearance	3.03 (20.3)	-	49.4 (15.8)	-
V_3 (L)	Volume of peripheral compartment	34.8 (13.0)	18.8	195 (27.7)	-
D	Duration of zero-order absorption	-	-	2.74 (8.90)	27.3
FK	Fraction of dose absorbed by the zero-order mechanism	-	-	0.25 (15.3)	56.4
V_{2_HIS}	Volume of central compartment for subjects with hepatic impairment in study AI444013	59.5 (20.1)	-	-	-
CL_DOSE	Impact of $\log_{10}$ -transformed dose on CL	-1.75 (28.3)	-	-	-
FK_DOSE	Impact of $\log_{10}$ -transformed dose on FK	-	-	-0.25 (9.75)	-
σ^2	Residual error	0.221 (28.4)	-	0.982 (21.5)	-

Results (continued):

Compared to the E_{MAX} model, significant improvement of the fit to the data was observed for both DCV and ASV when a sigmoid E_{MAX} model was applied for the exposure and antiviral effect relationship. IC_{50} of DCV was estimated to be 0.0306 μ g/L (41.4 pM, RSE 55%) and 0.0055 μ g/L (7.5 pM) for GT 1A and 1B replicons, respectively, indicating that DCV had a great potency against both the GT 1A and 1B HCV replicons. This result confirmed the previous estimate of IC_{50} towards the GT 1 replicons (50 pM against GT 1A, 9 pM against GT 1B). IC_{50} of ASV was estimated to be similar values, 2.28 μ g/L (3 nM, RSE 82%) and 0.685 μ g/L (0.91 nM) for GT 1A and 1B replicons, respectively. Coefficients of the exponential function describing IC_{50} of DCV changing over time for GT 1A and 1B replicons were estimated to be 0.432 and 0.13, respectively. This result revealed IC_{50} of DCV would increase up to 423.3 and 6.2 fold for GT 1A and 1B replicons after 2 weeks monotherapy of DCV, which may account for the viral rebound experienced in most patients on or before day 7 of treatment.

Table 2: Population parameters of the HCV viral dynamic model.

Parameter	Description	Unit	Estimate (%RSE)	IAV CV%
K_{10_DCV}	Rate constant from the central compartment to the effect compartment for DCV	Per day	0.0039 (36)	-
K_{10_ASV}	Rate constant from the central compartment to the effect compartment for ASV	Per day	1.23 (8)	44.7
T_{MAX}	Maximum number of hepatocytes	cells/mL	18.5×10^6 (FIX)	-
d	Death rate constant of target cells	Per day	300 (FIX)	-
R_0	Basic reproductive ratio	-	7.15 (FIX)	-
δ	Loss rate constant of infected cells	Per day	0.139 (FIX)	-
c	Clearance rate constant of virions	Per day	21.8 (7)	23.0
p	Production rate constant of virions	Virions/cells/day	154 (20)	142.5
$IC_{50_DCV_GT1A}$	IC_{50} of DCV blocking production of GT 1A virions	μ g/L	0.0306 (55)	224.3
$SCL_{IC_{50_DCV}}$	Scaling factor for IC_{50} of DCV between GT 1B and GT 1A virions	-	0.18 (FIX)	-
γ_{DCV}	Shape factor of the sigmoidal E_{MAX} model for DCV	-	2.21 (35)	28.3
$K_{r_DCV_GT1A}$	Coefficient of exponential function describing $IC_{50_DCV_GT1A}$ changing over time	Per day	0.432 (19)	70.1
$K_{r_DCV_GT1B}$	Coefficient of exponential function describing $IC_{50_DCV_GT1B}$ changing over time	Per day	0.13 (13)	70.1
$IC_{50_ASV_GT1A}$	IC_{50} of ASV blocking production of GT 1A virions	μ g/L	2.28 (82)	106.3
$SCL_{IC_{50_ASV}}$	Scaling factor for IC_{50} of ASV between GT 1A and 1B virions	-	0.30 (FIX)	-
γ_{ASV}	Shape factor of the sigmoidal E_{MAX} model for ASV	-	1.99 (42)	-
K_{r_ASV}	Coefficient of exponential function describing IC_{50_ASV} changing over time	Per day	0.0068 (19)	-
σ_{DCV}^2	Residual error for DCV	-	0.275 (10)	-
σ_{ASV}^2	Residual error for ASV	-	0.284 (9)	-

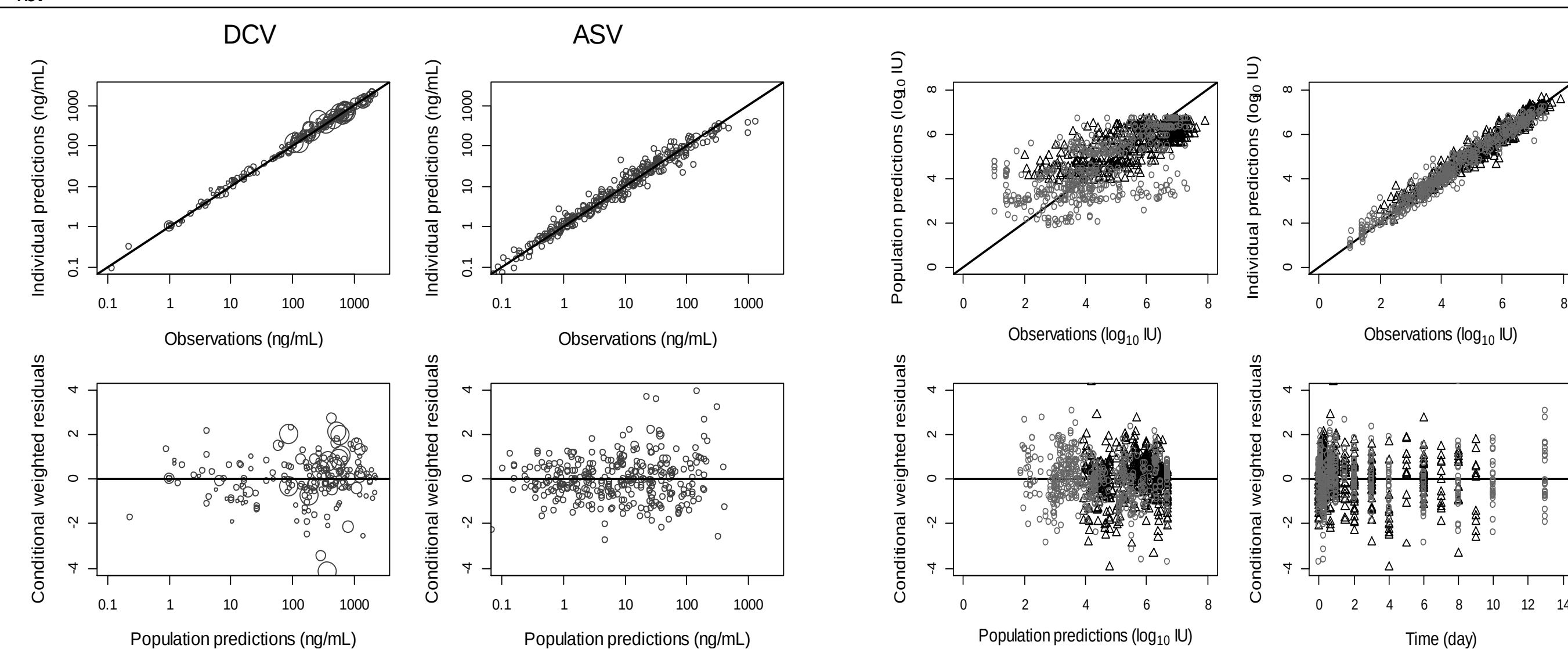


Figure 2: Goodness of fit plots for the pharmacokinetic models of DCV and ASV (A), goodness of fit plots for the final viral dynamic model (B).

Null virion production is triggered when there is less than one infected hepatocyte in the total plasma and extracellular fluid volume of distribution, thereby resulting in complete cure or SVR. A simulation was also performed by assuming the combined efficacy of DCV and ASV was based on the Loewe additivity theory, however, over-predictions were seen in some populations such as PR (PEG-Interferon/Ribavirin) null responders and PR ineligible/intolerant population because about 80% of population for modeling are treatment-naïve. Ideally, intensive viral load data from DCV and ASV combination therapy study could be used to investigate the potential pharmacodynamic interactions between DCV and ASV. However the individual-level viral load data obtained from some trials were too sparse for model building step. Red lines: predicted response rate curves; pink area: 95% prediction intervals of predicted response rates; black dots: observed response rates in study AI447028; blue dots: observed response rates in study AI447011; green dots: observed response rates in study AI447017; open circles: PR treatment-naïve population; open triangles: PR null responders; x-shaped dots: PR ineligible/intolerant population. The size of the symbol is proportional to the precision; a larger symbol indicates a more precise (i.e., based on a larger sample size) observation (Figure 3).

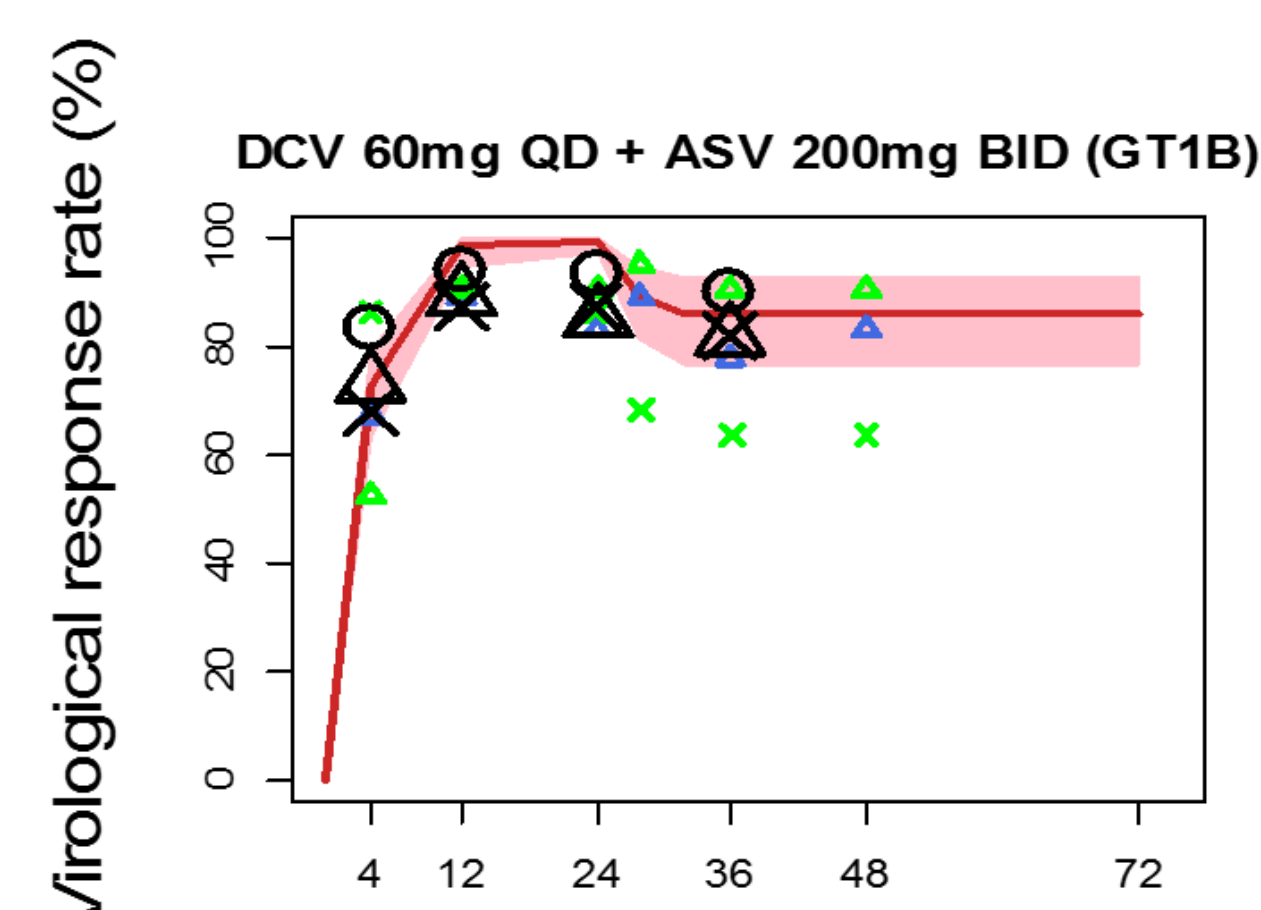


Figure 3: Predictive performance of the pharmacokinetic/viral dynamic model.

Conclusion:

The integrated pharmacokinetic/viral dynamic model developed in this study is the first effort to explain the complex relationships among pharmacokinetic exposure, short-term viral load changes and long-term virological response rates in HCV GT1 infected patients receiving monotherapy or combination therapy of DCV and ASV. Our model could be used for go/no-go decision-making, dose selection, optimization of clinical trial design for the future development of direct acting antiviral drugs.

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