

Pharmacokinetics of PEG-IFN Alpha in HCV Infected Patients

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INTRODUCTION

Mathematical models have been widely used for understanding viral dynamics of hepatitis C virus (HCV). Using a structural model of pharmacokinetics of PEG-IFN adapted from [1], PK profiles of 24 HCV/HIV coinfecting patients were analyzed. The population approach allowed to identify population and individual PEG-IFN PK parameters that are similar to defined in [1]. It was also shown that PK parameters don't correlate with any covariate parameters and are similar in sustained virological responders (SVRs) and nonresponders (NRs).

DATA

Plasma concentrations of PEG-IFN (350 samples) arising from 24 HIV/HCV-coinfecting patients were available from [1]. The patients were treated with PEG-IFN Alpha-2b 1.5 ug/kg once weekly and RBV 1,000-1,200 mg daily for up to 48 weeks.

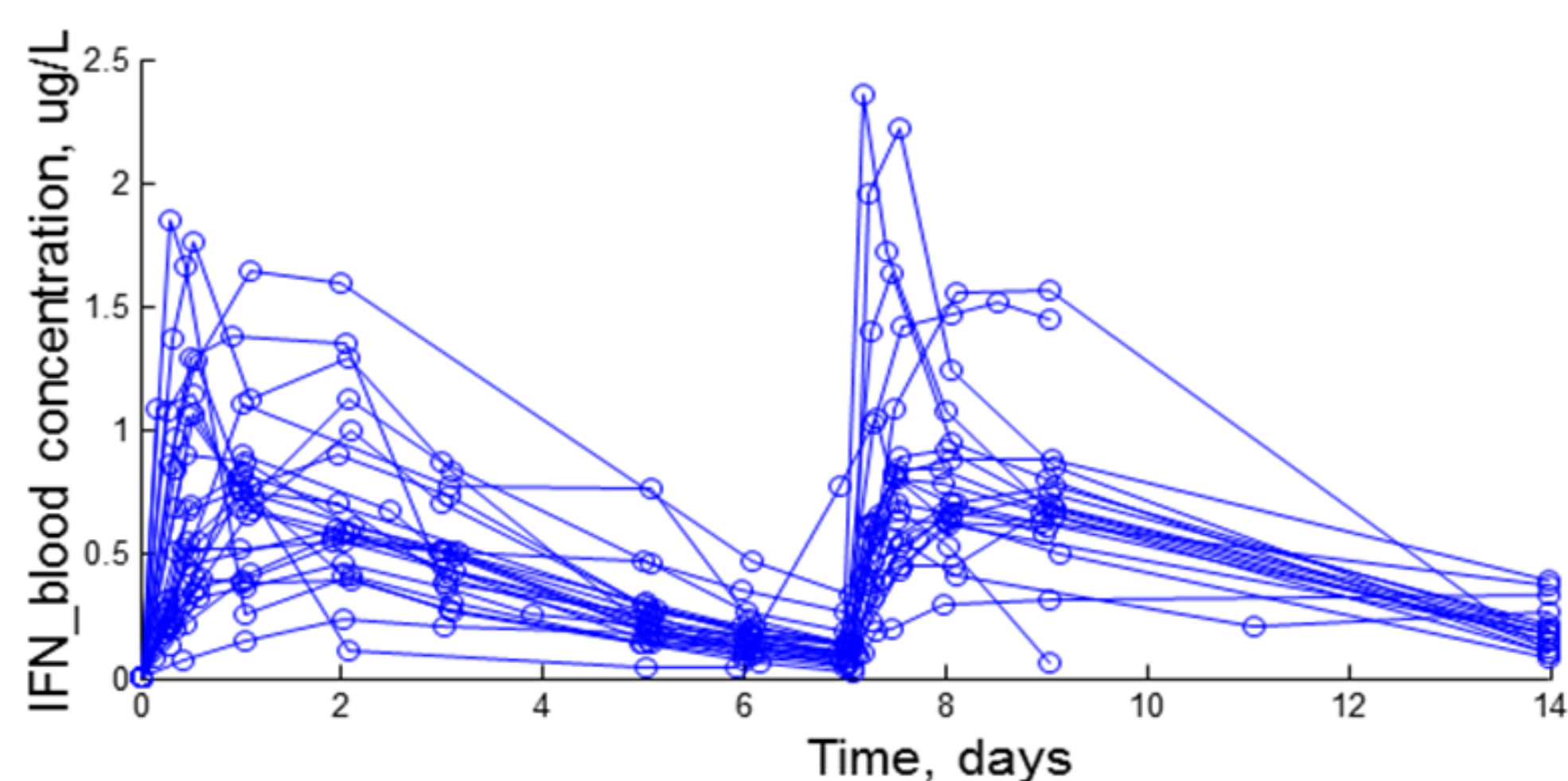


Fig. 1. PK profiles for 24 patients

METHODS

- ✓ Initial structural model was taken and adapted from [1]. This model is described as one compartment model with first order absorption and proportional error model in the following differential equations:

$$\frac{d}{dt} IFN_{source} = -k_{abs} \cdot IFN_{source} \quad (1)$$

$$\frac{d}{dt} IFN_{blood} = k_{abs} \cdot IFN_{source} - k_{el} \cdot IFN_{blood} \quad (2)$$

$$OUTPUT = \frac{IFN_{blood}}{V} \quad (3)$$

- ✓ We used first-order conditional estimation with interaction method algorithm, implemented in the NONMEM VII program (ADVAN6, TOL 3), and SAEM method of Monolix. The inter-individual variability of the model parameters was estimated by using exponential error models.
- ✓ Standard goodness of fit criteria such as assessment of the objective function value (OFV), parameter estimates, standard errors (SE) and relative standard errors (RSE), and diagnostic plots were used to assess model suitability.

REFERENCES

1) Talal, A.H., et al., *Pharmacodynamics of PEG-IFN alpha differentiate HIV/HCV coinfecting sustained virological responders from nonresponders*. Hepatology, 2006. **43**(5): p. 943-53.

RESULTS

The patient data was best described by a model with inter-individual variability (IIV) on k_{abs} and V (OFV in 261 points less compared to the basic model with no IIV). Individual PK parameters are similar to parameters from [1], but population approach allowed to identify these parameters more precise.

Table 1. Parameters estimates obtained with the use of NONMEM and Monolix, the best PK models with no IIV and with IIV on k_{abs} and V

	NONMEM, Estimates (%RSE)		Monolix, Estimates (%RSE)	
	model without IIV	model with IIV	model without IIV	model with IIV
Structural model				
k_{abs} , day ⁻¹	2.89 (24.3)	1.27 (20.2)	3.07 (16)	1.32 (19)
k_{el} , day ⁻¹	0.263 (13.7)	0.415 (6.8)	0.259 (9)	0.41 (3)
V , L/kg	1.69 (13.7)	1.1 (9.9)	1.73 (9)	1.08 (7)
IIV				
ωk_{abs} (%)	-	80.6 (16.1)	-	89 (15)
ωV (%)	-	30.6 (18.8)	-	29.8 (17)
Res. variability				
Prop. error (%)	47.3 (14)	16.5 (5.5)	69.2 (4)	39.9 (4)

The quality of fitting by final PK model is represented by Visual predictive check (VPC) plots with confidence intervals (Fig 2), based on simulations of model predictions including random effects and basic diagnostic plots (Fig.3).

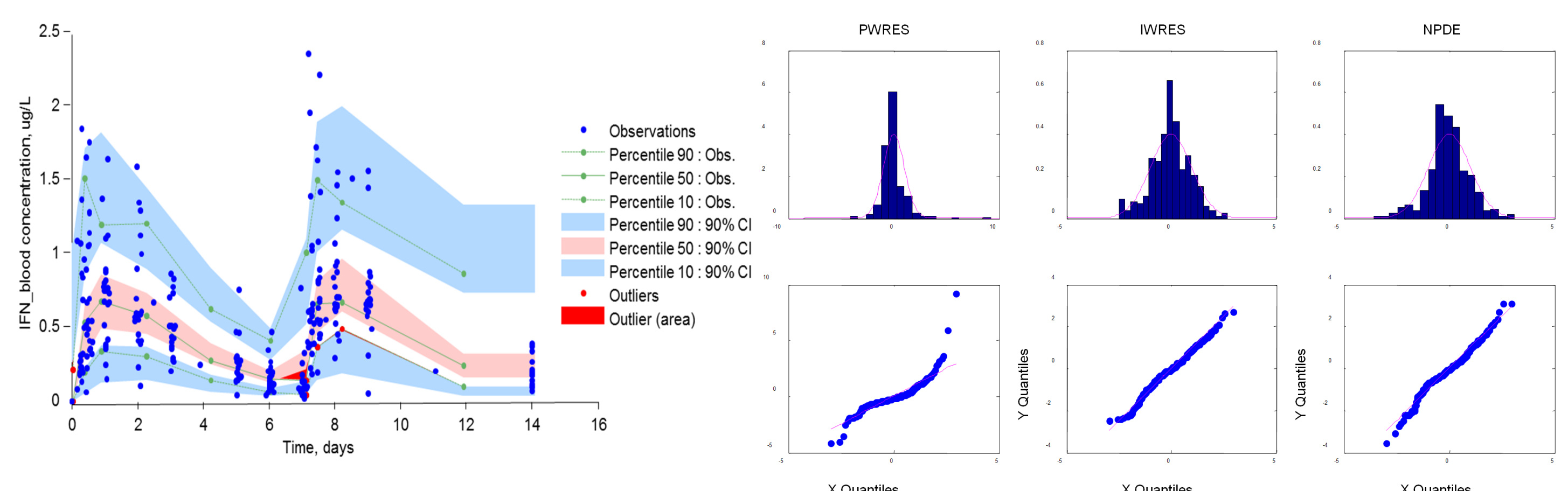


Fig. 2. Visual predictive check for final PK model

Fig. 3. Diagnostic plots for final PK model

Covariate analysis showed that there was no significant correlation between any of PK parameters and covariate variables, so the final PK model doesn't include any covariate variables. Individual PK parameters don't differ in sustained virological responders (SVRs) and nonresponders (NRs).

CONCLUSIONS

- ✓ Population approach allowed to identify individual PK parameters of PEG-IFN for HCV/HIV-coinfecting patients, and these parameters could be used as an input for pharmacodynamic analysis;
- ✓ Introduction of IIV for k_{abs} and V allowed to improve goodness of fit significantly;
- ✓ PK parameters don't correlate with any covariate parameters and are similar in sustained virological responders and nonresponders.

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CONTACTS

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