Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling for Integrase Inhibitors with a Simple Viral Dynamic Model

IV-5

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Abstract

Objectives: S/GSK1349572, S/GSK1265744 and S/GSK364735 are potent, low nanomolar inhibitors of both recombinant HIV integrase and HIV replication in cell culture assays. Currently in clinical development, S/GSK1349572 and S/GSK1265744 are unboosted, once daily integrase inhibitors with different resistance profiles than raltegravir or elvitegravir. A mathematical representation of viral dynamics for integrase inhibitors combined with a pharmacokinetic model are useful to assess dose-effect and concentration-effect relationships and thus aid in dose selection for clinical studies. The objective was to develop a simple and practical PK/PD model for describing plasma concentration profiles and viral dynamics of integrase inhibitors.

Methods: A simple viral dynamic model was developed. The PK part of the model is a conventional 1 compartment model with first-order absorption, and the PD part consists of 1 compartment for describing viral dynamics with first-order viral depletion and viral count-related viral replication, which is inhibited by integrase inhibitors with a Emax model. The model was applied to the profiles of plasma concentrations and HIV-1 RNA counts from 3-Phase IIa 10-day monotherapy studies. The model was fitted to 3 integrase inhibitors with adjustment by in vitro protein-adjusted IC50 (PA-IC50). Model evaluation was performed using classical diagnostic plots and the visual predictive check.

Results: The simple viral dynamic model described well the profiles of plasma concentrations and HIV-1 RNA counts in short-term monotherapy studies for these integrase inhibitors. The PD profiles for these 3 integrase inhibitors were described with a common virus-related PD parameter (first-order viral depletion constant) using in vitro PA-IC50 for each compound with adjustment by in vitro-in vivo scaling parameter. The first-order viral depletion constant was estimated to be 0.00305 hr-1. The in vivo-in vitro scaling factor was estimated to be 2.26, suggesting in vivo IC50 was higher than in vitro PA-IC50. Simulations suggest that S/GSK1349572 and S/GSK1265744 will have robust efficacy with once daily dosing.

Conclusions: A simple PK/PD model was developed for describing the relationships between PK and PD for integrase inhibitors. This model can be used to predict future clinical trial results for the drugs of interest but can also be used for predicting the PK/PD relationships for other drugs in the same class.

Introduction

- S/GSK1349572, S/GSK1265744 and S/GSK364735 are potent, low nanomolar inhibitors of both recombinant HIV integrase and HIV replication in cell culture assays.
- Currently in clinical development, S/GSK1349572 and S/GSK1265744 are unboosted, once daily integrase inhibitors with different resistance profiles than raltegravir or elvitegravir.
- A mathematical representation of viral dynamics for integrase inhibitors combined with a pharmacokinetic model are useful to assess dose-effect and concentration-effect relationships and thus aid in dose selection for clinical studies.

Objective

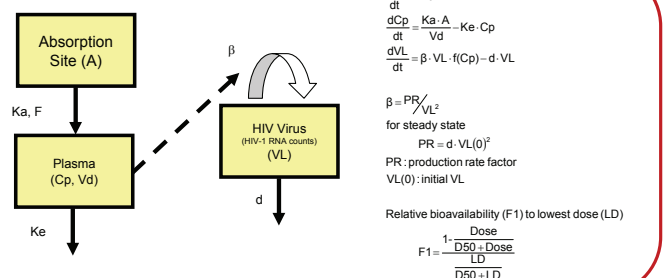
- To develop a simple and practical PK/PD model for describing plasma concentration profiles and viral dynamics of integrase inhibitors.

Methods

- 10-day monotherapy studies for 3 INIs
  - S/GSK1349572, S/GSK1265744 and S/GSK364735
- Data
  - PK: plasma concentrations
  - PD: HIV-1 RNA counts (log10-transformed, VL)
- A simple viral dynamic model
  - PK: One compartment model with first-order absorption
    - Non-linear (saturable) absorption for S/GSK1349572 and S/GSK364735
  - PD: One compartment for describing HIV RNA counts
    - Viral count-related replication rate of HIV virus: β*VL
    - *in vivo-in vitro* scaling factor for EC50 (SF)
    - First-order depletion of HIV-1 virus: d*VL
    - Common PD parameters for 3 INIs: d, SF
  - Concentration-dependent inhibition of virus replication (Emax model)

$$f(Cp) = \frac{Emax \cdot Cp}{C50 \cdot SF + Cp}$$

Figure 1. A PK/PD Model of Viral Dynamics for Integrase Inhibitors



$$\frac{dA}{dt} = -Ka \cdot A$$

$$\frac{dCp}{dt} = \frac{Ka \cdot A}{Vd} - Ke \cdot Cp$$

$$\frac{dVL}{dt} = \beta \cdot VL \cdot f(Cp) - d \cdot VL$$

$$\beta = PR / VL^2$$

for steady state

$$PR = d \cdot VL(0)^2$$

PR : production rate factor

VL(0) : initial VL

Relative bioavailability (F1) to lowest dose (LD)

$$F1 = \frac{1 - \frac{Dose}{D50 + Dose}}{\frac{LD}{D50 + LD}}$$

- PK/PD Parameters were estimated by NONMEM Ver.6.
  - First, PK parameters were estimated.
  - PD parameters were estimated by using the estimated PK parameters as inputs.

References

Yano, Y et al. *J. Pharm. Sci.* **87**:1177-83 (1998).
Min S. IAS (2009), Abstract #TUOR2120.
Min, S et al. 49th ICAAC, (2009) Abstract #H1228.

Results

- Model fitting was performed with a common *in vivo-in vitro* scaling factor (SF) for all 3 INIs.

Figure 2. Observed (plots) and Predicted (lines) Time Courses of Mean HIV-1 RNA Counts

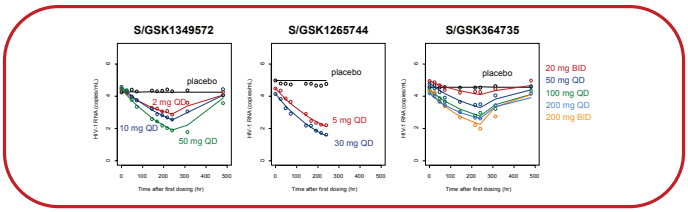


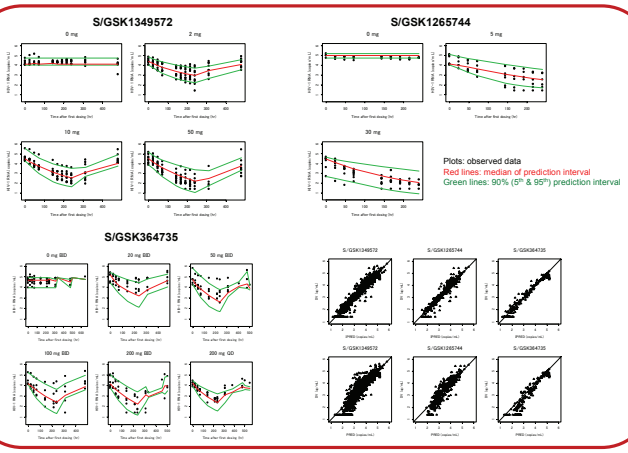
Table 1. Estimated PK/PD Parameters

	Parameter	S/GSK1349572 Population mean	S/GSK1349572 Inter-individual variability	S/GSK1265744 Population mean	S/GSK1265744 Inter-individual variability	S/GSK364735 Population mean	S/GSK364735 Inter-individual variability
PK	Ka (hr^{-1})	1.69	63.6%	1.29	50.2%	0.822	86.9%
	CL (L/hr)	0.829	25.9%	0.292	26.9%	8.38	36.2%
	Vd (L)	13.1	29.7%	11.4	22.7%	46.0	35.5%
	Intra-individual variability	21.3% (exponential error)		18.0% (exponential error) 0.0602 (additive error)		69.7 (exponential error) 0.00659 (additive error)	
PD		Population mean		Inter-individual variability			
	Emax	1 (fixed)		---			
	Scaling factor*	2.26		---			
	d (hr^{-1})	0.00305		50.7%			
	Intra-individual variability	0.299 (SD, additive error)					

* in vivo-in vitro scaling factor
in vitro PA-IC50: 0.0159 mg/mL for S/GSK1349572; 0.0405 mg/mL for S/GSK1265744; 0.0156 mg/mL for S/GSK364735

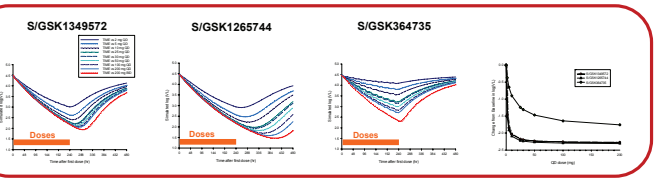
- *in vivo* IC50 was estimated to be higher than *in vitro* IC50 (PA-IC50). (*in vivo-in vitro* scaling factor (SF): 2.26)

Figure 3. Visual Predictive Check and Diagnostic Plots



- Model evaluation was performed by the visual predictive check and diagnostic plots. The results suggest that the model described the data well.

Figure 4. Simulated Mean Viral Responses in 10 Days Monotherapy



- Simulations suggest that
  - S/GSK1349572 and S/GSK1265744 would provide higher response on profiles of HIV-1 RNA count compared with S/GSK364735
  - S/GSK1349572 and S/GSK1265744 will have robust efficacy with once daily dosing.

Conclusions

- A simple PK/PD model was developed for describing the relationships between PK and PD for integrase inhibitors.
- The model can be used to predict future clinical trial results for the drugs of interest but can also be used for predicting the PK/PD relationships for other drugs in the same class.