Pharmacokinetic/pharmacodynamic Modeling and Long-term Simulation of Dolutegravir (DTG, S/GSK1349572) in Integrase Resistant Patients with a Simple Viral Dynamic Model

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Abstract

Objectives: **DTG is an unboosted, once daily integrase inhibitor (INI) currently under development for the treatment of HIV infection. Effectiveness of DTG is being examined for use across the treatment spectrum including treatment-naive to INI-resistant patients. [1, 2, 3]. A mathematical representation of viral dynamics for INIs combined with a pharmacokinetic model is useful to assess dose-effect and concentration-effect relationships and thus aid in dose selection. A simple PK/PD model was developed for describing antiviral activity in 10-day monotherapy studies for 3 INIs in INI-naive patients [4]. The objective was to apply the simple PK/PD model for describing short-term antiviral activity from a clinical study in INI-resistant patients and to simulate long-term efficacy of DTG.**

Methods: **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 INIs with an Emax model. The model was applied to the profiles of plasma concentrations and changes in HIV-1 RNA during 10-day monotherapy or functional monotherapy data from 2 clinical studies of DTG in INI-naive patients [2] and INI-resistant patients [1]. The effects of baseline HIV-1 RNA values, baseline fold-change and PSS (phenotypic susceptibility score) were included into EC50 parameter of the Emax model. Long-term efficacy of DTG for INI-resistant patients was simulated based on the developed PK/PD model. The effect of background therapy, dropout rate, adherence and viral mutation were incorporated into the model for simulating the long-term efficacy [5].**

Results: **The profiles of plasma concentrations and HIV-1 RNA counts in short-term studies of DTG for INI-naive patients and INI-resistant patients were well described by the simple PK/PD model. Moreover, the profiles of the probability of < 50 copies/mL RNA counts for 24 weeks in INI-resistant patients were well characterized by the model. The long-term simulations suggested that 50 mg BID would provide a higher response rate compared to 50 mg QD or 100 mg QD in INI-resistant patients.**

Conclusions: **The PK/PD model initially used for INI-naïve subjects was modified for describing viral dynamic profiles in INI-resistant patients. Simulations suggest that DTG will have robust long-term efficacy in this population and support 50 mg BID for difficult-to-treat patients with INI-resistance.**

Introduction

- **DTG is an unboosted, once daily integrase inhibitor (INI) currently under development for the treatment of HIV infection.**
- **Effectiveness of DTG is being examined for use across the treatment spectrum including treatment-naive to INI-resistant patients. [1, 2, 3, 6, 7].**
- **A mathematical representation of viral dynamics for INIs combined with a pharmacokinetic model is useful to assess dose-effect and concentration-effect relationships and thus aid in dose selection.**
- **A simple PK/PD model was developed for describing antiviral activity in 10-day monotherapy studies for 3 INIs in INI-naive patients [4].**

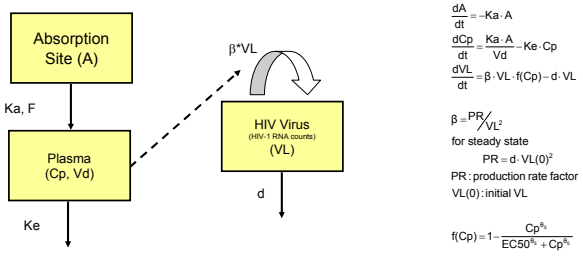
Objective

- **To apply the simple PK/PD model for describing short-term antiviral activity from a clinical study in INI-resistant patients and to simulate long-term efficacy of DTG.**

Methods

- **Clinical studies**
  - **10-day monotherapy for integrase-naïve patients**
  - **10-day functional monotherapy for INI-resistant patients**
- **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**
  - **PD: One compartment for describing HIV RNA counts**
    - **Viral count-related replication rate of HIV virus: β*VL**
    - **First-order depletion of HIV-1 virus: d*VL**
    - **Concentration-dependent inhibition of virus replication (Emax model)**
    - **Followings were tested as covariates.**
      - **Fold change (FC), phenotypic susceptibility score (PSS), baseline viral load**

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



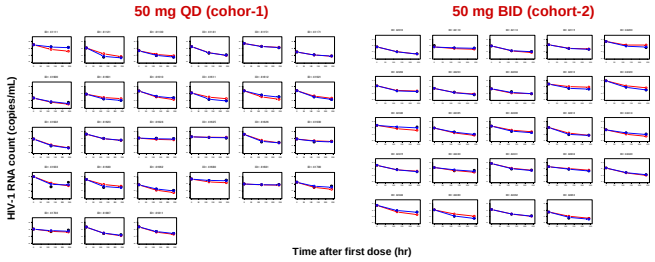
- **PK/PD parameters were estimated by NONMEM Ver.7.**
  - **First, PK parameters were estimated.**
  - **PD parameters were estimated by using the estimated PK parameters as inputs.**

References

1. Eron et al. 18th IAC (2010) Abstract MOAB0105
2. Min et al. 49th ICCAC (2009) Abstr #H1228
3. Rockstoh et al. JIAS (2010) 13(Suppl 4): O50
4. Wajima et al. PAGE 19 (2010) Abstr 1790
5. Kubota et al. PAGE 20 (2011) Abstr 1989
6. Zhang et al. 11th HIV Clin Pharm (2010) Abstr 51
7. Lovern et al. JIAS (2010) 13(Suppl 4): P182

Results

Figure 2. Fitting Results to HIV-1 RNA Count Data of 10-day Functional Monotherapy Phase in INI-Resistant Patients



- **The profiles of plasma concentrations and HIV-1 RNA counts in short-term studies of DTG for INI-naïve patients and INI-resistant patients were well described by the simple PK/PD model.**

Table 1. Estimated PK/PD Parameters

PK			PD		
Parameter	Population mean	Inter-individual variability	Parameter	Population mean	Inter-individual variability
Ka (hr^{-1})	1.63	63.4%	Emax	1 (Fixed)	---
CL/F (L/hr)	0.776	38.7%	θ_1 (μg/mL)	0.0155	190%
Vd/F (L)	13.4	30.5%	θ_2	1.98	---
D50 (mg)	84.3	---	θ_3	7.85	---
			θ_4	6.21	---
			θ_5	0.479	---
			d (hr^{-1})	0.00522	36.2%
Intra-individual variability	21.6% (exponential error)		0.299 (SD, additive error)		

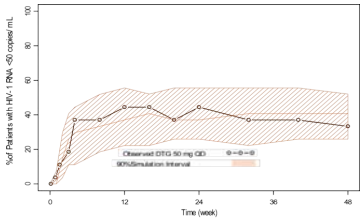
$F1 = \frac{1 - \frac{Dose}{D50 + Dose}}{1 - \frac{LD}{D50 + LD}}$ LD: lowest dose (2 mg)

$EC50 = \theta_1 \cdot FC^{\theta_2} \cdot (baseline/4.42)^{\theta_3} \cdot \theta_4^{PSSID}$ PSSID: 0 for PSS>=1, 1 for PSS=0

$f(Cp) = 1 - \frac{Cp^{\theta_5}}{EC50^{\theta_5} + Cp^{\theta_5}}$

- **Baseline viral counts, FC and PSS were found to be the significant influential factors on EC50.**

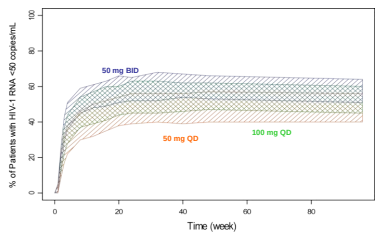
Figure 3. Evaluation of the Simulation Performance (Up to 48 Weeks Data)



Refer to the reference [5] for long-term simulation

- **Long-term simulation was performed by incorporating the effect of background therapy, dropout rate, adherence, viral mutation [5] and FC into the model, and compared with the observed data [3].**
  - **Baseline FC values were generated from log-normal distribution with mean 2.52 and sd(ln(x)) 1.18 based on the cohort-1 distributioin.**
- **The profiles of the probability of < 50 copies/mL RNA counts for 48 weeks in INI-resistant patients were well characterized by the model.**

Figure 4. Long-term Simulation of the Probability of <50 copies/mL for INI-Resistant Patients (96 weeks)



- **Long-term simulations for up to 96 weeks were performed based on the developed model.**
- **The long-term simulations suggested that 50 mg BID would provide a higher response rate compared to 50 mg QD or 100 mg QD in INI-resistant patients.**

Conclusions

- **The PK/PD model initially used for INI-naïve subjects was modified for describing viral dynamic profiles in INI-resistant patients.**
- **Simulations suggest that DTG will have robust long-term efficacy in this population and support 50 mg BID for difficult-to-treat patients with INI-resistance.**
- **Not all patients with INI resistant will have robust efficacy and it is highly depend on the mutation pattern (PSS & FC).**