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 monofunctional monotherapy data from 2 clinical studies of DTG in INI-naive patients [1] and INI-resistant patients [3]. 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-naive 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.

Methods

Clinical studies
- 10-day monotherapy for INI-naive 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
- PD: HIV-1 RNA counts (log10-transformed, VL)

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Objective

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Results

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References

1. Donnelly et al. 18th IAC (2010) Abstract MOAB0105