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A Pharmacokinetic-Pharmacodynamic (PK-PD) Disease Model to Describe Short- and Long-Term Antiviral Activity of Vicriviroc (VCV)

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Abstract

Background:

VCV is a potent CCR5 antagonist being developed for treatment of HIV infection. To understand interactions between CCR5 receptor binding and viral dynamics, PK of VCV in both RTV and non-RTV containing regimens were modeled mathematically.

Methods:

An integrated PK-PD disease model of VCV was based on clinical data from a 14-day monotherapy study and a long-term study in combination with Combivir® in treatment-naïve subjects. Model parameters were derived from literature and a model-based analysis of clinical data for other antiretroviral therapy (ART). The model incorporated a 2-compartment PK model to describe PK data and an Emax model to describe antiviral potency of VCV. Antiviral activity at higher doses was simulated using this model.

Results:

Diagnostic measures indicated the model described PK and antiviral activity of VCV with no systematic bias. Model-derived parameter values were: *in vivo* IC_{50} = 23 ng/mL (SE=34%); viral reproductive ratio = 8.1 (SE=18%); uninfected cell activation rate = 0.60 cells/uL/day (SE=20%); infected cell death rate = 0.39/day (SE=15%). Although there are no human clinical data, simulation results suggest that 1)30 mg VCV in a RTV-containing regimen should provide antiviral activity; (2)200 mg VCV in a non-RTV containing regimen should provide viral inhibition similar to 30 mg VCV in a RTV-containing regimen; (3)twice daily dosing would not substantially increase antiviral activity of VCV over once daily dosing.

Conclusions:

Exposure-response relationship of VCV was observed in combination with Combivir®. The PK-PD disease model allows simulation of antiviral activity at higher VCV doses and in combination with different ART backgrounds.

Introduction

To understand the interaction between CCR5 receptor binding and viral dynamics, VCV exposure with and without ritonavir (RTV) and antiviral activity without RTV were modeled mathematically.

Methods

- An integrated PK-PD model was developed based on literature data, a 14-day monotherapy study data and a long-term study in combination with Combivir®.
- A 2-compartment PK model was selected to describe the PK data.
- An Emax model was selected to describe the antiviral potency of VCV.
- Model parameter values were selected by matching simulated results with literature data (ref).
- Model validation was done using ACTG 5211 (ref IAC late breaker).
- Diagnostic measures indicated no systematic bias and the final model sufficiently described the observed data.

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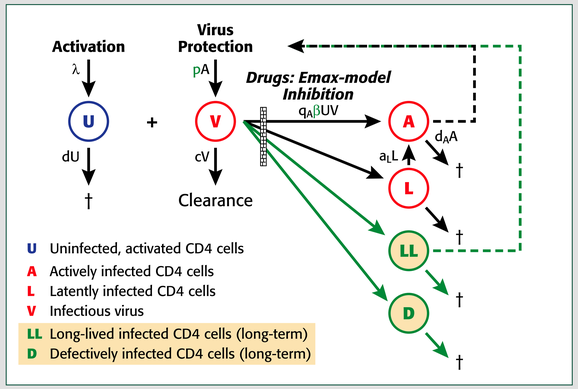
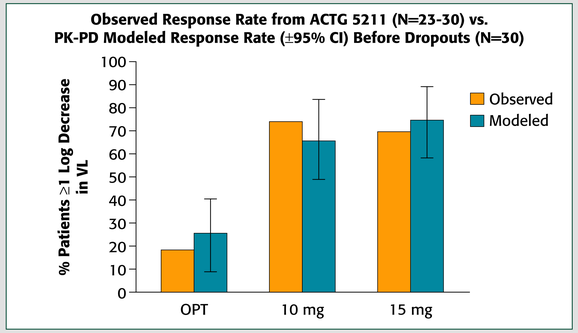
Results

Modeling Results

A PK-PD disease model was used to describe the short-term and long-term PK and antiviral activity of VCV in combination with Combivir®.

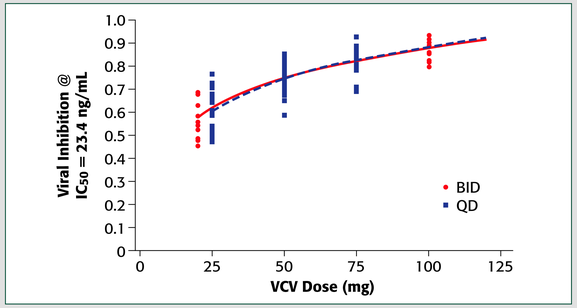


The model predicted response rate (±95% CI) for percentage of patients with a ≥1 log decrease in VL corresponds with the observed response rate at Week 24 in patients participating in the ACTG 5211 trial.

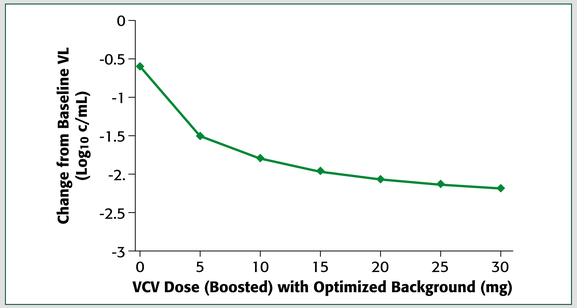


Simulation Results

1) Twice daily dosing for VCV alone at steady state (red) will not substantially increase the antiviral activity of VCV over once daily administration (blue).



2) Antiviral potency of VCV, with optimized background containing RTV, is predicted in treatment experienced patients. Higher exposure of VCV should provide incremental antiretroviral activity.



Simulation Suggests:

1) 30 mg VCV in a RTV-containing regimen should provide antiviral activity;

2) 200 mg VCV in a non-RTV containing regimen should provide viral inhibition similar to 30 mg VCV in a RTV-containing regimen;

3) twice daily dosing would not substantially increase antiviral activity of VCV over once daily dosing.

Conclusions

- **The integrated PK-PD disease model allows the simulation of antiviral activity at higher VCV doses in combination with different ART backgrounds.**
- **Data obtained from this model supports the use of 30 mg VCV in studies with RTV-containing regimens.**
- **VCV can be administered once daily.**
- **Higher VCV exposure may optimize antiviral activity by providing incremental benefit.**
- **VCV is a potent component of antiretroviral combination therapy.**

References

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