Abstract

Objectives: Vicriviroc is a potent CCR5 antagonist for treating HIV-1 infection. This study aimed to (1) describe vicriviroc population pharmacokinetic (PK) profile and population versus individual variability in HIV-positive patients using PK/PD; and (2) explore PK/PD association using drug-exposure and efficacy.

Methods: \( f(x) \) Base Model: A naive patient and the exposure-virologic response association was explored. The integrated population PK model and PK-PD association can be used to predict antiviral activity and select the optimal dose regimen in naive patients.

Results: Population PK model was amplified by capturing the non-linear relationship between exposure and virologic response. The concentration-time distribution was well described by a two-compartment model with first-order input and elimination. All inter-individual error terms in the PK model were significant. The drug exposure (AUC, Cmin and Cmax) was estimated for each patient and the exposure-virologic response association was explored.

Conclusions: A two-compartment model adequately described the vicriviroc PK in naïve HIV patients. Body weight and age were significant covariates. The integrated population PK model and PK/PD association can be used to predict antiviral activity and select the optimal dose regimen in naïve patients.

Methods

Data

Data Inclusion and Exclusion Criteria

- The following data inclusion criteria were employed in assembling data from Phase I and II studies:
- Subjects dosed with vicriviroc in combination with a ritonavir-containing regimen.
- Vicriviroc concentrations at steady-state.
- Subjects dosed with tablet or capsule formulations of vicriviroc.
- Subjects given doses of 30 mg.

- The following data exclusion criteria were used:
- Vicriviroc concentrations above limit of quantitation.
- PK samples without dosing record prior to PK sampling.
- PK samples without sampling weight.

PK Database:

- Since the sparse PK sampling scheme was utilized in Phase II study, data from Phase I studies were combined and used for the population PK analysis to estimate the pharmacokinetic parameters for HIV-infected subjects enrolled in Phase II study.

Population PK Analysis

- The population PK analysis was conducted using the pooled data from three Phase I studies (n = 28 subjects) and Phase II study (n = 100 subjects).
- Population PK analysis was conducted using conventional NONMEM approach.
- The population PK model was validated using VPC method and also by cross-validation of LNDV.

- Covariates included in the population PK database were age, body weight, gender, ethnicity, absolute phosphatase (ALT), AST, GGT, ALT (SGPT), total bilirubin, serum creatinine and disease status.

- The concentration (CRL) was calculated using Cockcroft-Gault equation. If the calculated creatinine clearance was > 100 mL/min, the value of creatinine clearance was entered as 100 mL/min.

- The final model was tested for stability by bootstrap technique. A minimum of 1000 replicates of the data were generated by bootstrapping to NONMEM analysis to obtain the mean and standard error of the bias-effect and random-effect parameters. An internal validation method was performed by generating a virtual predictive check of simulated concentrations (mean and 5% prediction interval) overlaid with observed concentrations to verify the stability of the final model. The random error component in the simulations was investigated and further model development was conducted as necessary.

Results

Figure 1: Diagnostic plots showing the observed data.

- Figure 2: Bootstrap Results.

Table 1: Population PK Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Estimate (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( CL/F )</td>
<td>3.39 (2.29, 4.60)</td>
<td>0.0001</td>
</tr>
<tr>
<td>( V_{1}/F )</td>
<td>329 (9, 9)</td>
<td>0.0001</td>
</tr>
<tr>
<td>( V_{2}/F )</td>
<td>26.3 (11)</td>
<td>0.0001</td>
</tr>
<tr>
<td>( V_{3}/F )</td>
<td>5.0 (15)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Figure 4: Visual predictive check with 5th, 50th, and 95th percentiles of simulated and observed vicriviroc concentration (mg/L) vs time (hr) stratified by age.

Figure 5: Visual predictive check with 5th, 50th, and 95th percentiles of simulated and observed vicriviroc concentration (mg/L) vs time (hr) stratified by body weight.

VPC: Stratify by Age

- Figure 6: PK-PD Relationship.

Table 2: Steady state vicriviroc mean pharmacokinetic parameters following 30 mg QD in combination with ritonavir in HIV treatment-naïve subjects.

- The PK/PD parameter estimates from the final model were nearly identical to the respective median values from the bootstrapping runs and the 85% CI had narrow widths, indicating that the performance and stability of the final population PK model were acceptable.

- A two-compartment model adequately described the vicriviroc PK in naïve HIV patients.

- Body weight and age were significant covariates.

- The integrated population PK model and PK-PD association can be used to predict antiviral activity and select the optimal dose regimen in naïve patients.