Pharmacokinetic-Pharmacodynamic Analysis Predicts a High Probability of Efficacy for Plazomicin in Against Serious Infections Caused by Carbapenem-Resistant Enterobacteriaceae

S. A. Van Wart1, A. Forrest1, G. L. Drusano2, S. M. Bhavnani1, C. C. Bulik1, C. F. Kostub1, P. G. Ambrose1, A. Louie2,3
1Institute of Clinical Pharmacology, Athens, NY; 2Institute for Therapeutic Innovation, University of Florida, Orlando, FL; 3Achaogen, Inc., South San Francisco, CA

ABSTRACT

Objectives: We assessed the P. aeruginosa PK and dose-response relationships for plazomicin to identify a PK/PD target that predicts clinical response in a neutropenic murine lung infection model.

Methods: A Phase 1, open-label, SD study to assess PK, safety, and tolerability in healthy subjects with normal renal function received plazomicin 10 or 15 mg/kg infused IV over 10 min, and 7.5 mg/kg infused IV for 7 days. A Phase 1, double-blind, randomized, placebo-controlled SD and MD study to assess the safety, efficacy, and tolerability in healthy adults (N=28). Phases 2 and 3 were carried out in adults with CRE bacterial pneumonia. Pharmacokinetic (PK) and pharmacodynamic (PD) analysis was performed using NONMEM and ADAPTIV Dev. Statistical analyses were performed using SAS V9.4. Population PK analysis was performed using a 3-compartment (CMT) model with zero-order input and first-order elimination. Population PK/ PD model was developed using data from a clinical trial in patients with varying renal function. The predicted percent of patients achieving plasma and ELF AUC0-24:MIC ratio targets was ≥ 97.7% for a 2-log10 CFU reduction from baseline. The predicted time for E. coli (non-MDR) to achieve the target AUC0-24, patients with CLcr of 30-150 mL/min/1.73 m2 required a plazomicin dose (mg/kg) of 0.14 ± 0.17 × CLcr (i.e. capped at 15 mg/kg) once daily, twice the dose given in the clinical trials for patients with CLcr of 15-30 mL/min/1.73 m2.

RESULTS

Identification of PK/PD Targets for Plazomicin Efficacy Based on a Murine-Lung Infection Model

A 3-compartment (CMT) model was developed using data from a clinical trial in healthy subjects with varying renal function. The predicted percent of patients achieving plasma and ELF AUC0-24:MIC ratio targets was ≥ 97.7% for a 2-log10 CFU reduction from baseline. The predicted time for E. coli (non-MDR) to achieve the target AUC0-24, patients with CLcr of 30-150 mL/min/1.73 m2 required a plazomicin dose (mg/kg) of 0.14 ± 0.17 × CLcr (i.e. capped at 15 mg/kg) once daily, twice the dose given in the clinical trials for patients with CLcr of 15-30 mL/min/1.73 m2.

Conclusions:

- The predicted percent of patients achieving plasma and ELF AUC0-24:MIC ratio targets was ≥ 97.7% for a 2-log10 CFU reduction from baseline. The predicted time for E. coli (non-MDR) to achieve the target AUC0-24, patients with CLcr of 30-150 mL/min/1.73 m2 required a plazomicin dose (mg/kg) of 0.14 ± 0.17 × CLcr (i.e. capped at 15 mg/kg) once daily, twice the dose given in the clinical trials for patients with CLcr of 15-30 mL/min/1.73 m2.

INTRODUCTION AND OBJECTIVE

- Plazomicin, a novel aminoglycoside under development to treat serious infections, is active against CRE, K. pneumoniae, E. coli, and Enterobacteriaceae, and is being evaluated as a potential candidate for the treatment of patients with serious infections due to carbapenem-resistant Enterobacteriaceae (CRE) for future clinical studies.

METHODS

- Four key steps were undertaken to identify initial plazomicin dosing regimens for further evaluation in clinical trials of patients with varying renal function. These four steps are described below:

  1. Identification of PK/PD Targets for Plazomicin Efficacy Based on a Murine-Lung Infection Model
  2. Derivation of Plazomicin Dosing Regimen Equation
  3. Identification of PK/PD Targets for Plazomicin Efficacy Based on a Murine-Lung Infection Model
  4. Comparison of simulated plasma and ELF AUC0-24:MIC ratio targets with those in the proposed approach to plazomicin dosing.

- The above-described data were used to identify the PK/PD index associated with the efficacy of plazomicin and the magnitude of such an index associated with a 2-log CFU decrease from baseline.

METHODS

Population PK Analysis

- A 3-compartment (CMT) model was developed using data from a clinical trial in healthy subjects with varying renal function (Table 1). The predicted percent of patients achieving plasma and ELF AUC0-24:MIC ratio targets was ≥ 97.7% for a 2-log10 CFU reduction from baseline. The predicted time for E. coli (non-MDR) to achieve the target AUC0-24, patients with CLcr of 30-150 mL/min/1.73 m2 required a plazomicin dose (mg/kg) of 0.14 ± 0.17 × CLcr (i.e. capped at 15 mg/kg) once daily.

Derivation of Plazomicin Dosing Regimen Equation

- The PK/PD target was defined as the PK-PD index associated with a 2-log10 CFU decrease from baseline.

RESULTS

- The predicted percent of patients achieving plasma and ELF AUC0-24:MIC ratio targets was ≥ 97.7% for a 2-log10 CFU reduction from baseline. The predicted time for E. coli (non-MDR) to achieve the target AUC0-24, patients with CLcr of 30-150 mL/min/1.73 m2 required a plazomicin dose (mg/kg) of 0.14 ± 0.17 × CLcr (i.e. capped at 15 mg/kg) once daily, twice the dose given in the clinical trials for patients with CLcr of 15-30 mL/min/1.73 m2.

PK/PD Target Attainment Analysis

- A 3-compartment (CMT) model was developed using data from a clinical trial in healthy subjects with varying renal function. The predicted percent of patients achieving plasma and ELF AUC0-24:MIC ratio targets was ≥ 97.7% for a 2-log10 CFU reduction from baseline. The predicted time for E. coli (non-MDR) to achieve the target AUC0-24, patients with CLcr of 30-150 mL/min/1.73 m2 required a plazomicin dose (mg/kg) of 0.14 ± 0.17 × CLcr (i.e. capped at 15 mg/kg) once daily, twice the dose given in the clinical trials for patients with CLcr of 15-30 mL/min/1.73 m2.

CONCLUSION

- The predicted percent of patients achieving plasma and ELF AUC0-24:MIC ratio targets was ≥ 97.7% for a 2-log10 CFU reduction from baseline. The predicted time for E. coli (non-MDR) to achieve the target AUC0-24, patients with CLcr of 30-150 mL/min/1.73 m2 required a plazomicin dose (mg/kg) of 0.14 ± 0.17 × CLcr (i.e. capped at 15 mg/kg) once daily, twice the dose given in the clinical trials for patients with CLcr of 15-30 mL/min/1.73 m2.

TABLES

Table 1: %Probability of patients achieving plasma or ELF AUC:MIC targets across renal function groups for MIC=2

<table>
<thead>
<tr>
<th>Renal Function Group</th>
<th>%Probability of Target Attainment (PTA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>97.7</td>
</tr>
<tr>
<td>Moderate Impairment</td>
<td>97.7</td>
</tr>
<tr>
<td>Severe Impairment</td>
<td>97.7</td>
</tr>
</tbody>
</table>

Figure 1: Comparison of simulated plasma and ELF AUC0-24:MIC ratio targets with those in the proposed approach to plazomicin dosing.

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Scott A. Van Wart, M.S.
Institute of Clinical Pharmacodynamics
43 British American Blvd.
Latham, NY 12110

Telephone: (518) 429-2600
E-Mail: SVanWart@icpdm.com

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