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

Scott A. Van Wart, M.S.
Institute for Clinical Pharmacodynamics
43 British American Blvd.
Latham, NY 12110
Telephone: (518) 429-2600
E-mail: SVanWart@icpd.com

S. A. Van Wart[1], A. Forrest[1], G. L. Drusano[2], S. M. Bhavnani[1], C. C. Bulik[1], C. F. Kostrub[3], P. G. Ambrose[1], A. Louie[2],

[1]Institute for Clinical Pharmacodynamics, Latham, NY, [2]Institute for Therapeutic Innovation, University of Florida, Orlando, FL, [3]Achaogen, Inc., South San Francisco, CA

ABSTRACT

Objectives: Plazomicin, a novel aminoglycoside (AG) under development to treat serious Gram-negative infections, is active against clinical isolates that possess a broad range of resistance mechanisms including AG-modifying enzymes, carbapenemases and fluoroquinolone target-site mutations that limit the utility of other antibiotics. Using Monte Carlo simulation (MCS), population PK (PPK), and pharmacokinetic-pharmacodynamic (PK-PD) targets from murine infection models, the efficacy of plazomicin against infections caused by carbapenem-resistant Enterobacteriaceae (CRE) was predicted.

Methods: Plazomicin plasma and epithelial lining fluid (ELF) PK from neutropenic infected mice and data from a neutropenic murine lung *Klebsiella pneumoniae* (Kp) infection model [ICAAC 2012, Abstract A-042] were used to determine plasma and ELF area under the concentration-time curve to MIC ratio (AUC:MIC) targets for efficacy. A plazomicin PPK model was built using clinical data from subjects and patients with varying renal function. Using this model, an individualized plazomicin dosing regimen approach was derived. Using MCS, the probability of target attainment (PTA) in simulated patients with varying renal function was evaluated by MIC and overall PTA was evaluated in the context of plazomicin's MIC distribution against multidrug-resistant (MDR) Kp.

Results: Median (range) plasma and ELF AUC:MIC targets associated with a 2-$\log_{10}$ CFU reduction in Kp in murine lung were 39 (17-137) and 32 (14-112), respectively. MCS was performed using the PPK model (3-compartment model including significant covariate relationships for weight and creatinine clearance [CLcr]) and PTA was assessed for patients receiving a plazomicin dose (mg/kg) of 0.14 + 0.17 x CLcr once daily or twice this dose every 48 h for patients with CLcr of 15-30 mL/min/1.73 m^2 (Table 1). Using median plasma and ELF AUC:MIC targets, PTA across renal function groups was ≥ 97.7% for MIC=2 mg/L. Overall PTA for both targets across renal function groups based on the plazomicin MIC distribution vs. MDR Kp [Galani I *et al.* J. Chemother. 2012;24:191-94] was ≥97.2%.

Conclusions: The predicted percentage of patients achieving plasma and ELF AUC:MIC targets for efficacy against MDR Kp is high (≥97.2%), suggesting that the proposed approach to plazomicin dosing will provide plasma exposures consistent with efficacy in the majority of patients with CRE bacterial pneumonia.

Table 1. %Probability of patients achieving plasma or ELF AUC:MIC targets across renal function groups for MIC=2 and over a MIC distribution for plazomicin against MDR Kp

Renal Function Group (CLcr range)	%Probability of patients achieving the plasma or ELF AUC_{0-24}:MIC ratio target associated with a 2-$\log_{10}$ CFU reduction in Kp from baseline			
	Plasma AUC_{0-24}:MIC target=39[a]		ELF AUC_{0-24}:MIC target=32[b]	
	MIC=2 mg/L	Overall[c]	MIC=2 mg/L	Overall[c]
Normal (90 to 150 mL/min/1.73 m^2)	99.6	99.0	97.7	97.2
Mild impairment (60 to <90 mL/min/1.73 m^2)	99.9	99.5	99.2	98.1
Moderate impairment (30 to <60 mL/min/1.73 m^2)	99.9	99.4	99.4	98.5
Severe impairment (15 to <30 mL/min/1.73 m^2)	100	99.6	99.2	98.5

a. PTA results based on Day 1 plasma AUC_{0-24} values and the median plasma AUC:MIC target of 39.
b. PTA results based on Day 2 ELF AUC_{0-24} values (assumes ELF to plasma equilibration by this time point) and the median ELF AUC_{0-24}:MIC target of 32.
c. Based on PTA by MIC results over the MIC distribution for MDR Kp(Galani *et al.* J. Chemother. 2012;24:191-194).

INTRODUCTION AND OBJECTIVE

- Plazomicin, a novel aminoglycoside under development to treat serious Gram-negative infections, is active against clinical isolates which possess a broad range of resistance mechanisms including aminoglycoside-modifying enzymes, carbapenemases, and fluoroquinolone target-site mutations.
- The goal of this analysis was to utilize non-clinical pharmacokinetic-pharmacodynamic (PK-PD) targets, a population PK (PPK) model for plazomicin derived using data from healthy subjects and infected patients with varying renal function, and Monte Carlo simulation (MCS) to evaluate plazomicin dosing regimens 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 studies of patients with varying renal function. These four steps are described below:

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

- Plazomicin plasma and epithelial lining fluid (ELF) PK and dose-response data collected using a neutropenic lung-*Klebsiella pneumoniae* (Kp) infection model [ICAAC 2012, Abstract A-042] were evaluated.
- 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-$\log_{10}$ CFU decrease from baseline.

Population PK Analysis

- A plazomicin PPK model was developed using data from 4 clinical trials in healthy subjects or infected patients with varying renal function (**Table 1**) receiving plazomicin once daily as an IV infusion.
- Blood samples were collected in each study up to 72 h post-dose; plasma plazomicin concentrations were quantified using LC-MS/MS with a lower limit of quantification of 0.01 mg/L.
- A 3-compartment (CMT) model with zero-order input and first-order elimination was fit to the data using NONMEM® 7.2 (FOCEI method). Clearance (CL), central volume of distribution (Vc), and the distribution CL (CLd) and volume (Vp) of each peripheral CMT were estimated.
- Interindividual variability (ω^2) was estimated for each PK parameter using an exponential error model; residual error (σ^2) was described using a combined additive plus proportional error model.
- Age, creatinine clearance (CLcr), weight, height, body surface area (BSA), gender, race, and presence of infection were evaluated as potential PK covariates using stepwise forward selection (α=0.05) and backward elimination (α=0.001).

Table 1. Clinical studies included in the plazomicin PPK analysis

Study (Number of subjects included in PPK analysis)	Plazomicin doses
Phase 1, double-blind, randomized, placebo-controlled, parallel-group single (SD) and multiple (MD) dose study to assess PK, safety, and tolerability in healthy adults (N=28)	1, 4, 7, 11, or 15 mg/kg infused IV over 10 min
Phase 2, double-blind, comparator-controlled study to assess PK, safety, and efficacy in adult patients with complicated urinary tract infection (cUTI) or acute pyelonephritis (AP) (N=91)	10 or 15 mg/kg infused IV over 30 min
Phase 1, double-blind, randomized, placebo-controlled SD and MD study to assess the safety, tolerability, plasma PK, and lung penetration in healthy adults (N=30)	11 or 15 mg/kg infused IV over 10 min
Phase 1, open-label, SD study to assess PK, safety, and tolerability in healthy subjects with normal renal function or otherwise healthy subjects with varying degrees of renal impairment (N=24)	7.5 mg/kg infused IV over 30 min

Derivation of Plazomicin Dosing Regimen Equation

- An individualized plazomicin dosing regimen equation was derived using the PPK model based upon renal function and body weight.
  - The dosing equation was designed to provide a target 24-h area under the plasma concentration-time curve (AUC_{0-24}) of 262 mg•L/h, comparable to the average AUC associated with plazomicin 15 mg/kg/day, a regimen which was well tolerated in subjects with normal renal function at a dosing duration of up to 5 days.

PK-PD Target Attainment Analyses

- For each renal function group, 2000 patients (50% male) were simulated using a uniform distribution of CLcr.
  - Age (18-90 yr) was normally distributed with a mean (SD) of 40 (10), 45 (10), 50 (10) and 60 (10) for normal renal function and mild, moderate, and severe renal impairment, respectively. Height was normally distributed with a mean (SD) of 175 (10) and 162 (10) cm for males and females, respectively.
  - Ideal body weight was calculated and 20% ± 5% excess mass was added to determine a more realistic body weight for dosing.
- Plasma plazomicin concentration-time data was generated for 2 days in each simulated patient using NONMEM® based on the final PPK model and using the derived plazomicin dosing regimen.
  - A Day 1 plasma AUC_{0-24} was calculated for use in assessing the percent probability of target attainment (%PTA).
  - Plasma plazomicin concentrations on Day 2 were multiplied by a steady-state ELF penetration ratio of 0.6 (based upon a previous PK analysis for tobramycin in patients with pneumonia [Carcas *et al.* Clin Pharmacol Ther, 1999; 65:245-50]) to generate the expected ELF plazomicin AUC_{0-24} in the simulated patients on Day 2 and assess %PTA.
- For each renal function group, %PTA was evaluated by MIC and overall %PTA was evaluated in the context of the MIC distribution for plazomicin against Kp [Landman *et al.* J Antimicrob Chemother 2010; 65:2123-7] and MDR Kp [Galani *et al.* J Chemother 2012;24:191-4].

RESULTS

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

- AUC_{0-24}:MIC ratio was identified as the PK-PD index associated with plazomicin efficacy based on assessments of both ELF and plasma exposures. The median (min, max) plasma and ELF AUC_{0-24}:MIC targets associated with a 2-$\log_{10}$ CFU reduction from baseline for the 7 Kp isolates were 38.8 (16.8, 137) and 31.7 (13.7, 112), respectively. The second highest plasma and ELF AUC_{0-24}:MIC targets associated with this endpoint among the 7 Kp isolates were 64.8 and 56.5, respectively. The median and second largest targets were selected for evaluation in the %PTA analysis.

Population PK Model

- A 3-CMT model with zero-order input and first-order elimination best described the data (**Table 2**). CLcr was the most statistically and clinically significant predictor of plazomicin CL when modeled using a sigmoidal function (**Figure 1**). Height, BSA, age, and presence of cUTI or AP were also significant predictors of plazomicin PK.
- There was excellent agreement between both the population mean (r^2=0.81) and individual post-hoc (r^2=0.95) predicted concentrations versus the observed data.
- A prediction-corrected visual predictive check also confirmed the adequacy of the PPK model to simulate data across renal function groups (**Figure 2**).

Figure 1. Individual post-hoc CL versus CLcr with population model fit overlaid

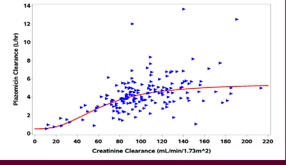

Figure 2. Visual predictive check for the final PPK model

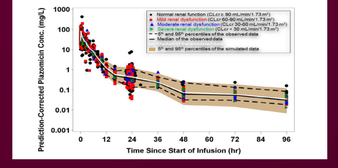

Table 2. PPK parameter estimates (%SEM) for plazomicin

Parameter	Final estimate	%SEM
CL (L/hr)		
CL_{typ} (L/hr)	0.487	7.95
$CL_{R,max}$ (L/hr)	4.95	7.08
$CLcr_{50}$ (mL/min/1.73 m^2)	63.8	6.16
Hill coefficient	2.56	9.65
CL-HTCM power	1.23	23.4
Vc (L)		
Healthy subjects	7.98	5.03
Fractional increase for AP patients	0.395	32.9
Fractional increase for cUTI patients	0.996	17.2
CLd1 (L/hr)	8.36	8.47
Vp1 (L)		
Coefficient	7.08	4.26
Vp1-BSA power	1.15	29.5
Vp1-age slope	0.0585	23.8
CLd2 (L/hr)		
Coefficient	0.169	5.01
CLd2-HTCM power	4.45	15.1
Vp2 (L)	7.10	9.14
ω^2_{CL}	0.136 (36.9 % CV)	20.0
ω^2_{Vc}	0.415 (64.4% CV)	22.1
ω^2_{CLd1}	0.276 (52.6% CV)	46.8
ω^2_{Vp1}	0.108 (32.8% CV)	34.0
ω^2_{CLd2}	0.0643 (25.4% CV)	37.6
ω^2_{Vp2}	0.239 (48.8% CV)	30.0
Covariance (CL, Vc)	0.201 (r^2 = 0.716)	23.3
Covariance (CL, Vp1)	0.104 (r^2 = 0.736)	30.5
Covariance (Vc, Vp1)	0.172 (r^2 = 0.660)	31.0
σ^2_{CCV}	0.0396 (19.9% CV)	11.3
σ^2_{ADD}	0.0000239 (0.00489 mg/L)	47.5

a. Population Mean $CL\,(L/hr) = \left(0.487 + \frac{4.95 \bullet CrCl^{2.56}}{63.8^{2.56} + CrCl^{2.56}}\right) \bullet \left(\frac{HTCM}{165}\right)^{1.23}$

b. Population Mean $Vc\,(L) = 7.98 \bullet (1 + AP \bullet 0.395) \bullet (1 + cUTI \bullet 0.996)$

c. Population Mean $Vp1(L) = 7.08 \bullet (BSA/1.8)^{1.15} + (Age - 39) \bullet 0.0585$

d. Population Mean $CLd2 = 0.169 \bullet \left(\frac{HTCM}{165}\right)^{4.45}$

Derivation of Plazomicin Dosing Regimen Equation

- A simplified linear representation of the population mean CL equation was used to describe the relationship between weight-normalized CL and CLcr [CL (L/h/kg) = 0.00053 + 0.000645 • CLcr]. To achieve the target AUC_{0-24}, patients with CLcr of 30-150 mL/min/1.73 m^2 required a plazomicin dose (mg/kg) of 0.14 + 0.17 x CLcr (capped at 15 mg/kg) once daily; twice this dose every 48 h was required for patients with CLcr of 15-30 mL/min/1.73 m^2.

PK-PD Target Attainment Analyses

- %PTA by MIC for simulated patients with normal renal function (CLcr 90 to 150 mL/min/1.73 m^2), based on Day 1 plasma and Day 2 ELF exposures and AUC_{0-24}:MIC ratio targets and overlaid on MIC distributions for plazomicin against Kp and MDR Kp, is shown in **Figure 3.**
- As shown by the boxplots in **Figure 4**, use of the plazomicin dosing regimen equation provided similar Day 2 plasma AUC_{0-24} values among simulated patients grouped by severity of renal impairment as compared to those with normal renal function.
- As shown in **Table 3**, %PTA by MIC across renal function groups based on plasma and ELF AUC_{0-24}:MIC ratio targets was ≥ 97.7% for MIC=2 mg/L. Overall %PTA across renal function groups based on plasma and ELF AUC_{0-24}:MIC ratio targets over the MIC distribution for plazomicin against MDR Kp was ≥97.2%.

Figure 3. %PTA by MIC among simulated patients with normal renal function based on plasma and ELF AUC_{0-24}:MIC ratio targets

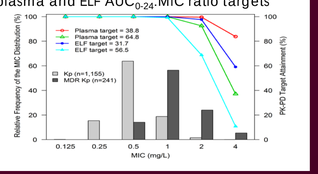

Figure 4. Comparison of simulated plasma AUC_{0-24} on Day 2 by renal function group

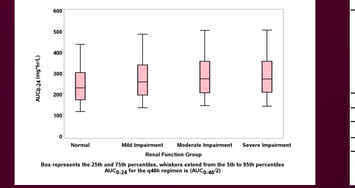

Table 3. %PTA across renal function groups based on plasma and ELF AUC_{0-24}:MIC ratio targets for MIC=2 mg/L and over a MIC distribution for plazomicin against MDR Kp

Renal function group (CLcr range, in mL/min/1.73 m^2)	%PTA based on plasma or ELF AUC_{0-24}:MIC ratio targets associated with a 2-$\log_{10}$ CFU reduction from baseline in Kp			
	Plasma AUC_{0-24}:MIC target=39[a]		ELF AUC_{0-24}:MIC target=32[b]	
	MIC=2	Overall[c]	MIC=2	Overall[c]
Normal (90 to 150)	99.6	99.0	97.7	97.2
Mild impairment (60 to <90)	99.9	99.5	99.2	98.1
Moderate impairment (30 to <60)	99.9	99.4	99.4	98.5
Severe impairment (15 to <30)	100	99.6	99.2	98.5

a. %PTA results based on Day 1 plasma AUC_{0-24} values and median plasma AUC:MIC target of 39.
b. %PTA results based on Day 2 ELF AUC_{0-24} values (which assumed ELF to plasma equilibration by this time point) and the median ELF AUC_{0-24}:MIC target of 32.
c. Based on %PTA by MIC results over the MIC distribution for MDR Kp.

CONCLUSION

- The predicted percent of patients achieving plasma and ELF AUC_{0-24}:MIC ratio targets for efficacy against MDR Kp was high (≥ 97.2%), suggesting that the proposed approach to plazomicin dosing will provide plasma exposures consistent with efficacy in the majority of patients with CRE bacteremia and ELF exposures consistent with efficacy in the majority of patients with CRE bacterial pneumonia.

Acknowledgement: This project has been funded in whole or in part with federal funds from the Biomedical Advanced Research and Development Authority (BARDA), Office of the Assistant Secretary for Preparedness and Response, Office of the Secretary, Department of Health and Human Services, under Contract No. HHSO100201000046C.