A Simulated Application of the Hartford Hospital Aminoglycoside Dosing Nomogram for Plazomicin Dosing Interval Selection in Patients With Serious Infections Caused by Carbapenem-Resistant Enterobacterales

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ABSTRACT

Purpose: In the Phase III Study of Plazomicin Compared With Colistin in Patients With Infection Due to Carbapenem-Resistant Enterobacteriaceae (CARE), plazomicin was studied for the treatment of critically ill patients with infections caused by carbapenem-resistant Enterobacterales. Initial plazomicin dosing was guided by creatinine clearance (CrCl) and subsequent doses adjusted by therapeutic drug monitoring to achieve AUC_{0-24} exposures within a target range (210−315 mg·h/L). We applied the Hartford nomogram to evaluate whether this clinical tool could reduce plazomicin troughs levels and increase the proportion of patients within the target AUC range.

Methods: Thirty-seven patients enrolled in cohorts 1 or 2 of CARE were eligible for analyses. Observed 10-hour concentrations after the initial dose were plotted on the Hartford nomogram to determine an eligible dosing interval group (q24h, q36h or q48h). On the basis of baseline CrCl, a 15- or 10-mg/kg dose was simulated with the nomogram-recommended dosing interval. The proportion of patients in each dosing interval group with a trough ≥3 mg/L (trough threshold associated with serum creatinine increases ≥0.5 mg/dL in product label) was quantified. Simulated interval-normalized AUC_{0-24} was compared with the target AUC range.

Findings: Among the 28 patients with a CrCl ≥60 mL/min, the nomogram recommended every-24-hour dosing in 61% and an extended-interval (q36h or q48h) in 39% of patients. For patients with a CrCl ≥30−59 mL/min (n = 9), the nomogram recommended every-24-hour dosing and an extended-interval in 22% and 78% of patients, respectively. Among both renal function cohorts, exposure simulation with the nomogram significantly reduced the proportion of patients with trough concentrations ≥3 mg/L (CrCl ≥60 mL/min cohort: 91% vs 9%, $P < 0.001$; CrCl ≥30−59 mL/min cohort, 100% vs 0%, $P < 0.001$). Relative to the observed mean (SD) AUC_{0-24} of 309 mg·h/mL (96 mg·h/mL), simulation of extended intervals resulted in a mean interval-normalized AUC_{0-24} of 210 mg·h/mL (40 mg·h/mL) in all patients eligible for an extended interval, resulting in a similar proportion (49% vs 54%) of patients within the target AUC_{0-24} range after the first dose.

Implications: Application of the Hartford nomogram successfully reduced the likelihood of elevated plazomicin trough concentrations while improving AUC exposures in these patients with carbapenem-resistant Enterobacterales infections. (*Clin Ther*. 2019;41:1453−1462)

Keywords: bloodstream infection, extended-interval aminoglycoside dosing, nephrotoxicity, once-daily aminoglycoside dosing, therapeutic drug monitoring.

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INTRODUCTION

Bloodstream infections (BSIs) and hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP) remain leading causes of death among hospitalized patients.[1–3] Recent reports describe an increasing incidence of BSIs and HABP/VABP caused by gram-negative pathogens, including the Enterobacterales (former taxonomy: Enterobacteriaceae).[4,5] In a longitudinal study of >27,000 BSI episodes during 22 years, the rate of gram-negative BSIs increased from 64 to 142 episodes per 100,000 inhabitants, and the rate of BSIs at the end of the study period was higher for gram-negative pathogens than for gram-positive pathogens.[6]

Resistance to β-lactams among Enterobacterales occurs primarily through production of β-lactamases, with carbapenemases representing the most challenging β-lactamase family owing to their ability to hydrolyze almost all β-lactams.[7] Furthermore, the worldwide emergence of Ambler class A serine carbapenemases, particularly *Klebsiella pneumoniae* carbapenemases, is a cause of concern given the limited selection of treatment options for carbapenemase-resistant Enterobacterales (CRE) infections.[8,9] In the most recent assessment from the Centers for Disease Control and Prevention, *Klebsiella pneumoniae* carbapenemase–producing CRE have been reported in every state and Washington, DC.[10] In response to poor patient outcomes and an increasing economic burden, the Centers for Disease Control and Prevention designated CRE an urgent bacterial threat to our public health.[11]

Plazomicin is a next-generation aminoglycoside with potent *in vitro* activity against multidrug-resistant Enterobacterales, including extended-spectrum β-lactamase–producing, carbapenem-resistant, and aminoglycoside-resistant isolates.[12,13] Plazomicin was recently approved by the US Food and Drug Administration for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis on the basis of a Phase III clinical trial (Study of Plazomicin Compared With Meropenem for the Treatment of Complicated Urinary Tract Infection Including Acute Pyelonephritis).[14] In another Phase III randomized trial (Study of Plazomicin Compared With Colistin in Patients With Infection Due to Carbapenem-Resistant Enterobacteriaceae [CARE]), plazomicin was compared with colistin (both drugs in combination with meropenem or tigecycline) for the treatment of patients with BSIs and HABP/VABP due to CRE.[15] A second cohort in the CARE trial permitted enrollment and treatment with plazomicin for CRE infections in patients who otherwise did not meet cohort 1 inclusion and exclusion criteria. During the CARE trial, plazomicin dose adjustments were determined by $AUC_{0–24}$-based therapeutic drug monitoring (TDM) to ensure plazomicin exposures were within a prespecified $AUC_{0–24}$ target range. Data from the CARE trial indicated improved survival and tolerability with plazomicin compared with colistin, although the number of study patients was limited.[15]

Plazomicin *in vivo* efficacy is correlated with increasing the AUC/MIC ratio. Notably, increasing the C_{max} of aminoglycosides is one method to increase overall AUC and can best be optimized by a once-daily dose administration. The Hartford Hospital extended interval aminoglycoside dosing nomogram (referred to as the Hartford nomogram) is a simple and reliable clinical tool for determining an appropriate dosing interval for daily administration of gentamicin, tobramycin, and amikacin.[16] Reductions in aminoglycoside-induced nephrotoxicity have been observed with application of the Hartford nomogram.[17,18]

Given the similarity of the pharmacokinetic profile of plazomicin with other aminoglycosides, the aims of the present study were to assess the utility of the Hartford nomogram in reducing plazomicin trough levels and, using simulated plazomicin $AUC_{0–24}$ plasma exposures, evaluate the proportion of patients with $AUC_{0–24}$ within the $AUC_{0–24}$ target range.

PATIENTS AND METHODS

Study Design and Population

This was a retrospective analysis of patient data collected during the Phase III CARE trial. All data were provided by Achaogen Inc to investigators for analyses. The study was reviewed and approved by the Hartford Hospital Institutional Review Board. Informed consent was waived because all patient data were available and collected for the purposes of the CARE trial.

Patients aged 18 to 85 years with BSIs or HABP/VABP suspected or confirmed to be due to CRE and

an Acute Physiology and Chronic Health Evaluation II score between 15 and 30 were eligible for enrollment in CARE. Detailed information on screening, enrollment, and patient demographic characteristics have previously been published.[15] Patients enrolled in CARE who received at least 1 dose of plazomicin in cohort 1 or cohort 2 were considered for inclusion in this analysis. Patients were excluded from this analysis if pharmacokinetic parameter estimates were unavailable or if they were receiving renal replacement therapy during plazomicin concentration determination. During CARE, plazomicin was administered as an intravenous infusion for 30 minutes with the initial dose administered as 15 mg/kg q24h or at a reduced dose based on estimated creatinine clearance (CrCl) or type of renal replacement therapy.[15] Subsequent dosing regimens were determined by AUC_{0-24}–based TDM to ensure plazomicin exposures were within a prespecified AUC_{0-24} range of 210 to 315 mg·h/L (±20% of the AUC_{0-24} target of 262 mg·h/L).[15] As a result of required TDM, as well as pharmacokinetic sampling, plazomicin concentrations for patients in the CARE trial were available at 0.75, 1.5, 4, 6, 10, 18, and 24 hours after the start of infusion on day 1. A 3-compartment model with a zero-order rate constant and linear first-order elimination kinetics best described the plazomicin plasma pharmacokinetic profile from the CARE trial.[19] The following patient characteristics were extracted from the CARE trial data set: age, sex, height, total weight, ideal weight, date and time of all plazomicin doses, CrCl on study day 1, and individual pharmacokinetic parameter estimates, which included the following parameters based on the 3-compartment fitting of observed concentration data: CL/F, $V_{d,}$ distributional clearance of peripheral compartments 1 and 2 (CLD1 and CLD2, respectively), volume of peripheral compartments 1 and 2 (VP1 and VP2, respectively), and estimated day 1 AUC_{0-24}. CrCl was estimated by Cockcroft-Gault formula using total weight or ideal weight for patients with total weight greater than ideal weight by ≥25%. The incidence of nephrotoxicity (defined in the CARE trial as any increase in serum creatinine ≥0.5 mg/dL above the baseline value at any time on study, including on and/or after intravenous drug therapy) was extracted.

Hartford Nomogram Application

The following strategy was used to identify the initial dose and dosing interval for each individual simulation. First, patients were assigned a dose based on renal function. A 15-mg/kg dose was selected for patients with a baseline CrCL ≥60 mL/min (normal renal function and mild renal impairment), and a 10-mg/kg dose was selected for patients with a CrCl ≥30 to 59 mL/min (moderate renal impairment). Dose was calculated based on actual weight unless the patient was obese (ie, ≥25% ideal weight). If the patient was obese, adjusted weight was used to derive the dose. Second, a daily (q24h) or extended dosing interval (q36h or q48h) was determined by application of the Hartford nomogram. Clinical application of the nomogram is performed by obtaining a single random blood sample between 6 and 14 hours after the start of an aminoglycoside infusion (Figure 1). In this case, the observed 10-hour postdose plazomicin concentration from the CARE trial was plotted on the nomogram after application of a ratio based on the dose received as follows:

$$PlotC = ObsC\ x \frac{7\ \left(\frac{mg}{kg}\right)}{dose\left(\frac{mg}{kg}\right)}$$

where *PlotC* denotes concentration plotted on nomogram, *ObsC* is the observed plazomicin concentration, and *dose* is the plazomicin dose received. The extended-dosing interval recommended by the Hartford nomogram was used for each patient's simulation. Concentration thresholds for extending the plazomicin dosing interval were at a corrected 10-hour level as follows: 4.8 to 7 mg/L, q36h interval, and >7 mg/L, q48h interval (Figure 1).

Simulation of Plazomicin Concentrations

A 3-compartment pharmacokinetic simulation was performed using Crystal Ball (Oracle Inc., Redwood Shores, CA), in which first-dose plazomicin concentrations were simulated in 6-minute intervals for up to the nomogram-derived interval (24, 36, or 48 hours). Simulations were based on all 3 of the following: (1) individual patient pharmacokinetic parameter estimates, (2) a 15-mg/kg or 10-mg/kg dose (determined by baseline CrCl), and (3) a nomogram recommended dosing interval (based on observed 10-hour sampling concentration). From these simulations, a trough (0.5 hours before the subsequent dose) and

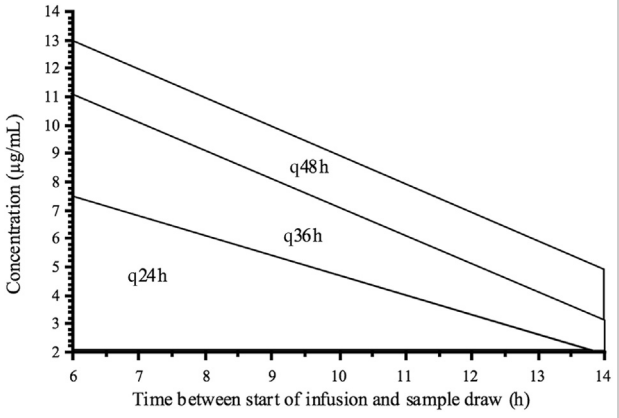

Figure 1. Hartford Hospital once daily aminoglycoside nomogram showing q24h, q36h, and q48h intervals. Concentration thresholds for extending the plazomicin dose interval were at a corrected 10-hour level as follows: <4.8 mg/L q24h, 4.8 to 7 mg/L q36h, and >7 mg/L q48h. Adapted with permission: Copyright © American Society for Microbiology, [Antimicrobial Agents and Chemotherapy, Mar. 1995, p. 650–655].

interval-normalized AUC_{0-24} (*n*AUC) based on dosing interval were determined. All AUC values were determined using the trapezoidal rule. The *n*AUC for the simulated patients was defined as the AUC_{0-24} for patients eligible for a q24h interval, AUC over the initial 36 hours divided by 1.5 for patients eligible for a q36h interval, and AUC over the initial 48 hours divided by 2 for patients eligible for a q48h interval. When the nomogram derived a dosing regimen equal to what the actual patient received in the CARE trial (ie, 15 mg/kg q24h), the patient's estimated day 1 AUC_{0-24} exposure from the CARE trial was used in analysis.

Toxicodynamics and Pharmacodynamics

To evaluate trough concentrations after Hartford nomogram application, the proportion of patients with an observed or simulated plazomicin trough ≥3 mg/L was evaluated because this threshold was associated with serum creatinine increases ≥0.5 mg/dL within the cUTI population (Study of Plazomicin Compared With Meropenem for the Treatment of Complicated Urinary Tract Infection Including Acute Pyelonephritis [EPIC]). As a measure of plazomicin exposure, the proportion of patients with an *n*AUC within the prespecified AUC_{0-24} range (210–315 mg·h/L) range was determined. Percent probability of target attainment by MIC was estimated using the *n*AUC achieved after Hartford nomogram application. The median and mean pharmacodynamic threshold was a total drug *n*AUC/MIC ≥85 and *n*AUC/MIC ≥110.7, respectively, which was associated with a 1-log reduction in murine thigh infection studies.[20] The probability of target attainment curves were overlaid on the baseline CRE MIC distribution observed in the CARE trial.

Statistical Analysis

Descriptive statistics were performed using Sigma Plot 14 (Systat Software Inc, San Jose, CA). Differences in the proportion of patients with trough <3 mg/L or ≥ 3mg/L were determined using the χ^2 test or Fisher exact test. The Welch *t* test was used to determine differences in *n*AUC, whereas comparisons in mean trough concentrations were determined by a paired *t* test or Wilcoxon signed-rank test when appropriate. In each instance, a 2-tailed test was performed and a prespecified α level of 0.05 was used.

RESULTS

Patients

Of the 48 patients who received at least 1 dose of plazomicin in the CARE trial, 9 patients were excluded from these analyses because of the need for renal replacement therapy during plazomicin concentration determination and 2 patients were excluded because individual pharmacokinetic parameter estimates were not available, leaving 37 patients available for inclusion in this analysis. Patient demographic and clinical characteristics are presented in Table I.

Hartford Nomogram Application

The observed mean (SD) plazomicin concentration at 10 hours was 9.2 (4.8) mg/L for the 37 patients. The mean (SD) 10-hour concentrations were higher for patients with lower CrCl (CrCl ≥30–59 mL/min: 10.7 [4.8] mg/L; CrCl ≥60 mL/min: 8.7 [4.7] mg/L). When corrected by the dose ratio (above Equation), 19 (51%), 10 (27%), and 8 (22%) patients were

Table I. Demographic and baseline characteristics of plazomicin-treated patients from the Phase III CARE trial who were included in this analysis of the Hartford nomogram.

Characteristic	Finding (N = 37)
Male sex, No. (%)	26 (70.3)
Age, mean (SD), y	62 (17)
Total body weight, mean (range), kg	84 (44–165)
CrCl,* median (IQR), mL/min	83 (62–142)
CrCl, No. (%)	
≥60 mL/min	28 (75.7)
30–59 mL/min	9 (24.3)
Plazomicin dose received,† median (IQR), mg	1040 (825–1223)
Any increase in Scr ≥0.5 mg/dL, No. (%)	10 (27.0)
Infection type, No. (%)	
BSI	23 (62)
HABP/VABP	11 (30)
cUTI	3 (8)

BSI = bloodstream infection; CARE = Study of Plazomicin Compared With Colistin in Patients With Infection Due to Carbapenem-Resistant Enterobacteriaceae; CrCl = creatinine clearance; cUTI, complicated urinary tract infection; HABP/VABP = hospital-acquired/ventilator-associated bacterial pneumonia; IQR = interquartile range; Scr = serum creatinine.

* CrCl (as calculated by site) obtained on day 1 of plazomicin dosing.

† Initial dose received in CARE trial.

eligible for a q24H, q36H, and q48H dosing interval, respectively. A significantly larger proportion of patients with CrCl ≥30 to 59 mL/min were eligible for an extended dosing-interval compared with patients with CrCl ≥60 mL/min (78% vs 39%, $P < 0.001$).

Simulated Plazomicin Exposures and Pharmacodynamic Analyses

Plazomicin trough concentrations were simulated and *n*AUC values calculated for patients eligible for an extended dosing interval (q36H or q48H) and compared with the troughs and AUC_{0-24} values observed after the first dose in the CARE trial (Table II). Dose simulation with the nomogram-derived extended intervals in eligible patients resulted in significant reductions in mean trough concentrations compared with observed trough concentrations. For patients with CrCl ≥60 mL/min, simulation of extended intervals increased the proportion of patients with a mean *n*AUC that fell within the prespecified target range (73% vs 45%).

The probability of patients achieving or exceeding the exposure target of *n*AUC/MIC ratio ≥85 or *n*AUC/MIC ratio ≥110.7, given the frequency distribution of MICs reported from clinical CRE isolates, is shown in Figure 2. The probability of achieving the *n*AUC/MIC ratio ≥85 target at the US Food and Drug Administration susceptibility breakpoint (2 mg/L) was 76% for simulated patients using the nomogram-derived interval.

DISCUSSION

Aminoglycosides continue to have a central role in the treatment of gram-negative infections because of their spectrum of activity and unique mode of bacterial killing.[21] Conventionally, aminoglycosides have been administered as multiple daily doses in conjunction with TDM to target exposures associated with maximal efficacy and minimal toxicity. However, based on pharmacodynamic characteristics, the once-daily dosing strategy was developed to maximize concentration-dependent bactericidal activity and the post-antibiotic effect and minimize adaptive resistance.[18,22,23] The Hartford nomogram, a simple and reliable tool, has been routinely used in clinical practice to optimize aminoglycoside dosing regimen and reduce the risk of nephrotoxicity through the once-daily extended dosing interval approach.[16,17,24]

A major limitation regarding the clinical use of aminoglycosides has been concern for the development of nephrotoxicity manifesting as nonoliguric renal failure and an increase in serum creatinine levels.[21,25] Plazomcin, a recently approved aminoglycoside antibiotic, is not exempt from this toxicity risk. During the Phase III study of patients with cUTI (EPIC), serum creatinine increases ≥0.5 mg/dL above baseline was observed in approximately 7% and 4% of the plazomicin-treated and meropenem-treated patients, respectively.[14] Notably, relatively fewer serum creatinine increases

Table II. Summary of plazomicin trough concentrations and comparison of *n*AUC (after dose simulation with an extended interval derived from the Hartford nomogram) with prespecified AUC_{0-24} target range.

Characteristic	Eligible for q24h			Eligible for an extended interval*		
	Observed†	Simulated	*P*	Observed†	Simulated	*P*
CrCl ≥60 mL/min (n = 28)						
No. of patients	17	17		11	11	
Trough concentration, mean (SD), mg/L	1.28	—‡	ND	4.24 (1.35)	1.94 (0.78)	<0.001
No. (%) with trough ≥3 mg/L	1 (6)	—		10 (91)	1 (9)	<0.001
*n*AUC,§ mean (SD)	205 (56)	—		311 (87)	225 (32)	0.009
Place in range, No. (%)						
Above range‖	0	—		4 (36)	0	
Within range	9 (53)	—		5 (45)	8 (73)	
Below range	8 (47)	—		2 (18%)	3 (27)	
CrCl ≥30−59 mL/min (n = 9)						
No. of patients	2	2		7	7	
Trough concentration, mean (SD), mg/L	2.03 (1.10)	1.77 (0.83)	ND	5.13 (1.53)	1.87 (0.51)	0.016
No. (%) with trough ≥3 mg/L	1 (50)	0		7 (100)	0	<0.001
*n*AUC,§ mean (SD)	202 (44)	182 (24)		305 (108)	186 (41)	0.027
Place in range, No. (%)						
Above range‖	0	0		3 (43)	0	
Within range	1 (50)	0		3 (43)	3 (43)	
Below range	1 (50)	2 (100)		1 (14)	4 (57)	

CrCl = creatinine clearance; *n*AUC, interval-normalized AUC_{0-24}; ND, not determined.

* Extended interval: CrCl ≥60 mL/min: q36h (n = 10) or q48h (n = 1); CrCl ≥30 to 59 mL/min: q48h (n = 7).

† Observed (derived from the population pharmacokinetic analysis) AUC_{0-24} and trough values based on initial q24h regimen received during the Study of Plazomicin Compared With Colistin in Patients With Infection Due to Carbapenem-Resistant Enterobacteriaceae (CARE).

‡ Simulation of trough concentrations and *n*AUC not performed because patients were Hartford nomogram eligible for an interval that was used in CARE (ie, plazomicin 15 mg/kg q24h).

§ The *n*AUC is AUC_{0-24h} for q24h patients, AUC_{0-36} divided by 1.5 for q36h patients, and AUC_{0-48} divided by 2 for q48h patients.

‖ Prespecified AUC_{0-24} target range used in the CARE trial: 210 to 315 mg•h/L.

≥0.5 mg/dL above baseline were noted in the plazomicin arm (10.0%) relative to colistin (41.7%) in the CARE trial.[15] Although there are no data to support an association between plazomicin trough and nephrotoxicity in the CARE trial based on the limited population enrolled, a trough concentration of ≥3 mg/L was identified as a risk factor for serum creatinine elevations in the much larger cUTI trial.[26] This 3-mg/L trough threshold was therefore applied in the present study to assess the potential for the nomogram to reduce trough concentrations while maintaining therapeutic AUC exposures. Herein, we observed a >2-fold decrease in plazomicin trough concentrations after application of the Hartford nomogram. The extended period with low plasma plazomicin concentrations achieved with the Hartford nomogram may mitigate the risk of aminoglycoside-induced nephrotoxicity.[27–29] Our findings are consistent with a nomogram application study conducted in 281 patients with cUTI or acute pyelonephritis and treated with plazomicin.[30] Compared with the 15-mg/kg q24h regimen, a Hartford nomogram–derived extended interval reduced the proportion of patients with troughs ≥3 mg/L (q36h: 27% vs 0%, $P = 0.021$; q48h: 57% vs 0%, $P = 0.002$).[30]

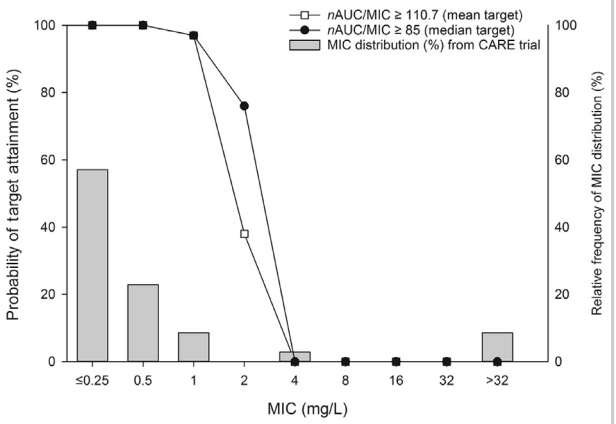

Figure 2. Simulated probability of target attainment for plazomicin pharmacokinetic/pharmacodynamic targets of interval-normalized AUC_{0-24} (*n*AUC)/MIC ≥85 (median target) and *n*AUC/MIC ≥110.7 (mean target) after a 15-mg/kg or 10-mg/kg dose (depending on creatinine clearance) and Hartford nomogram application in all 37 patients. CARE = Study of Plazomicin Compared With Colistin in Patients With Infection Due to Carbapenem-Resistant Enterobacteriaceae.

Application of the Hartford nomogram approach resulted in an improvement in the number of patients with a simulated mean *n*AUC falling within the target AUC_{0-24} range after the first dose. By convention, optimizing exposures of appropriate antimicrobial agent to achieve the pharmacokinetic/pharmacodynamic target with the first dose should positively affect clinical outcomes. In addition, achieving a pharmacokinetic/pharmacodynamic target depends on the pathogen MIC.[31–35] In a recent study by Castanheira et al,[36] the MIC_{50} and MIC_{90} of plazomicin against 4362 Enterobacteriaceae isolates was 0.5 and 2 mg/L, respectively, demonstrating potent activity overall. Notably, a total of 97 CRE isolates (2.2%) were identified, which included 87 isolates carrying *Klebsiella pneumoniae* carbapenemases. Against these CRE, the MIC_{50} and MIC_{90} was 0.5 and 1 mg/L, respectively, with an MIC range of ≤0.06 to >128 mg/L.[36] With the use of the MIC distribution of CRE isolates from the CARE trial, our results indicate that after simulated application of the Hartford nomogram, >90% of patients achieved the median and mean pharmacokinetic/pharmacodynamic target with an MIC up to 1 mg/L after the first plazomicin dose. A recent plazomicin population–pharmacokinetic analysis reported comparable results using dosing recommendations from the plazomicin product label.[20] Percent probabilities of attaining the total-drug plasma pharmacokinetic/pharmacodynamic target (AUC/MIC ≥85) at MIC values of 1 mg/L approached 100% in simulated patients. These data were interpreted relative to *in vitro* surveillance data for Enterobacteriaceae isolates (n = 16,296).[20]

TDM can be used to maximize the efficacy and minimize the toxicity of antimicrobial therapy for individual patients and has become standard of practice for dosing aminoglycosides.[17,37] Like the traditional aminoglycosides, plazomicin does not undergo metabolism, displays linear dose-proportional pharmacokinetic properties, and is primarily eliminated from the body via urinary excretion.[26,38] Furthermore, the plazomicin AUC/MIC ratio best correlates with efficacy in animal and *in vitro* models of infection against gram-negative bacteria.[26,39] As a result, AUC-based TDM was used in the CARE trial to optimize plazomicin exposures to help achieve AUC exposures with the target range. In a study by Trang et al,[40] simulations with an AUC-based TDM strategy resulted in exposures that were consistent with those observed when TDM was implemented in patients with BSIs in the CARE trial.[40] Although TDM-based AUC derivation would be ideal for achieving exposures precisely within the AUC target range, there are no data on its ability to reduce trough concentrations to <3 mg/L.

The use of *n*AUC for comparison among the q24h, q36h, and q48h dosing intervals is recognized as a study limitation. This approach has the potential to underestimate drug exposure for the first 24 hours and overestimate the exposure for the next 12 or 24 hours for a q36h and q48h regimen, respectively. The effect of this method on bacterial regrowth, resistance, and clinical failure is unknown at this time; however, given the wide adoption and use of aminoglycoside extended dosing intervals during

several decades, there are no data to suggest such an approach is associated with negative outcomes.

The observation that 1 in 3 patients with adequate renal function (ie, baseline CrCl ≥60 mL/min) was eligible for an extended dosing interval based on their elevated 10-hour plazomicin plasma level is notable. Given the well-described association between decreasing renal function and decreased aminoglycoside drug clearance, this finding suggests that in this patient population with infections due to CRE, use of CrCl alone may not be an accurate estimate of renal function. Critically ill patients are sensitive to changes in renal function, and aminoglycoside plasma levels may in fact be a more robust marker for true renal function.[27,41]

Through the leveraging of clinical trial pharmacokinetic data, simulation of plazomicin exposures provided an efficient means of assessing the tolerability and efficacy of the Hartford nomogram in a limited population of patients with infections due to CRE. Overall, the Hartford nomogram offers clinicians a simple tool for monitoring and individualizing plazomicin therapy in these patients with challenging-to-treat infections. Clinicians should ensure that patients match the population for which the original nomogram was developed (ie, exclude pediatric, pregnant, burn, ascites, and dialysis patients) until otherwise validated. Notably, patients with CrCl <30 mL/min were unavailable for inclusion in the current analysis. Prospective studies are warranted to assess the real-world incidence of plazomicin nephrotoxicity and to clinically validate our findings.

CONCLUSION

The availability of plazomicin provides a therapeutic option for the treatment of serious and life-threatening CRE infections. On the basis of individual patient simulations, this study indicates that use of the Hartford nomogram after the first plazomicin dose reduces the proportion of patients with trough concentrations >3 mg/L while maximizing exposures. In addition, half of the patients included in these analyses were eligible for an extended interval based on their plazomicin pharmacokinetic profile, indicating an opportunity to integrate the Hartford nomogram in routine clinical practice.

FUNDING SOURCES

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CONFLICTS OF INTERESTS

At the time of the study, A.S. Komirenko and J.D. Seroogy were employees of Achaogen Inc. D.P. Nicolau and J.L. Kuti are members of the speakers bureau for Achaogen Inc. The study sponsor was involved in collection of data through the CARE trial. Study conceptualization, data simulation, interpretation of the results, and manuscript writing were conducted by T.E. Asempa, J.L. Kuti, and D.P. Nicolau, who were responsible for the decision to submit the manuscript for publication in *Clinical Therapeutics*. All authors reviewed and contributed to the manuscript. The authors have indicated that they have no conflicts of interest regarding the content of this article.

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