Utility of Therapeutic Drug Management (TDM) in Managing Plazomicin Pharmacokinetic (PK) Variability in Patients With Infections due to Carbapenem-resistant Enterobacteriaceae (CRE)

Poster
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INTRODUCTION

- Variability of antibiotic PK in the critically ill may lead to subtherapeutic or elevated drug exposure and result in adverse outcomes.[1]
- TDM for aminoglycosides helps to reduce PK variability and risk of nephrotoxicity.[2]
- Plazomicin, a new aminoglycoside with in vitro activity against multidrug-resistant Enterobacteriaceae, including CRE, is currently in phase 3 development for the treatment of patients with serious infections.[3]
- The phase 3 Combating Antibiotic Resistant Enterobacteriaceae (CARE) study is a resistant pathogen–specific trial that describes the efficacy and safety of plazomicin in patients with infections due to CRE. In this study, plazomicin dosing was guided by TDM.

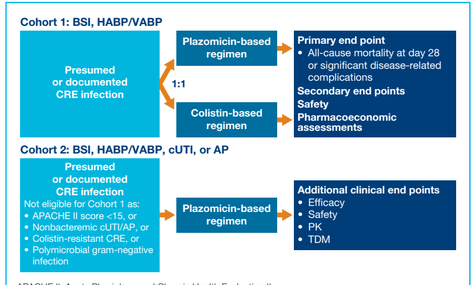
OBJECTIVES

- The aims of this analysis were to assess the frequency of dose adjustment for plazomicin based on TDM and to evaluate renal function in the first 10 patients enrolled in Cohort 2 of the CARE study.

METHODS

- This phase 3 multicenter study was initiated in February 2014 and was conducted at 78 sites in 12 countries (NCT01970371). Enrollment was closed in August 2016.
- Two cohorts of patients were enrolled (**Figure 1**):
  - A randomized, open-label cohort (Cohort 1) of patients with bloodstream infection (BSI) or hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP) due to CRE
  - A nonrandomized, single-arm cohort (Cohort 2) of patients with BSI, HABP/VABP, complicated urinary tract infection (cUTI) or acute pyelonephritis (AP) due to CRE who were ineligible for enrollment in Cohort 1.

Figure 1. The CARE Study Design



APACHE II, Acute Physiology and Chronic Health Evaluation II.

Plazomicin Dosing, TDM, and Dose Adjustment

- Initial plazomicin doses were chosen based on weight, with adjustment by estimated creatinine clearance or use of continuous renal replacement therapy (CRRT).
- Plazomicin was administered up to 15 mg/kg/dose once daily as a 30-minute intravenous (IV) infusion. The planned duration of plazomicin treatment was 7 to 14 days for BSI and HABP/VABP and 4 to 7 days for cUTI and AP, with optional switch to oral antibiotic therapy.
- Following the initial dose of plazomicin, subsequent doses were determined by TDM.
- Blood samples for TDM were drawn at 2 time points after the end of the plazomicin infusion on days 1, 4, and 8, and on other days if warranted by the patient's status.
- Plazomicin plasma concentrations were analyzed by a homogeneous enzyme immunoassay using a clinical chemistry analyzer at regional laboratories.
- Plazomicin doses were adjusted based on TDM results to achieve a steady-state area under the concentration curve calculated from 0 to 24 hours ($AUC_{0\text{-}24\ h}$) of 262 mg/L·h.[4]

Renal Function Assessments

- Serum creatinine was evaluated at baseline, daily on therapy, and at the test-of-cure visit 5 to 9 days after the end of plazomicin therapy.

RESULTS

- The first 10 patients were enrolled in Cohort 2 between November 2015 and February 2016, in Greece (**Table 1**).
- All 10 infections met the microbiology criteria for enrollment (presumptive or documented CRE infection) and were found to be multidrug resistant on central laboratory testing (**Table 2**).

Table 1. Patient Demographic and Clinical Characteristics at Baseline (Cohort 2, N = 10)

Characteristics	
Age, y, mean (range)	62 (25-82)
Sex, male, n	9
Infection type, n	
BSI	4
VABP	5
cUTI	1
Baseline creatinine clearance,[a] n	
>150 mL/min, augmented renal clearance	2
80-150 mL/min, normal renal function	2
60-<80 mL/min, mild renal impairment	1
30-<60 mL/min, moderate renal impairment	4
On CRRT[a]	1
Country, Greece, n	10

[a]Prior to enrollment.

Table 2. Antibiotic Susceptibility of Baseline Pathogens

	MIC (µg/mL)								
Patient #	MEM	IPM	DOR	AMK	GEN	TOB	COL	TGC	SXT
1	128	>32	>32	32	1	16	0.25	1	>64/1216
2	64	32	32	1	0.25	0.25	0.25	1	1/19
3	128	32	32	>64	>64	>64	>128	2	>64/1216
4	8	2	4	64	>64	>64	8	1	2/38
5	8	4	8	16	64	32	16	1	1/19
6	4	8	16	4	2	8	1	1	>64/1216
7	256	>32	>32	16	1	16	64	2	>64/1216
8	128	>32	>32	32	1	16	0.25	0.5	>64/1216
9	1	1	0.5	8	4	8	0.25	0.5	>64/1216
10	16	16	16	1	0.25	0.25	0.25	2	≤0.25/4.8
% S	10	10	10	60	70	20	60	100	40

AMK, amikacin; COL, colistin; DOR, doripenem; GEN, gentamicin; IPM, imipenem; MEM, meropenem; MIC, minimum inhibitory concentration; SXT, trimethoprim/sulfamethoxazole; S, susceptible; TGC, tigecycline; TOB, tobramycin.

All isolates were *Klebsiella pneumoniae* and were resistant to levofloxacin, ceftazidime, ceftriaxone, aztreonam, and piperacillin/tazobactam. Clinical and Laboratory Standards Institute (M100-S25, 2015) breakpoints were applied where available; European Committee on Antimicrobial Susceptibility Testing (Version 5.0, 2015) breakpoints were applied for COL; US Food and Drug Administration breakpoints were applied for TGC. Isolates that were susceptible to the antibiotic are shown in black. Isolates that were nonsusceptible to the antibiotic are shown in red.

Plazomicin Dose Adjustments

- Patients received 4 to 14 days of plazomicin.
- One to 3 dose adjustments, informed by TDM, were required in 8 of 10 patients (**Table 3**).

Table 3. Summary of Plazomicin Dose Adjustments (Cohort 2, N = 10)

Category of Dose Adjustment	No. of Patients
Any dose adjustment due to TDM	8
Dose adjustment due to TDM after day 1	7
Dose adjustment due to TDM after day 4	4
Dose adjustment due to TDM after day 8	2
Dose adjustment due to TDM after unscheduled TDM	2
Dose adjustment in response to changes in clinical status[a]	4

[a]Reasons for dose adjustment included a significant change in creatinine clearance or initiation of CRRT.

Figure 2. Serum Creatinine (A) and Percentage Change in Serum Creatinine (B) From Day 1 Pretreatment Through End of Plazomicin Treatment

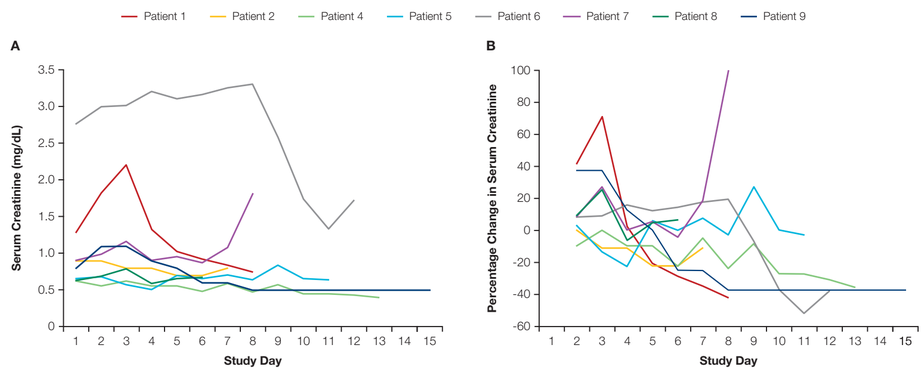


Figure excludes 2 patients who were on CRRT for most of the study duration (Patient 3, who received CRRT pretreatment and for the entire duration of plazomicin therapy, and Patient 10, who received CRRT from day 2 of plazomicin therapy). Patient 6, who received CRRT from day 9 to 11 of plazomicin therapy, is included.

Renal Function

- Renal function at baseline was highly variable, ranging from renal failure requiring CRRT to augmented renal clearance (creatinine clearance [range, 36-194 mL/min] by Cockcroft-Gault). One patient with renal failure at baseline received CRRT prior to enrollment and throughout the study (**Table 1**) (Patient 3; not shown in Figure 2).
- Two patients experienced clinically significant transient rises in serum creatinine early in therapy.
  - In 1 patient, an increase of 71% (from 1.29 to 2.21 mg/dL) on day 3 resolved to baseline within 1 day, after adjustment of plazomicin dosing (Patient 1, **Figure 2**)
  - In the second case, an increase of 61% (from 1.55 to 2.49 mg/dL) on day 2 was detected in a patient with an ongoing baseline condition of "deterioration of renal function," and CRRT was initiated (Patient 10, not shown in Figure 2).
- In the absence of an acute rise in serum creatinine, 1 patient received CRRT on the last 3 days of plazomicin therapy for treatment of preexisting chronic renal failure (Patient 6, **Figure 2**).
- Renal injury (defined by RIFLE criteria[5] [100% rise in serum creatinine from baseline]) was first detected on day 8 in a patient who received 7 days of plazomicin therapy. On day 9, this patient was diagnosed with multiorgan failure, which was assessed by the investigator as related to septic shock, and which led to the patient's death on day 11 (Patient 7, **Figure 2**).
- Among the remaining 9 patients, none had serum creatinine levels above baseline values at the end of therapy or test-of-cure (if applicable) visits.

CONCLUSION

- Plazomicin dosing, including the use of TDM, was not associated with substantial kidney injury in this small set of critically ill patients with CRE.

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