INTRODUCTION

- Variability of antibiotic pharmacokinetics (PK) in certain patient populations, including critically ill, may lead to subtherapeutic or elevated drug exposures. Therapeutic drug management (TDM) allows for individualized drug dosing at high risk of PK variability ([1,2]).

- TDM is recommended to optimize exposures and clinical outcomes in certain patient treated with aminoglycosides (AG) [3,4]. Plazomicin is an AG that was engineered to overcome aminoglycoside-resistance mechanisms, the most common aminoglycoside-resistance mechanism in Enterobacteriaceae.

- An area under the concentration-time curve (AUC) based approach for TDM was used in the CARE clinical trial, evaluating plazomicin in therapy for patients with serious infections due to carbapenem-resistant Enterobacteriaceae to help achieve plazomicin AUC_{24h} exposures within a target range.

- The objectives of these analyses were to evaluate the performance of the AUC-based TDM algorithms used in the CARE clinical trial among the subset of patients with bloodstream infections (BSI) and to assess the performance of this TDM approach in simulated patients with BSI.

METHODS

- The performance of the TDM algorithms that were employed in the CARE clinical trial was evaluated using individual fitted plazomicin exposures for enrolled patients based on the actual dosing regimens administered and observed treatment duration.

- Using the subset of patients with BSI from the CARE clinical trial, the population of simulated patients was generated by replicating the demographics for each patient a sufficient number of times in order to generate a population of at least 3,000 simulated patients.

- A plazomicin population PK model [5] and a plazomicin exposure-response model that characterized creatinine clearance (CLcr) changes during therapy were utilized to simulate plazomicin concentration-time profiles for each simulated patient receiving 14 days of therapy.

- Initial plazomicin dosing regimens were based on baseline renal function (Table 1) and subsequent doses were either maintained at the starting dose (without TDM) or periodically adjusted consistent with the dosing adjustments used by patients in the CARE trial (with TDM).

<table>
<thead>
<tr>
<th>Renal Function*</th>
<th>Plazomicin Dosage Regimen</th>
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</thead>
<tbody>
<tr>
<td>Ccr ≥ 60 mL/min</td>
<td>15 mg/kg q24h</td>
</tr>
<tr>
<td>Ccr &lt; 60 mL/min</td>
<td>10 mg/kg q24h</td>
</tr>
<tr>
<td>Ccr &lt; 30 mL/min</td>
<td>10 mg/kg q48h</td>
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</tbody>
</table>

* IBW = Ideal body weight; TBW = Total body weight.

Table 1. Initial plazomicin dosage regimens based on renal function.

- The AUC-based TDM algorithm involved sampling on Day 1, Day 4 (±1 day), and Day 8 (±1 day). Two TDM samples were obtained, one at the patient’s dosing schedule (Table 2).

- The estimated AUC_{24h} was determined by inputting the TDM sample concentrations into the corresponding equation based on the simulated dosing schedule (Table 2).

- With AUC_{24h} target of 210-315 mg/h/L, an adjusted dose estimation was utilized to calculate the new dose (Table 2). The adjusted dose was implemented 48 hours after the target dose was set.

- Summary statistics for average AUC_{24h} over 48 hours by study day with and without TDM and the percentage of AUC_{24h} values below, within, and above the recommended target AUC range were compared for simulated patients.

RESULTS

- Evaluations of the performance of the TDM algorithms in the subset of patients with BSI in the CARE trial (n=23) demonstrated a higher percentage of post-dose total drug plasma AUC_{24h}-adjusted plazomicin doses.

- The percentage of plazomicin doses with total drug plasma AUC_{24h} values that were >210 to ≤315 mg/h/L for doses 1, 3 to 5, 6 to 9, and >9 was 30.4, 50.7, 58.3, and 57.8%, respectively.

- Comparisons of AUC_{24h} metrics for simulated patients with BSI who did and did not undergo TDM are provided in Tables 2 and 3. AUC_{24h} data are shown in Figure 1.

- Following initial dosing based on renal function, 47.3% of simulated patients had exposures within the targeted AUC range, with 31.9% of simulated patients having exposures above the target range.

- With AUC-based TDM, the variability in average total drug plasma AUC_{24h} was notably reduced from a percent coefficient of variation (%CV) of 34.2% after initial dosing to 17.3% after doses administered on Days 9 to 11. Without AUC-based TDM for subsequent doses, the variability increased from a %CV of 31.9% to 47.5% after doses administered on Days 9 to 11.

- With the use of TDM, the percentage of simulated patients who had AUC_{24h} values within the target range increased to 79.9%, <42% of simulated patients had exposures above the target AUC range.

- Without the use of TDM for subsequent doses, the percentage of simulated patients with AUC_{24h} values below and above the target range decreased to 36.8% and increased to 47.2%, respectively, on Days 9 to 11.

CONCLUSIONS

- Simulations with AUC-based TDM resulted in exposures that were consistent with those observed when TDM was implemented in patients with BSI in the CARE trial.

- Relative to dosing based on baseline renal function alone, results of assessments based on data from simulated patients with BSI demonstrated the benefit of using an iterative AUC-based TDM approach that consisted of two-sampling time points and dose adjustment equations.

- The AUC-based TDM approach resulted in decreased variability in exposures and an increased percentage of AUC_{24h} values within the targeted range of 210-315 mg/h/L.

- Results of simulations suggest that AUC-based TDM may prevent sustained high plasma exposures of plazomicin.

REFERENCES