Introduction and purpose

Avibactam is a novel first-in-class, non-β-lactam β-lactamase inhibitor that restores the in vitro activity of ceftazidime against pathogens producing Ambler class A, C and some class D β-lactamases.1,3

Surveillance studies show that ceftazidime-avibactam has activity in vitro against Gram-negative isolates from patients with pneumonia.1,3 Moreover, ceftazidime-avibactam is effective in animal models of lung infection with Pseudomonas aeruginosa.1,6

Ceftazidime-avibactam is currently under development in Phase III clinical trials,1 including a study into its efficacy and tolerability in patients with nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP) (NCT01808092).

Patients with VAP often have augmented renal clearance (ARC), which may result in under-dosing of antibiotics, which are predominantly renally cleared, and has been suggested as a potential reason for treatment failure in antibiotic trials.2,5

The use of population pharmacokinetic (PK) and probability of PK/pharmacodynamic (PK/PD) target attainment (PATA) analyses helps support dose adjustments in patients with different types of infection using patient- and disease-related covariates.

The aim of this study was to incorporate literature-reported demographics and renal function data from patients with NP including VAP into the simulation settings for ceftazidime and avibactam for calculation of PTAs in patients with NP in order to ensure appropriate dose selection in patients with NP, accounting for certain risk factors such as ARC.

Methods

Population PK models of ceftazidime and avibactam have been developed previously from data obtained from five Phase I studies in healthy volunteers and a Phase II study in patients with complicated intra-abdominal infection (cIAI).3

For both ceftazidime and avibactam, the final models were two-compartmental, with body surface area normalised creatinine clearance (CrCL), age, body weight and study population (healthy subjects vs patients) identified as covariates affecting the PK of ceftazidime and avibactam.

Previously published ceftazidime PK data in patients with NP7,12 were found to be similar to those reported from the population PK model in patients with cIAI.8 Blinded ceftazidime and avibactam PK data from an ongoing Phase III trial in patients with NP including VAP (NCT01808092) revealed concentrations of ceftazidime and avibactam to be comparable to those from Phase III studies in patients with cIAI (NCT01499290 and NCT01500239). These observations validate the use of ceftazidime and avibactam population PK models developed in patients with cIAI to be used to simulate exposures in patients with NP.

For the simulations described as Case 1 and 2 above, Monte Carlo simulations for 3000 patients were used to calculate the PTA at minimum inhibitory concentration (MICs) of 0.25–64 mg/L. Of these, 2000 simulated subjects had a CrCL >80 mL/min and 1000 had a CrCL 50–80 mL/min. The other covariates (age, weight, height and gender) were simulated from their distribution functions. The joint PTA of ceftazidime-avibactam was calculated by MIC, and compared with the ceftazidime-avibactam MIC90 distributions for 1391 P. aeruginosa isolates from patients with healthcare-associated pneumonia (HAP) patients and 339 from VAP patients, which are shown in Figure 2.14

Results

90% PTA was predicted for patients with NP including VAP up to ceftazidime-avibactam MICs of 8 mg/L (MIC90 of the ceftazidime-avibactam MIC distributions for P. aeruginosa isolates from patients with HAP and VAP) using the dose of 2000 mg ceftazidime and 500 mg avibactam given as a 2-h infusion every 8 h (Table 1 and Figure 3).

In simulated patients with high CrCL, it was also estimated that >90% PTA would be achieved with ceftazidime-avibactam 2000–500 mg by 2-h infusion at the MIC of 8 mg/L (Table 1).