P1185

Pharmacokinetic/pharmacodynamic validation of the ceftazidime-avibactam dose in patients with nosocomial pneumonia, including ventilator-associated pneumonia

Shampa Das[1], Todd Riccobene[2], Timothy Carrothers[2], James Wright[3], Merran Macpherson[3], Mark Lovern[4], Jeremy Hing[4], Yuan Xiong[4], Adekemi Taylor[4], Craig Comisar[4]

[1]AstraZeneca, Macclesfield, UK; [2]Allergan Inc., Jersey City, NJ, USA; [3]Wright Dose, Altrincham, UK; [4]Certara Strategic Consulting, Princeton, NJ, USA

Contact information:
Shampa Das
AstraZeneca
Antibiotics Business Unit
Alderley Park
Macclesfield
UK
Email: Shampa.Das@astrazeneca.com

Background

- Ceftazidime-avibactam is a novel β-lactam/β-lactamase inhibitor combination which was recently approved by the US Food and Drug Administration and European Medicines Agency (EMA) for the treatment of adults with complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI).[1,2] The EMA also approved the combination for the treatment of hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP), before the completion of the Phase III trial in patients with nosocomial pneumonia (NP), including VAP (REPROVE; NCT01808092).[2]
- Population pharmacokinetic (PK) modelling and simulations played an important role in supporting the EMA approval of the ceftazidime-avibactam dosage regimen for patients with HAP and VAP, prior to the availability of clinical trial data.[1,3]
- The approved ceftazidime-avibactam dosage regimen across all indications is 2000-500 mg 2-h infusion, every 8 h (q8h), with adjustments for patients with creatinine clearance (CrCL) ≤50 mL/min.[1,2] The recently completed REPROVE trial demonstrated the efficacy of this ceftazidime-avibactam dosage regimen in patients with NP, including VAP.[4]
- NP and VAP are often complicated by critical illness, which can affect the PK of other antibiotics.[5] It is therefore important to confirm that appropriate exposures and high target attainment are maintained in this patient population, and in subgroups of patients with characteristics of critical illness.
- The objective of this analysis was to use patient PK data from REPROVE to update ceftazidime and avibactam population PK models and examine the impact of NP, VAP and other patient covariates on systemic exposures and target attainment.

Methods

Population PK modelling

- Ceftazidime and avibactam population PK models were developed previously using data from healthy subjects and patients with cIAI or cUTI from six Phase III trials (RECLAIM 1 and 2, RECLAIM 3, REPRISE, RECAPTURE 1 and 2), two Phase II trials and 11 Phase I trials.[6]
- These models were extended to include patient PK data from patients with NP, including VAP, from REPROVE, comprising 412 NP patients (138 VAP, 274 non-VAP) for ceftazidime and 413 NP patients (138 VAP, 275 non-VAP) for avibactam. The final datasets included 1975 subjects for ceftazidime, and 2249 subjects for avibactam.
- A wide range of patient covariates assessed in the previous analysis[6] (CrCL, age, body weight, sex, race, indication, geographic region, and markers of disease severity) were re-evaluated and tested for their impact on ceftazidime and avibactam PK.
- Patients with NP were further stratified into VAP and non-VAP patient subgroups for the covariate analysis. However, as the presence of mechanical ventilation was not perfectly correlated with assignment of VAP status, an additional subgroup was defined for patients receiving ventilation on the day of PK sampling (denoted as NPv) to further assess the impact of ventilation.
- Visual predictive checks were used to evaluate the predictive performance of the final models.

Individual predictions of exposure and joint target attainment

- Joint target attainment was calculated based on the achievement of the joint PK/pharmacodynamic (PD) targets for ceftazidime and avibactam: 50% *f*T>8 mg/L for ceftazidime and simultaneously 50% *f*T>1 mg/L for avibactam.[7,8]
- Individual predictions of systemic ceftazidime and avibactam steady state exposures (maximum concentration [$C_{ss,max}$] and area under the curve over 24 h [$AUC_{ss,0-24}$]) and joint target attainment were calculated for all Phase III patients with ≥1 PK sample (n=1764) and summarised for the following subgroup categories: indication, CrCL, age, body mass index (BMI) and markers of disease severity (baseline Acute Physiology and Chronic Health Evaluation [APACHE] II score, baseline white blood cell [WBC] count, presence or absence at baseline of each of bacteraemia, systemic inflammatory response syndrome [SIRS], or fever)

Probability of target attainment (PTA) simulations

- Monte Carlo simulations were conducted to assess joint PTA and steady-state exposures of ceftazidime and avibactam for 5000 patients in each indication (cIAI, cUTI and NP, including non-VAP, VAP and NPv subgroups).
- Covariate values for simulations in the different indications were obtained by sampling with replacement from the corresponding set of Phase III study patients for each indication. Covariates used in the simulations were matched so that any given value of the subject identification variable had exactly the same covariates (and random effects) in the simulation data sets for both ceftazidime and avibactam, thereby preserving any underlying correlations.
- Exposures and joint PTA were simulated for NP patients with normal renal function and for patients with different levels of renal impairment receiving recommended ceftazidime-avibactam dosage adjustments.[1] For simulations of patients with CrCL<80 mL/min, CrCL values were assumed to follow a uniform distribution within the designated range for each category.

Results

Population PK models

- Consistent with previous analyses,[6] ceftazidime and avibactam PK were both well described by a two-compartment disposition model, with first-order disposition and elimination.
- CrCL was the key covariate predicting the clearance of both drugs. A number of other covariate effects on clearance and volume of the central compartment (V_c) were included in the final ceftazidime and avibactam population PK models; however, only CrCL had sufficiently large effects on drug exposures to warrant dosage adjustments and only for patients with CrCL <50 mL/min.
- The final population PK models performed well on visual predictive testing, both overall and for key patient subgroups based on CrCL, age, or obesity, confirming that the models are suitable for simulating exposures and PTA in the patient populations of interest.

Individual predictions of exposure and joint target attainment

- Individual predicted ceftazidime and avibactam systemic exposures ($AUC_{ss,0-24}$ and $C_{max,ss}$) were broadly similar across indications (Table 1):
  - Patients in the non-VAP subgroup had the highest ceftazidime and avibactam exposures ($C_{max,ss}$ and $AUC_{ss,0-24}$), whereas patients with cIAI had the lowest $AUC_{ss,0-24}$ values for both drugs, and patients with VAP had the lowest $C_{max,ss}$ values for both drugs.
  - Exposures for both ceftazidime and avibactam were approximately 20% lower in the VAP subgroup than in the non-VAP subgroup, reflecting the increased V_c and generally higher CrCL in the VAP population.
- Despite these apparent exposure differences, the estimated joint target attainment in Phase III patients was 97.8–99.0% in all NP subpopulations.
- In patients with augmented renal clearance (CrCL >150 mL/min), joint target attainment was >95%, despite decreases in $AUC_{ss,0-24}$ by up to 35% relative to those with normal renal function (CrCL >80–150 mL/min) (Table 1). High joint target attainment (>98%) was maintained across all other renal function groups, including patients with mild or moderate renal impairment (CrCL >50–80 or >30–50 mL/min).
- Age- or weight-related changes in exposure were adequately captured by changes in CrCL and high joint target attainment (>97%) was achieved in all age and BMI subgroups (Table 1).
- With the exception of APACHE II score, ceftazidime and avibactam exposures were similar across different markers of disease severity (bacteraemia, SIRS, WBC count and fever) (Table 1).
  - Patients with baseline APACHE II score >10 had ceftazidime $C_{max,ss}$ and $AUC_{ss,0-24}$ that were 8% and 25% higher, respectively, than in patients with a score ≤10, whereas avibactam $C_{max,ss}$ and $AUC_{ss,0-24}$ were 13% and 30% higher in patients with APACHE II score >10 compared with the ≤10 group.
- Increased severity of illness did not adversely affect joint target attainment, which was >98% across all markers of disease severity (Table 1).

PTA analyses

- PTA for the joint PK/PD target was >90% across all indications, with PTA >96% for patients with NP, including non-VAP, VAP and NPv subgroups (Table 2). Predicted exposures from the simulations were similar to the individual predicted exposures and showed the same trends across indications.
- High PTA (>96%) and appropriate levels of exposure were achieved across renal function categories in patients with NP receiving the recommended ceftazidime-avibactam dosage adjustments for renal impairment (Table 3).

Table 1. Geometric mean (CV%) individual predicted steady-state exposures and joint PK/PD target attainment for ceftazidime and avibactam in Phase III patients summarised by subgroups of clinical interest

Patient subgroup	N	Ceftazidime $C_{max,ss}$ (mg/L)	Ceftazidime $AUC_{ss,0-24}$ (mg.h/L)	Avibactam $C_{max,ss}$ (mg/L)	Avibactam $AUC_{ss,0-24}$ (mg.h/L)	Joint target attainment, % (95% CI)[a]
Indication						
cIAI	703	66.9 (105.0)	749 (114.0)	12.8 (155.3)	132 (152.0)	98.6 (97.7, 99.5)
cUTI	648	77.9 (114.2)	979 (119.7)	12.1 (161.9)	138 (164.1)	98.5 (97.5, 99.4)
NP	413	72.9 (125.2)	950 (131.0)	14.2 (166.1)	169 (168.5)	99.0 (98.1, 100)
Non-VAP	275	79.0 (120.0)	1016 (122.0)	15.5 (166.9)	183 (168.7)	99.6 (98.9, 100)
VAP	138	61.9 (127.0)	830 (142.7)	12.0 (157.6)	146 (163.0)	97.8 (95.4, 100)
CrCL (mL/min)[b]						
>30–50	128	58.8 (120.5)	938 (122.9)	10.2 (147.6)	148 (153.3)	98.4 (96.3, 100)
>50–80	418	90.0 (108.0)	1213 (110.4)	15.3 (142.9)	186 (144.5)	99.0 (98.1, 100)
>80–150	955	72.9 (105.9)	828 (112.4)	13.2 (165.5)	138 (163.4)	99.0 (98.3, 99.6)
>150–180	123	58.5 (93.0)	652 (112.8)	9.9 (124.5)	103 (137.5)	98.4 (96.1, 100)
>180–610	116	51.2 (109.6)	542 (108.1)	9.9 (171.6)	96 (155.9)	95.7 (92.0, 99.4)
Age (y)						
18– 65	1192	70.0 (113.5)	800 (122.7)	12.5 (167.1)	131 (166.8)	98.4 (97.7, 99.1)
>65–75	284	77.1 (109.4)	997 (107.6)	13.2 (119.0)	156 (118.4)	99.6 (99.0, 100)
>75–89	288	76.8 (120.5)	1102 (120.6)	14.0 (169.6)	180 (164.7)	98.6 (97.3, 100)
BMI (kg/m^2)[c]						
<29.9	1441	73.0 (115.5)	878 (124.2)	13.0 (160.2)	144 (161.4)	98.7 (98.1, 99.3)
≥29.9—<34.9	208	67.9 (111.8)	841 (125.2)	12.0 (178.4)	136 (179.1)	97.6 (95.5, 99.7)
≥34.9—<39.9	74	73.7 (109.6)	894 (115.2)	13.2 (139.7)	141 (140.0)	100 (NA)
≥39.9	32	64.2 (93.6)	806 (119.4)	9.68 (116.9)	115 (128.5)	100 (NA)
Baseline bacteraemia						
No	1465	71.9 (116.1)	881 (125.5)	12.6 (157.3)	141 (161.2)	98.6 (98.0, 99.2)
Yes	88	73.6 (102.8)	919 (120.1)	14.2 (164.1)	161 (161.3)	100 (NA)
Baseline APACHE II score[c]						
≤10	677	67.0 (105.0)	748 (113.8)	12.7 (154.3)	131 (150.6)	98.5 (97.6, 99.4)
>10	438	72.3 (124.3)	938 (130.9)	14.3 (167.0)	170 (168.7)	99.1 (98.2, 100)
Baseline SIRS[c]						
No	770	72.3 (108.9)	895 (120.5)	12.8 (159.2)	143 (162.0)	99.1 (98.4, 99.8)
Yes	773	71.5 (121.3)	869 (129.7)	12.6 (157.1)	142 (161.3)	98.3 (97.4, 99.2)
Baseline WBC count (cells/μL)[c]						
≤12 000	876	74.6 (110.9)	923 (118.9)	12.8 (159.1)	145 (161.7)	98.9 (98.2, 99.6)
>12 000	486	67.6 (119.4)	801 (128.4)	12.5 (160.4)	136 (161.5)	98.6 (97.5, 99.6)
Baseline fever[c]						
No	1166	71.9 (113.4)	888 (123.9)	12.9 (154.5)	146 (159.2)	99.1 (98.5, 99.6)
Yes	343	72.1 (121.8)	859 (130.3)	12.2 (165.7)	134 (167.4)	98.3 (96.9, 99.6)

[a]The joint PK/PD target was defined as 50% *f*T>8 mg/L for ceftazidime and 50% *f*T>1 mg/L for avibactam. [b]Twenty-four patients had CrCL ≤30 mL/min. [c]Data were missing for patients in the following subgroup categories: BMI (nine patients missing), baseline bacteraemia (211 patients missing), baseline APACHE II score (649 patients missing), baseline SIRS (221 patients missing), baseline WBC count (402 patients missing), baseline fever (255 patients missing). Disease severity markers were not measured in the RECAPTURE 1 and 2 studies. CV, coefficient of variation; NA: not applicable.

Table 2. Geometric mean (CV%) steady-state exposures and joint PTA for ceftazidime and avibactam in simulated patients summarised by indication and by NP subgroup for patients with normal renal function

	Ceftazidime $C_{max,ss}$ (mg/L)	Ceftazidime $AUC_{ss,0-24}$ (mg.h/L)	Avibactam $C_{max,ss}$ (mg/L)	Avibactam $AUC_{ss,0-24}$ (mg.h/L)	Joint PTA, %[a]
cIAI	61.1 (43.6)	683 (45.2)	11.5 (83.1)	121 (72.0)	94.9
cUTI	73.0 (47.3)	880 (48.9)	11.2 (87.0)	126 (82.0)	95.2
NP	65.4 (52.6)	805 (55.1)	12.8 (93.6)	147 (88.9)	98.3
NPv	56.8 (51.4)	723 (56.3)	11.2 (81.5)	131 (74.8)	97.2
VAP	55.1 (58.7)	719 (63.7)	10.7 (85.3)	129 (78.9)	96.1
Non-VAP	75.7 (43.0)	894 (47.6)	14.7 (92.4)	164 (93.4)	100

[a]The joint PK/PD target was defined as 50% *f*T>8 mg/L for ceftazidime and 50% *f*T>1 mg/L for avibactam. Simulations were conducted for 5000 patients with normal renal function (CrCL >80 mL/min) in each indication, receiving ceftazidime-avibactam 2000-500 mg, q8h as a 2-h infusion.

Table 3. Geometric mean (CV%) steady-state exposures and joint PTA for ceftazidime and avibactam in simulated patients summarised by renal impairment category and NP subgroup

Renal function category (CrCL); approved ceftazidime-avibactam dosage regimen[a]	NP subgroup	Ceftazidime $C_{max,ss}$ (mg/L)	Ceftazidime $AUC_{ss,0-24}$ (mg.h/L)	Avibactam $C_{max,ss}$ (mg/L)	Avibactam $AUC_{ss,0-24}$ (mg.h/L)	Joint PTA, %[b]
Mild impairment (51–80 mL/min) 2000-500 mg, q8h	All NP	86.0 (53)	1260 (55)	16.0 (95)	211 (87)	98.9
	NPv	76.0 (52)	1160 (56)	14.2 (82)	193 (73)	98.4
	VAP	74.8 (60)	1160 (62)	13.9 (88)	193 (78)	97.6
	Non-VAP	97.1 (44)	1370 (48)	17.7 (93)	226 (92)	100
Moderate impairment (31–50 mL/min) 1000-250 mg, q8h	All NP	59.7 (54)	1020 (55)	11.1 (97)	175 (88)	98.8
	NPv	53.4 (54)	940 (56)	10.0 (84)	161 (74)	98.3
	VAP	52.8 (62)	941 (62)	9.8 (90)	160 (78)	97.7
	Non-VAP	66.7 (45)	1110 (48)	12.3 (96)	189 (92)	100
Severe impairment category 1 (16–30 mL/min) 750-187.5 mg, q12h	All NP	52.3 (56)	903 (56)	10.0 (101)	159 (88)	98.8
	NPv	46.8 (56)	829 (57)	9.0 (88)	146 (75)	97.9
	VAP	46.4 (65)	830 (64)	8.8 (95)	145 (79)	97.3
	Non-VAP	58.4 (46)	982 (50)	11.0 (100)	171 (93)	100
Severe impairment category 2 (6–15 mL/min) 750-187.5 mg, q24h	All NP	59.1 (59)	1010 (60)	11.7 (109)	186 (92)	99.2
	NPv	52.6 (61)	924 (62)	10.4 (94)	169 (79)	98.7
	VAP	52.3 (70)	929 (68)	10.3 (102)	170 (84)	98.0
	Non-VAP	65.5 (48)	1090 (55)	12.8 (107)	198 (98)	100
End-stage renal disease (<6 mL/min) 750-87.5 mg, q48h	All NP	96.1 (70)	1860 (74)	10.7 (113)	157 (85)	99.5
	NPv	87.2 (72)	1720 (75)	9.5 (95)	143 (71)	99.1
	VAP	86.2 (81)	1700 (81)	9.3 (103)	143 (76)	98.8
	Non-VAP	106.0 (60)	2040 (69)	11.8 (108)	168 (90)	100

[a]All ceftazidime-avibactam dosage regimens given as 2-h infusions. [b]The joint PK/PD target was defined as 50% *f*T>8 mg/L for ceftazidime and 50% *f*T>1 mg/L for avibactam. Simulations were conducted for 5000 patients in each NP subgroup and renal function category. q12h, every 12 h; q24h, every 24 h; q48h, every 48 h.

Conclusions

- Plasma exposures of ceftazidime and avibactam in patients with NP were broadly comparable to those in patients with cIAI and cUTI.
- The recommended ceftazidime-avibactam dosage regimens, with adjustments for renal impairment (CrCL ≤50 mL/min),[1,2] provide high PTA (>96%) in patients with NP, including VAP and non-VAP subgroups.
- High actual target attainment rates were maintained in Phase III patients treated with ceftazidime-avibactam regardless of the presence of SIRS, bacteraemia, high APACHE II score, high WBC count, fever or augmented renal clearance.
- Together with the clinical efficacy and safety findings from REPROVE,[4] these data confirm that the same ceftazidime-avibactam dosage regimen that has demonstrated efficacy in patients with cIAI and cUTI (2000-500 mg q8h, adjusted for renal function) is also appropriate for patients with NP, including VAP.

References

1. AVYCAZ prescribing information. Available from: https://www.allergan.com/assets/pdf/avycaz_pi.
2. Summary of Product Characteristics: Zavicefta. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004027/WC500210234.pdf.
3. Li J et al. ECCMID 2015. Abstract P1289.
4. Torres A et al. ECCMID 2017. Abstract 2556.
5. Roberts JA et al. *Lancet Infect Dis.* 2014;14:498–509.
6. Das S et al. ASM Microbe 2016. Abstract 500.
7. Berkhout J et al. *Antimicrob Agents Chemother.* 2015;60 :368–375.
8. Coleman K et al. *Antimicrob Agents Chemother.* 2014;58: 3366–3372.

Disclosures

This study was supported by AstraZeneca (AZ) and Allergan. The AZ product ceftazidime-avibactam was acquired by Pfizer in December 2016. The AZ share of the study data, and associated records and documentation, are now wholly owned by Pfizer. SD is an employee of and shareholder in AZ. TR and TC are employees of and shareholders in Allergan. JW is an employee of and shareholder in Wright Dose. MM is an employee of Wright Dose and is a former employee of and current shareholder in AZ. ML, JH, YX, AT and CC are employees of Certara Strategic Consulting. Both Wright Dose and Certara Strategic Consulting received funding from AZ for support and assistance with the population PK and target attainment analyses.

Medical writing support was provided by Risha Bulusu of Prime, Knutsford, Cheshire, UK, funded by AstraZeneca and Pfizer.
Presented at 27th European Congress of Clinical Microbiology and Infectious Diseases, 22–25 April 2017, Vienna, Austria.