Comparative Monte Carlo Analysis of Aztreonam-avibactam and Ceftazidime-avibactam against Carbapenem-resistant Gram-negative Pathogens

Aaron Smith, PharmD Candidate, Roger L. White, PharmD
South Carolina College of Pharmacy—Medical University of South Carolina

MUSC Medical University of South Carolina

SOUTH CAROLINA COLLEGE OF PHARMACY

ABSTRACT

Background: The new β-lactamase inhibitor, avibactam (AVI), has recently been combined with ceftazidime (CAZ) as CAZ-AVI. AVI is also in Phase 3 clinical trials combined with aztreonam (ATM) as ATM-AVI. Both drug combinations have similar in vitro activity against some organisms, but ATM-AVI is more potent against metallo-β-lactamase (MBL) producing organisms. However, against P. aeruginosa (PA), CAZ-AVI is more potent. Since these compounds have similar pharmacokinetic (PK)/pharmacodynamic (PD) profiles, and there is a need for drugs for the treatment of resistant microorganisms, a Monte Carlo Analysis (MCA) was used to assess their potential efficacy against carbapenem-resistant pathogens.

Methods: MCA (n=10,000) was performed for ATM-AVI and CAZ-AVI using PK parameters, CrCl vs. Cl regression, PD targets, and recent MICs from peer-reviewed literature against five carbapenem-resistant (CR) organisms: P. aeruginosa (CR-PA), E. cloacae (CR-EC), K. pneumoniae (CR-KP), Enterobacteriaceae (CR-ENT), and MBL producing Enterobacteriaceae (MBL-ENT). Only MIC studies that directly evaluated both combinations were utilized. Our institution's inpatient CrCl distribution (range: 10-120 ml/min) was used to assess drug clearance. The ATM-AVI regimen was 1.5g q6h with a 3h infusion and adjusted for renal function) and the CAZ-AVI regimen was 2g q8h with a 2h infusion and adjusted for renal function. PD targets (%fT>MIC) for ATM-AVI were 40% and 60% and for CAZ-AVI were 40% and 70%.

Results: Target attainment (TA%) for each regimen and organism was:

Drug	ATM-AVI		CAZ-AVI	
Regimen	1.5 g q6h (3 hr. infusion)		2 g q8h (2 hr. infusion)	
fT>MIC (% of interval)	40%	60%	40%	70%
CR-PA	48	43	93	87
CR-EC	100	100	100	100
CR-KP	100	100	100	100
CR-ENT	100	100	96	96
MBL-ENT	100	99	2	2

Conclusions: Both ATM-AVI and CAZ-AVI displayed very high TA% (>95%) for CR-EC, CR-KP, and CR-ENT at both PD targets. However, TA% for MBL-ENT was very low for CAZ-AVI and ≥99% for ATM-AVI. Against CR-PA, CAZ-AVI had much higher TA% than ATM-AVI (87 – 93% vs. 43 – 48%). These differences suggest different roles for each drug combination in clinical practice.

INTRODUCTION

Avibactam has been recently combined with the cephalosporin ceftazidime (CAZ) as CAZ-AVI. AVI is also currently being investigated in Phase 3 clinical trials with the monobactam aztreonam (ATM) as ATM-AVI. The aztreonam monobactam ring is resistant to hydrolysis by metallo-β-lactamase enzymes (MBLs) that often cause carbapenem-resistance in many highly resistant Gram-negative pathogens. However, when MBLs are present, ATM alone is often ineffective due to the co-expression of other serine β-lactamase enzymes capable of ATM hydrolysis. As a result, the combination of CAZ-AVI+ATM has recently been used to treat patients with infections caused by Gram-negative pathogens expressing MBLs while ATM-AVI is in clinical trials.[1] This is due to the observed synergy of CAZ-AVI+ATM versus using CAZ-AVI or ATM alone. Monte Carlo Analysis (MCA) was used to assess each individual antimicrobial combination's pharmacodynamic profile for potential efficacy.

METHODS

Microbiology

Recent MICs from peer-reviewed literature for five carbapenem-resistant (CR) organisms were utilized and included: P. aeruginosa[2] (CR-PA, n=100), E. cloacae[3] (CR-EC, n=104), K. pneumoniae[4] (CR-KP, n=42), a more broad class of Enterobacteriaceae[5] (CR-ENT, n=110), and a more specific resistant subpopulation of MBL-producing Enterobacteriaceae[6] (MBL-ENT, n=43). Only MIC studies that directly evaluated both combinations were utilized. Due to limited direct comparison data for CR-PA, MIC-50 and MIC-90 data were utilized and curve fitting was performed to generate a full MIC distribution. This datum is displayed in Figures 1 through 5.

Pharmacokinetic (PK) Parameters

The following PK parameters were collected from peer reviewed literature for both ceftazidime and aztreonam: volume of distribution (V), serum protein binding percentage (PB%), and creatinine clearance (CrCl) vs. total drug clearance (Cl) regression relationship. Because avibactam has been shown to have no impact on the PK parameters of both aztreonam and ceftazidime, articles relating to only the β-lactam portion of the drug combinations could be utilized. One V, representative of a "patient volume" was utilized (Table 1). The CrCl-Cl linear regression line for aztreonam was constructed using study data from 89 subjects (Figure 6). Similarly, the ceftazidime CrCl-Cl regression line was constructed using data from 86 study subjects (Figure 7).

Dosing Regimens

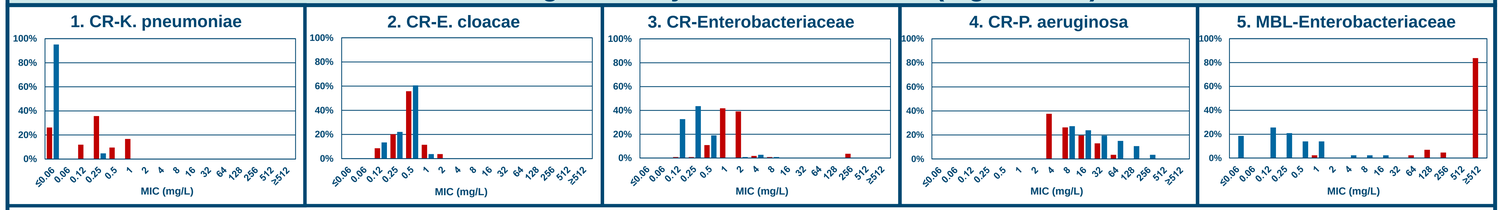
The dosing regimen utilized for CAZ-AVI was based on the recommended product label dosing. For CAZ-AVI, dose regimens were adjusted for CrCl per the product label. The ATM-AVI dosing was based on phase 3 trials. For ATM-AVI, dose regimens were adjusted for CrCl per the clinical trial protocol (Table 2).

Pharmacodynamic (PD) Targets

Pharmacodynamic targets were derived from peer reviewed literature. A low PD target and high PD target for %fT>MIC of the dose interval were determined for both drug combinations. The low PD target for both aztreonam-avibactam (ATM-AVI) and ceftazidime-avibactam (CAZ-AVI) used in the MCA was %fT>MIC ≥ 40. The high PD target for ATM-AVI was %fT>MIC ≥ 60 and for CAZ-AVI it was %fT>MIC ≥ 70.

METHODS (Continued)

Microbiologic Activity: MIC Distributions (Figures 1-5)



Aztreonam-avibactam Ceftazidime-avibactam

Monte Carlo Analysis (MCA)

MCA was performed utilizing derived PK parameter values, MIC distributions, PD targets, and a CrCl distribution from our own institution (range 10-120 ml/min, mean~65 ml/min). The MCA simulated 10,000 individual PK profiles to assess %fT>MIC for an 80 kg subject. TA(%)>90 was denoted as high TA and shaded green in tables. TA(%)<50 was denoted as low TA and shaded red in tables. Figures 10, 11, and 12 show TA for organisms that did not display 100% TA at all %fT>MIC values.

Table 1: PK Parameters

Drug	Patient Volume (L/kg)	Protein Binding (%)
Aztreonam	0.30	55
Ceftazidime	0.32	20

Figure 6: ATM CrCl-Cl Regression

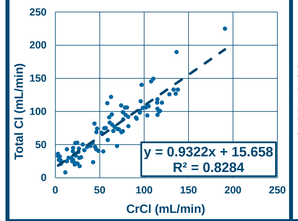


Figure 7: CAZ CrCl-Cl Regression

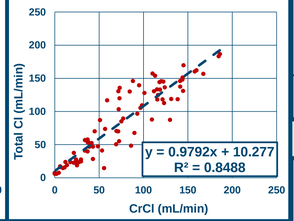


Table 2: Dosing Regimens

	CrCl Low (mL/min)	CrCl High (mL/min)	Dose (g)	Dose Interval (hours)	Infusion Time (hours)
ATM-AVI Clinical Trial Dose Regimen	>	50	1.5	6	3
	31	50	0.75	6	3
	16	30	0.675	8	3
	<	16	0.50	8	3
CAZ-AVI Product Label Dose Regimen	>	50	2	8	2
	31	50	1	8	2
	16	30	0.75	12	2
	6	15	0.75	24	2
	<	6	0.75	48	2

RESULTS

Relationship Between Target Attainment (%) and MIC

Figure 8: Low Pharmacodynamic Target

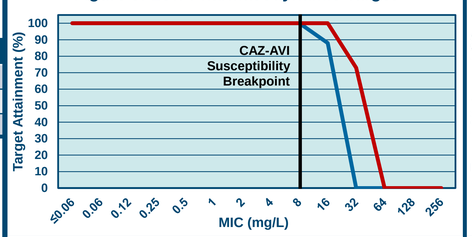
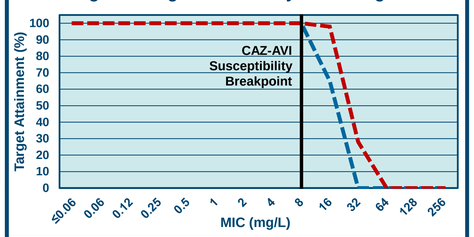


Figure 9: High Pharmacodynamic Target



Monte Carlo Analysis: Target Attainment (%) vs. %fT>MIC

Figure 10: CR-P. aeruginosa

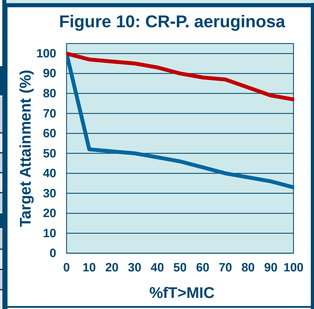


Figure 11: CR-Enterobacteriaceae

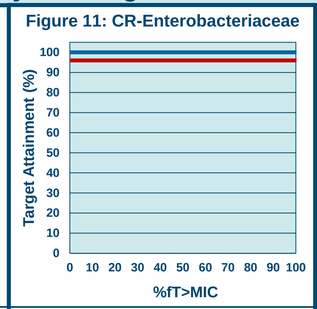
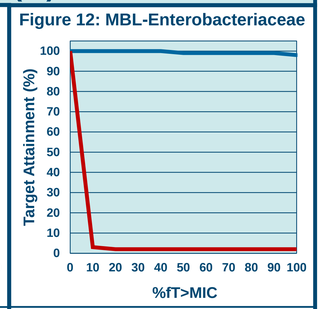


Figure 12: MBL-Enterobacteriaceae



RESULTS (Continued)

MCA: Target Attainment (%)

- Table 3 displays TA(%) for both ATM-AVI and CAZ-AVI for all 5 organisms assessed at each PD target.
- Table 3 is a tabular representation of Figures 10, 11 and 12.

Table 3: Target Attainment (%)

	ATM-AVI		CAZ-AVI	
PD Target	40%fT>MIC	60%fT>MIC	40%fT>MIC	70%fT>MIC
CR-PA	48	43	93	87
CR-KP	100	100	100	100
CR-EC	100	100	100	100
CR-ENT	100	100	96	96
MBL-ENT	100	99	2	2

Green Cells = TA >90% Red Cells = TA <50%

- The susceptibility breakpoint for CAZ-AVI is ≤8 mg/L; however, this analysis found that ≤16 mg/L may be acceptable for both PD targets.
- The susceptibility breakpoint for ATM-AVI has not yet been established; however, this analysis found that the ATM-AVI clinical trial dosing regimen had 100% TA for both PD targets for MIC values ≤8 mg/L.

DISCUSSION AND LIMITATIONS

- The optimal approach for MCA of β-lactam/β-lactamase inhibitor combinations has not been defined. Most MCAs are currently performed utilizing PK parameters for the active β-lactam component and MIC values utilizing the combination. Ideally, both components of the combination may need to be modeled independently.
- Due to the similar daily dose of each drug combination's dosing regimen and similar PK/PD profiles of ATM-AVI and CAZ-AVI, protein binding appears to be the differentiating factor for TA when MIC values are ≥8.

CONCLUSION

- ATM-AVI and CAZ-AVI had >95% TA at both PD targets for CR-KP, CR-EC, and CR-ENT, suggesting likely clinical efficacy.
- Against CR-PA, CAZ-AVI had much higher TA than ATM-AVI. CAZ-AVI achieved ≥87% TA at either target, whereas ATM-AVI achieved ≤48% TA.
- Against MBL-ENT, ATM-AVI had very high TA (≥99%); however, TA was very low (≤2%) for CAZ-AVI at both PD targets.
- These differences suggest different clinical roles for ATM-AVI and CAZ-AVI, with ATM-AVI being preferred in MBL+ Enterobacteriaceae infections and CAZ-AVI being preferred for CR-PA infections not expressing MBLs.

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The authors have nothing to disclose