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Comparative pharmacokinetics/pharmacodynamics (PK/PD) of telavancin and vancomycin in the murine thigh and lung infection models against Staphylococcus aureus (SA)

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Background: Telavancin exhibits potent in vitro activity against SA including beta-lactam resistant isolates. Study aim was to examine and compare the PK/PD properties of telavancin and vancomycin, including plasma and ELF drug exposure-response relationships, against SA in the neutropenic murine thigh and lung infection models.

Material/methods: Four SA (1 MSSA, 2 MRSA, 1 VISA) strains were used. MICs were determined by CLSI methods. Plasma and ELF PK of both drugs were determined in mice after subcutaneous administration of 1.25, 5, 20, and 80 mg/kg. Efficacy studies were performed with each isolate for both drugs (dose range: telavancin 0.3-80 mg/kg/6h, vancomycin 0.3-1280 mg/kg/6h). Treatment outcome was determined by organism burden (CFU) in the thigh or lungs after 24h. Correlation between efficacy and AUC/MIC was determined by nonlinear least-squares multivariate regression using the Hill equation. PD target exposures (AUC/MIC) were determined for net stasis, 1-, and 2-log kill.

Results: Telavancin MICs were 0.06-0.25 mg/L and vancomycin 1-4 mg/L. PK was linear over the dose range for both drugs. After accounting for differences in protein binding, penetration into ELF was similar with >80% of free plasma telavancin levels and >90% of free plasma vancomycin levels. Stasis and 1-log kill endpoints were achieved in the thigh model for both drugs. The exposure-response relationship in the thigh model was well described by AUC/MIC (telavancin R^2 0.85,

vancomycin R^2 0.93). 24h plasma free drug AUC/MIC targets are shown (**Table**). The PK/PD targets were lower in the lung model with the achievement of 2-log kill for both drugs. The exposure-response relationship in the lung model was also well described by AUC/MIC using plasma and ELF PK (telavancin R^2 0.91, vancomycin R^2 0.77). For each drug, the PD targets (AUC/MIC) in the lung model were remarkably congruent comparing free plasma concentrations and total ELF concentrations (**Table**).

Drug	Model	PK measure	Stasis AUC/MIC	1-log kill AUC/MIC	2-log kill AUC/MIC
TLV	Thigh	Plasma free drug	83	215	
	Lung	Plasma free drug	40	76	156
		ELF total drug	32	61	132
VAN	Thigh	Plasma free drug	78	282	
	Lung	Plasma free drug	45	113	482
		ELF total drug	51	92	375

Conclusions: Telavancin demonstrated potent bactericidal efficacy in both murine infection models. AUC/MIC was a robust predictor of efficacy. AUC/MIC targets in the thigh were congruent between the two drugs with net stasis observed at ~80 and 1-log kill at 200-300. Lung model targets were 2-3 fold lower than the thigh model for both drugs; however, telavancin targets were 33-66% lower than vancomycin for killing endpoints. Interestingly, ELF AUC/MIC targets were nearly identical to free plasma targets after accounting for 80-90% penetration. These findings confirm telavancin's continued role in the treatment of SA pneumonia including MRSA and VISA isolates.