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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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Introduction & Aim

- Telavancin exhibits potent SA activity including MRSA
- SA infections cause significant morbidity and mortality
- SA therapuetics are limited, especially for MRSA pneumonia
- Comparative PK/PD analyses are lacking for optimizing SA therapy

Aim: Define and compare telavancin (TLV) and vancomycin (VAN) AUC/MIC target exposures associated with efficacy endpoints of net stasis and 1 log kill in murine thigh and lung SA infection models

Materials & Methods

Strains and susceptibility testing:

- 4 SA (1 MSSA, 2 MRSA, 1 MRSA & VISA), CLSI methods

Pharmacokinetic studies and analysis:

- Plasma & ELF PK by LC-MS/MS (SC doses 1.25-80 mg/kg)
- Non-compartmental model was used for PK analysis
- Protein binding of 96% (TLV) and 25% (VAN)

Murine thigh and lung model:

- Six-week-old, female ICR/Swiss mice (23-27 g)
- Neutropenia induced by cyclophosphamide injection
- Log-phase cultures of each strain were utilized to produce infection in each model
  - Thigh –inoculum $10^{7.0}$ CFU/ml. Four replicates.
  - Lung – inoculum $10^{7.7}$ CFU/ml. Three replicates.
  - Zero h and no treatment controls included
- Treatment duration was 24 hours
- TLV, 5 SC dose regimens (range 1.25–320 mg/kg/24h)
- VAN, 7 SC dose regimens (range 1.25–5120 mg/kg/24h)
- Treatment effect was determined by CFU counts

PK/PD Analyses:

- 24-h AUC/MIC was the PK/PD parameter utilized
- Correlation between efficacy and AUC/MIC was analyzed by nonlinear least-squares multivariate regression (Hill equation)
- Static and 1 log kill AUC/MIC targets were determined for each isolate in each model

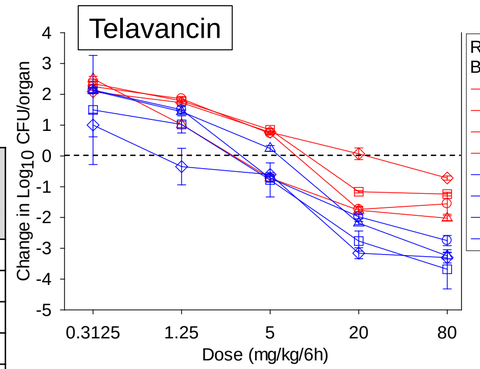
Results

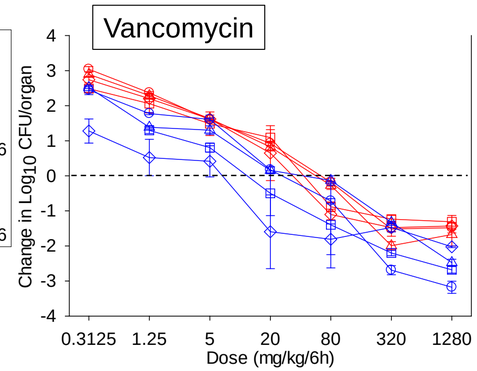
Organism	TLV (mg/L)	VAN (mg/L)	Phenotype
29213	0.06	1	MSSA
33591	0.12	1	MRSA
LSI653	0.12	2	MRSA
LSI1856	0.25	4	MRSA, VISA

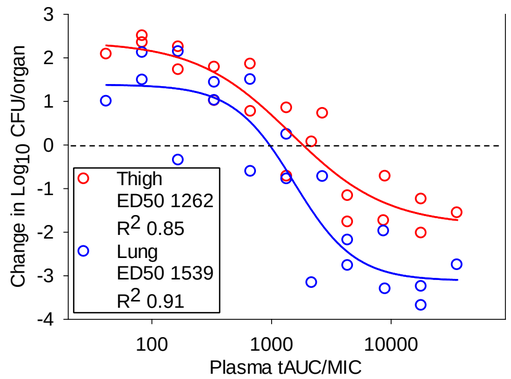
Drug	Dose (mg/kg)	Plasma 24-h tAUC (mg*h/L)	Plasma 24-h fAUC (mg*h/L)	ELF 24-h tAUC (mg*h/L)	Penetration into ELF (%)
TLV	1.25	10.5	0.42	0.42	100
	5	42.3	1.69	1.28	76
	20	139	5.55	5.11	92
	80	595	23.8	19.2	81
VAN	1.25	1.4	1.07	1.1	103
	5	6.2	4.69	4.53	97
	20	19	14.25	15.7	110
	80	68.1	51.1	40.1	78

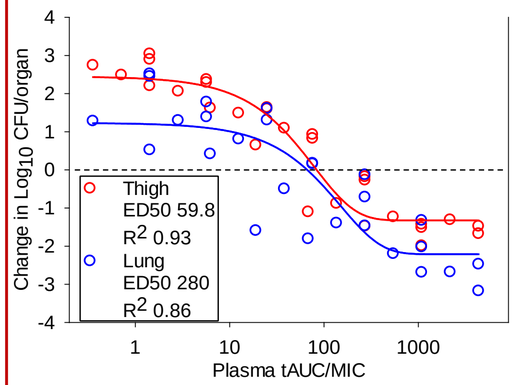
Mean PK/PD Targets			24 h Stasis		24 h 1-log kill		24 h 2-log kill	
	Model	PK	tAUC/ MIC	fAUC /MIC	tAUC/ MIC	fAUC/ MIC	tAUC/ MIC	fAUC/ MIC
TLV	Thigh	Plasma	2075	83	5369	215	---	---
	Lung	Plasma	1010	40	1910	76	3891	156
	Lung	ELF	32	---	61	---	132	---
VAN	Thigh	Plasma	104	78	376	282	---	---
	Lung	Plasma	60	45	151	113	642	482
	Lung	ELF	51	---	92	---	375	---

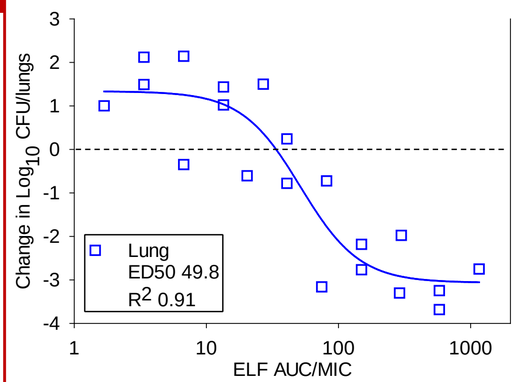
--- cells, not applicable or not achieved

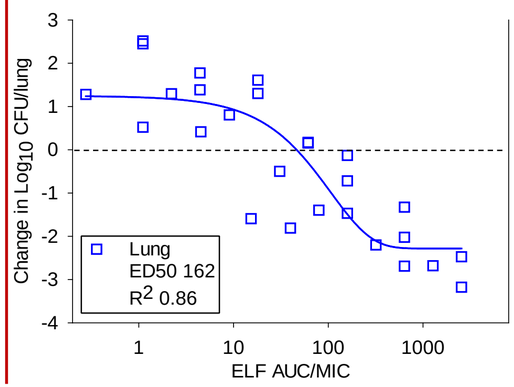












Conclusions

- TLV demonstrated *in vivo* potency against a diverse group of SA strains with maximum kill of >3 log in the pneumonia model
- AUC/MIC was a robust predictor of efficacy
- The relevance of protein binding for both drugs is demonstrated in ELF penetration and comparing total vs free drug AUC/MIC targets
- Free drug plasma AUC/MIC targets in the lung model were 2- to 3-fold lower than thigh model
- TLV had 24-33% lower free AUC/MIC targets for 1-log kill and 65-70% lower free AUC/MIC targets for 2-log kill than VAN in the lung model
- Human TLV PK studies indicate fAUC/MIC exposures would meet or exceed the 1-log kill targets identified in this study for ≥99% SA strains
- These findings confirm TLV's continued role in the treatment of SA pneumonia including MRSA and VISA strains

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