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Comparative In vivo Pharmacokinetics/Pharmacodynamics of Telavancin and Vancomycin in the Neutropenic Murine Thigh Infection Model Against *Staphylococcus aureus*

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ABSTRACT (rev.)

Background: Telavancin (TLV) is a lipoglycopeptide with potent activity against *S. aureus* (SA), including beta-lactam resistant isolates. The aim of this study was to examine the pharmacodynamic (PD) targets of TLV against SA in the neutropenic murine thigh model and compare those targets to vancomycin (VAN).

Methods: Four clinical isolates of SA (1 MSSA, 2 MRSA, 1 MRSA/VISA) were used. MICs were determined using current CLSI methods. The neutropenic murine thigh infection model was used for all treatment studies. Treatment outcome was determined by organism burden in the thigh (CFU) at the end of each experiment (24 h). Dosing was by subcutaneous (SC) route. Plasma PK of TLV and VAN were determined after administration of 1.25, 5, 20, and 80 mg/kg. Drug exposure-response studies were performed with each isolate for both drugs. Five total doses of TLV were studied (range 1.25 - 320 mg/kg/24h) and seven total doses of VAN were studied (range 1.25 - 5120 mg/kg/24h). The doses were fractionated into 6-hourly dosing regimens. The PD index 24 h AUC/MIC was used for all analyses. The correlation between treatment efficacy and AUC/MIC was determined by nonlinear least-squares multivariate regression using the Hill equation. The AUC/MIC exposure associated with net stasis and 1-log kill (when achieved) were determined.

Results: MICs to TLV were 0.06-0.25 mg/L and to VAN 1-4 mg/L. SC administration resulted in linear PK over the dose range for both drugs. Stasis endpoints were achieved against all strains for both drugs. A 1-log kill was achieved in 3 of 4 isolates for TLV and against all isolates for VAN. The drug exposure-response model was well described by the PD index AUC/MIC (TLV R^2=0.85, VAN R^2=0.93). The mean (range) 24 h total dose and PD target free drug AUC/MIC for net stasis and 1-log kill for all isolates are listed in the table.

Drug	Endpoint	24 h dose (mg/kg)	24 h fAUC/MIC
TLV	Stasis	39 (10-84)	166 (57-261)
TLV	1-log kill	74 (26-127)	430 (130-602)
VAN	Stasis	159 (115-186)	78 (20-122)
VAN	1-log kill	582 (365-792)	282 (58-505)

Conclusion: TLV exhibits dose-dependent in vivo activity against SA in the neutropenic murine thigh model. AUC/MIC was a robust predictor of treatment efficacy. Static and killing endpoints were similar for TLV compared to VAN and were achieved at relatively modest AUC/MIC targets. The current dosing regimen of TLV would be expected to meet or exceed 1-log kill AUC/MIC exposures identified in this study.

BACKGROUND

- Telavancin is a lipoglycopeptide with potent activity against *S. aureus* including MRSA
- Telavancin has a dual mechanism of action targeting peptidoglycan synthesis and cell membrane function
- MRSA pneumonia causes significant morbidity and mortality; unfortunately treatment options for MRSA pneumonia are quite limited
- Pharmacodynamic analyses to optimize antimicrobial therapy for *S. aureus* pneumonia are limited
- The goal of the current study was to determine the PD target 24 h AUC/MIC associated with stasis and 1 log kill efficacy in the murine neutropenic pneumonia model against *S. aureus* including drug-resistant isolates (MRSA and VISA)

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METHODS

Strains and susceptibility testing: 4 SA (1 MSSA, 2 MRSA, 1 MRSA & VISA) were used for the *in vivo* studies. All isolates were tested in accordance with CLSI methodology. MICs were performed on three separate occasions in duplicate.

Pharmacokinetic studies and analysis: Single dose PK of both telavancin and vancomycin was performed after SC administration of 1.25, 5, 20, and 80 mg/kg. Plasma from groups of three mice per time point were collected. Drug concentration measurements were performed by LC-MS/MS by the sponsor. A non-compartmental model was used for PK analysis.

Murine thigh model: Six week-old, specific pathogen free, female ICR/Swiss mice weighing 23-27 g were used. Mice were rendered neutropenic by cyclophosphamide injection. Broth cultures of freshly plated bacteria were grown overnight to logarithmic phase. The inoculum ranged from $10^{7.0}$ – $10^{7.1}$ CFU/mL. Thigh infections were produced by injection of 0.1 ml of the inoculum into the thighs of isoflurane-anesthetized mice 2 h before treatment. Organism burden was determined by CFU quantitation from thigh homogenates after 24 h. Zero hour and untreated controls were included in all experiments.

Treatment Efficacy - Pharmacodynamic Target Determination: *In vivo* treatment studies were performed with all four isolates. Telavancin was administered by SC route in 4-fold increasing doses from 0.3125 mg/kg to 80 mg/kg every 6 h. Vancomycin was administered by SC route in 4-fold increasing doses from 0.3125 mg/kg to 1280 mg/kg every 6 h. Four thigh infections were used for each dosing regimen. At the end of the treatment period, organism burden was determined by CFU counts. The data was fit to a sigmoid dose-response (Hill equation) model. The dose required to produce net static effect (Static Dose, SD) and 1-log kill was calculated for each organism. The associated 24 h total drug AUC/MIC targets were determined for each isolate. Free drug AUC/MIC targets were calculated using protein binding estimates of 92% for telavancin (data on file) and 75% for vancomycin.

RESULTS

In vitro Susceptibility Testing:

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

Pharmacokinetics: Results of plasma PK of Telavancin and Vancomycin for the doses studied and select PK parameters including $AUC_{0-\infty}$, Cmax, and elimination half-life (T1/2) are shown in **Figure 1** and **Figure 4**, respectively. $AUC_{0-\infty}$ was linear over the dose range for both drugs (R^2 = 1 for both drugs).

Pharmacodynamic Target Determination: *In vivo* dose-response curves for SA isolates are shown in **Figure 3** for telavancin and **Figure 4** for vancomycin**.** Each symbol represents the geometric mean ± standard deviation of organism burden in four thighs. The relationship between PD index AUC/MIC and treatment efficacy is shown in **Figure 5** for telavancin and **Figure 6** for vancomycin. Each data point represents the geometric mean of organism burden from four thighs. A best-fit line based on the Hill equation is included. The PD parameters E_{max}, ED_{50}, slope (N), and coefficient of determination (R^2) are shown in the figure legend.

RESULTS (cont.)

Figure 1. Telavancin PK

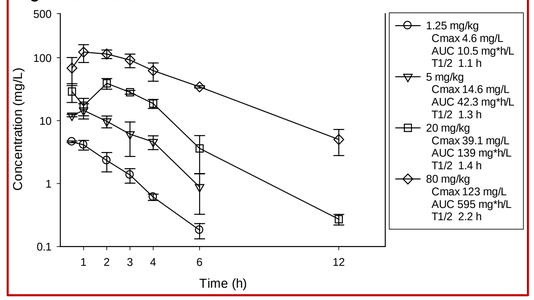


Figure 2. Telavancin Dose-Response

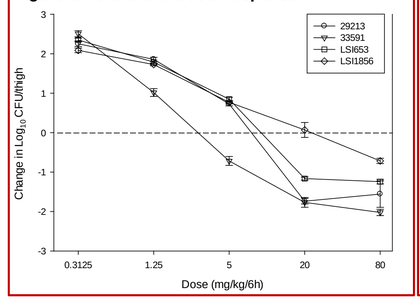


Figure 3. Telavancin AUC/MIC

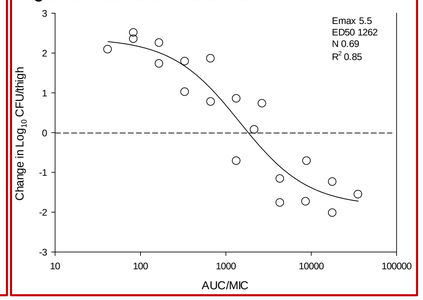


Figure 4. Vancomycin PK

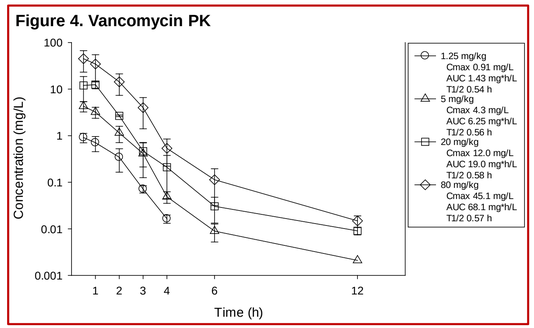


Figure 5. Vancomycin Dose-Response

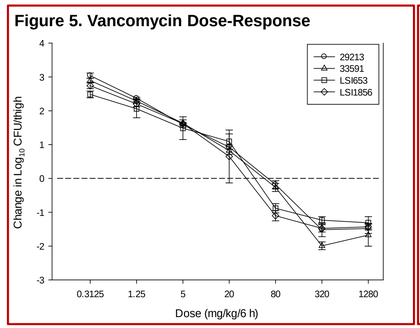
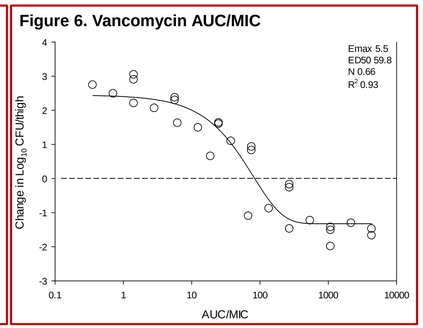


Figure 6. Vancomycin AUC/MIC



Pharmacodynamic Target AUC/MIC exposures associated with net stasis and 1 log kill for telavancin (left) and vancomycin (right)

Telavancin Organism	MIC (mg/L)	24 h Static Dose mg/kg)	Total 24 h AUC/MIC	Free 24 h AUC/MIC	24 h 1 log kill dose (mg/kg)	Total 24h AUC/MIC	Free 24h AUC/MIC
SA 29213	0.06	25.82	3260.46	260.84	68.41	7519.35	601.55
SA 33591	0.12	10.73	717.27	57.38	25.60	1619.17	129.53
SA LSI653	0.12	34.28	2053.24	164.26	126.79	6969.88	557.59
SA LSI1856	0.25	83.48	2267.52	181.40			
mean		**38.58**	**2074.62**	**165.97**	**73.60**	**5369.46**	**429.56**
median		**30.05**	**2160.38**	**172.83**	**68.41**	**6969.88**	**557.59**
sd		**31.48**	**1046.62**	**83.73**	**50.79**	**3259.45**	**260.76**

Vancomycin Organism	MIC (mg/L)	24 h Static Dose (mg/kg)	Total 24 h AUC/MIC	Free 24 h AUC/MIC	24 h 1 log kill dose (mg/kg)	Total 24h AUC/MIC	Free 24h AUC/MIC
SA 29213	1	186.28	162.71	122.03	605.89	515.00	386.25
SA 33591	1	179.91	157.50	118.13	791.56	672.82	504.62
SA LSI653	2	156.44	69.16	51.87	565.60	240.38	180.28
SA LSI1856	4	115.06	26.13	19.59	364.87	77.53	58.15
mean		**159.42**	**103.88**	**77.91**	**581.98**	**376.43**	**282.32**
median		**168.18**	**113.33**	**85.00**	**585.74**	**377.69**	**283.27**
sd		**32.24**	**67.30**	**50.47**	**175.02**	**267.64**	**200.73**

CONCLUSIONS

1] The pharmacokinetics were linear over the dose range studied for both drugs.

2] Telavancin exhibited potent dose-dependent activity against *S. aureus*, including MRSA/VISA isolates, in the neutropenic murine thigh model.

3] AUC/MIC was a robust predictor of efficacy for both drugs (R^2 0.85 and 0.93 for telavancin and vancomycin, respectively).

4] In the model, maximal efficacy for vancomycin was slightly over 1 log kill. This coincides with total drug AUC/MIC targets of almost 400 in the model and provides supportive evidence of often used clinical total drug AUC/MIC targets of >400. Given the congruency of PD targets between the model and clinical medicine, the telavancin 1 log kill targets identified in this study would be expected to be highly relevant to clinical application for dosing regimen design and breakpoint determination for *S. aureus*.

5] Current dosing regimens in patients would be expected to achieve free AUC/MIC targets in excess of the identified 1 log kill targets in this study for over 99% of SA isolates.

6] These findings confirm telavancin is a promising addition to the armamentarium for *S. aureus* treatment including isolates with MRSA and VISA resistance mechanisms.