A-009 Pharmacodynamics of single dose Oritavancin against *Staphylococcus aureus*

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Amended Abstract

Background:

Oritavancin (ORI) is a semi-synthetic lipoglycopeptide with potent *in vitro* bactericidal activity against *S. aureus*. Its PK-PD properties allow it to be given as single dose therapy in skin infection. For this reason, it is important to establish the exposure response relationship for ORI over prolonged time courses of drug exposures. Such experiments are difficult to perform *in vivo* but *in vitro* pharmacokinetic (PK) models offer a flexible platform in studying drug exposure over several days. We used such an *in vitro* PK model to study the PD of single dose exposures of ORI against *S. aureus* over 96h.

Methods:

7 strains of *S. aureus* (all MRSA) were used with oritavancin MIC of 0.12 (n=5), MIC 0.25 (n=1), MIC 0.5mg/L (n=1). A dilutional *in vitro* model using polypropylene bottles was used to simulate a range of AUC/MIC ratios. ORI was infused over 3h at time zero. Simulations were performed over 96h. Antibacterial effect (ABE) was measured by log change at 24h (d24h) (log CFU/mL), 48h (d48h), 72h (d72h) and 96h (d96h) compared to the initial inoculum. The initial inoculum was 10^6 CFU/mL. AUC/MIC was related to ABE, i.e. AUC24/MIC to d24, AUC48/MIC to d48, etc.

Results:

In all simulations with an ORI Cmax 20mg/L – modelling free drug associated with a 1200mg dose– there was rapid killing and no regrowth. The mean AUC/MIC for stasis or -1 log, -2 log or -3 log reductions in viable count at 24h, 48h, 72h and 96h are shown below.

ORI was cidal versus all *S. aureus* strains with the AUC/MIC for -3 log reduction in count compared to initial inoculum being 2-3 fold greater than that for static effect. The AUC/MIC increased for each antibacterial effect over time, being 8-10 times greater at 96h than at 24h. The two strains with higher ORI MICs had similar AUC/MIC to ABE response characteristics to those with lower MICs.

Conclusion:

Free drug ORI concentrations associated with a single 1200 mg dose produced rapid clearance of *S. aureus* strains from an *in vitro* model of infection. AUC/MIC for ABE varied over time and also with static or cidal endpoints.

	ABE			
	Static effect	-1 log drop	-2 log drop	-3 log drop
*f*AUC 24/MIC vs d24h	14.2	17.9	22.919.1	28.7
*f*AUC 48/MIC vs d48h	34.7	50.7	61.9	87.6
*f*AUC 72/MIC vs d72h	53.5	62.7	72.6	93.7
*f*AUC 96/MIC vs d96h	111.8	137.1	163.4	217.2

Introduction

Oritavancin is a semi synthetic lipoglycopeptide with broad activity against Gram-positive pathogens and a mode of action which involves inhibition of cell-wall synthesis via inhibition of transglycosylation and transpeptidation, and increasing membrane permeability.

Oritavancin is rapidly bactericidal against MRSA and MSSA strains in concentration-time kill curves at pharmacokinetic relevant concentrations – i.e. 0.5-16mg/L.

The MIC_{90} for oritavancin against staphylococci are ≤0.25mg/L, enterococci ≤0.25mg/L, β.haemolytic streptococci ≤0.25mg/L and *S. pneumoniae* ≤0.004mg/L. Against hVISA, VISA and VRSA, the MIC_{90} are in the range 0.5-2mg/L[1].

Population PK modelling shows that 1200 mg oritavancin administered over 3h produced a C_{max} of 129mg/L, an 0-24h AUC of 854mg/L, an alpha phase half life of 2.0h, beta phase half-life of 31h and a gamma phase half life of 393h.[2] Protein binding is approx 85% in man and other species.[3]

In neutropaenic mouse thigh infection (NMTI) models, Cmax was strongly correlated with antibacterial effect (ABE) for a single strain of *S. aureus.* Further NMTI model studies have indicated that a 1200mg single dose was more effective than 400mg oritavancin once daily for three days.[4]

Human PD analyses have been less informative; neither AUC_{24}/MIC, C_{max}/MIC nor *f*T>MIC could be convincingly related to outcome in daily-dosing studies conducted to date.

The objective of this study was to establish the C_{max}/MIC, AUC/MIC and AUC, ABE relationship at 24h, 48h, 72h and 96h for *S. aureus* using a dose ranging study design based on free drug serum concentrations associated with a 1200mg dose oritavancin.

Materials

- 100% Mueller-Hinton broth plus 0.01% polysorbate (P80) was used for all experiments.

- A dilutional *in vitro* pharmacokinetic model utilising polypropylene bottles was used to simulate a range of oritavancin *f*C_{max} concentrations 20, 10, 5, 1.0, 0.5, 0.25mg/L and 0mg/L infused over 3h. Oritavancin concentrations were confirmed using bioassay methodology and *Bacillus subtilis* as the indicator organism. The limit of detection was 1mg/L.

- Seven strains of MRSA (including one MRSA-hVISA) with oritavancin MICs in the range 0.12-0.5mg/L were utilised including *S.aureus* 46951 (NRS123) obtained through the Network of Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) program supported under NIAID/NIH Contract #HHSN272200700055C. The inoculum was 10^6CFU/ml and experiments were conducted over 96h. Change in population profile was determined by broth micro-dilution MICs on survivors at 96h.

- ABE measured by log change in viable count at 24h (d24), 48h (d48), 72h (d72) and 96h (d96) was correlated to *f*C_{max}/MIC, *f*AUC/MIC, *f*AUC and the average *f*AUC24h using a sigmoid Emax curve (Graph Pad Prism©).

Results

- Oritavancin, vancomycin, oxacillin and daptomycin MICs for the *S. aureus* strains tested are shown in Table 1.

- At the standard 1200mg dose (*f*Cmax 20mg/L) rapid bacterial killing was observed with all strains with viable counts below the limit of detection at 3-4h. No re-growth was seen. The two strains with higher oritavancin MICs (0.25 and 0.5mg/L) had a similar ABE response to the strains with MICs of 0.12mg/L.
- Figures 1-3 show the relationship between C_{max}/MIC, AUC/MIC and AUC with log reduction in viable count for all strains at 24h.

- There was a clear relationship between *f*C_{max}/MIC, *f*AUC/MIC and *f*AUC with antibacterial effect (ABE) for all strains (r>0.83), (Tables 2-7). The *f*C_{max}/MIC, *f*AUC/MIC and fAUC increased with time.
- The mean *f*C_{max}/MIC at 24h for a static, -1log, 2 log and -3 log reduction in viable count was 2.1 ± 1.4, 2.4 ± 1.5, 3.0 ±2.1 and 4.0 ± 3.7 respectively. The mean *f*C_{max}/MIC ratios at 96h increased to 8.2 ± 5.3, 8.9 ± 5.4, 9.4 ± 5.5 and 10.6 ± 5.9 respectively.
- The mean *f*AUC/MIC at 24h for a static, -1log, 2 log and -3 log reduction in viable count was 14.2 ± 9.7, 17.9 ± 11.7, 22.9 ± 14.3 and 28.7 ± 19.9 respectively. The *f*AUC/MIC ratios at 96h were 111.8 ± 113.8, 137.1 ± 143.4, 163.4 ± 188.0 and 217.2 ± 217.2.
- The mean *f*AUC at 24h for a static, -1log, 2 log and -3 log reduction in viable count was 2.7 ± 2.1, 3.2 ± 2.1, 4.0 ± 2.2 and 5.3 ± 3.0 respectively. The *f*AUC ratios at 96h increased to 14.9 ± 14.1, 17.6±18.6, 20.4 ± 23.0 and 24.8 ± 30.1
- The average daily *f*AUC/MIC was also related to change in viable count at 24h. The average daily *f*AUC/MIC for a 24h static, -1 log drop, -2 log drop were 4.38±3.3, 6.4±4.5 and 8.9±6.4 respectively.
- No emergence of resistance as indicated by an increased MIC was observed.
- We were unable to determine the dominant pharmacodynamic driver for oritavancin. However, PDI targets can be suggested for 24h antibacterial effects for *f*C_{max}/MIC, *f*AUC/MIC and *f*AUC. Suggested PDI targets are *f*C_{max}/MIC >3-5; *f*AUC/MIC>15-20; *f*AUC >6-10
- A 24h antibacterial endpoint is predictive of effect up to 96h for human dose simulations.

Conclusions

- In conclusion, this series of experiments clearly showed an oritavancin exposure response relationship for *f*C_{max}/MIC, *f*AUC/MIC and *f*AUC against *S. aureus.*

- They confirm the marked and sustained bactericidal action of oritavancin at simulations of human free drug concentrations associated with a dose of 1200mg over 4 days.

References
1. Mendes et al. Clin Infect Dis. 2012 Apr;54 Suppl 3:S203-13.
and to Francis' note on hVISA, VISA, and VRSA?

2. Belley et al. Antimicrob Agents Chemother. 2013 Jan;57(1):205-11

3. Arhin et al. Antimicrob Agent Chemother .2010 54, 3481-3483
4. Ambrose et al. Clin Infect Dis. 2012 Apr;54 Suppl 3:S220-8.

Table 1: Oritavancin, vancomycin, oxacillin and daptomycin MICs for the seven strains of *S.aureus*

Strain	**MIC (mg/L)**			
Reference	**Oritavancin**	**Vancomycin**	**Oxacillin**	**Daptomycin**
46951	0.12	1	32	1
45796	0.12	1	128	2
36895	0.12	1	128	0.5
43456	0.12	1	128	0.5
31236	0.12	1	8	0.5
45800	0.25	1	128	1
45798	0.5	2	>128	8

Table 2: *f*Cmax/MIC required for a static, one and two log reduction in viable count at 24h

strain		MIC (mg/L)	static	-1log drop	-2log drop	-3log drop
S.aureus NRS123	46951	0.12	4.5	4.5	4.5	4.5
S.aureus	45796	0.12	3.4	4.5	6.7	12.3
S.aureus	36895	0.12	1.1	1.1	1.1	1.1
S.aureus	43456	0.12	1.1	2.2	3.4	5.0
S.aureus	31236	0.12	0.6	0.6	0.6	0.6
S.aureus	45800	0.25	3.1	3.5	4.0	4.1
S.aureus	45798	0.5	0.8	1.2	1.5	2.4
S.aureus	45798	0.5	1.9	2.0	2.1	2.3
Mean			2.1±1.4	2.4±1.5	3.0±2.1	4.0±3.7

Table 3: *f*Cmax/MIC required for a static, one and two log reduction in viable count at 96h

strain		MIC	static	-1log drop	-2log drop	-3log drop
S.aureus NRS123	46951	0.12	13.4	14.5	15.7	17.9
S.aureus	45796	0.12	8.9	8.9	8.9	10.2
S.aureus	36895	0.12	7.8	9.0	9.0	10.1
S.aureus	43456	0.12	4.0	4.0	4.0	4.0
S.aureus	31236	0.12	3.5	4.7	5.9	7.6
S.aureus	45800	0.25	3.8	4.0	4.0	4.3
S.aureus	45798	0.5	5.8	7.1	8.3	10.5
S.aureus	45798	0.5	18.5	18.9	19.3	20.5
			8.2±5.3	8.9±5.3	9.4±5.5	10.6±5.9

Table 4: *f*AUC24/MIC required for a static, one and two log reduction in viable count at 24h

strain		MIC (mg/L)	static	-1log drop	-2log drop	-3log drop
S.aureus NRS123	46951	0.12	22.0	36.6	51.3	73.3
S.aureus	45796	0.12	27.0	29.2	29.2	29.3
S.aureus	36895	0.12	4.1	6.2	12.5	20.8
S.aureus	43456	0.12	4.9	10.4	17.4	29.2
S.aureus	31236	0.12	7.3	7.3	7.3	4.8
S.aureus	45800	0.25	24.5	26.3	28.1	28.1
S.aureus	45798	0.5	18.0	19.2	27.1	27.9
S.aureus	45798	0.5	5.5	7.6	10.0	16.5
Mean			14.2±9.7	17.9±11.7	22.9±14.3	28.7±19.9

Table 5: *f*AUC96/MIC required for a static, one and two log reduction in viable count at 96h

strain		MIC	static	-1log drop	-2log drop	-3log drop
S.aureus NRS123	46951	0.12	358.8	463.2	565.8	720.4
S.aureus	45796	0.12	94.3	148.8	230.4	385.9
S.aureus	36895	0.12	70.0	75.8	90.4	99.2
S.aureus	43456	0.12	37.9	49.6	72.9	107.9
S.aureus	31236	0.12	40.8	46.7	58.3	67.1
S.aureus	45800	0.25	33.1	40.7	42.3	45.3
S.aureus	45798	0.5	201.4	201.1	2.2.7	203.3
S.aureus	45798	0.5	58.4	70.9	83.6	108.6
Mean			111.8±113.8	137.1±143.4	163.4±188.0	217.2±230.4

Table 6: *f*AUC24 required for a static, one and two log reduction in viable count at 24h

strain		MIC (mg/L)	static	-1log drop	-2log drop	-3log drop
S.aureus NRS123	46951	0.12	3.0	3.2	3.4	3.4
S.aureus	45796	0.12	2.2	3.3	5.3	9.9
S.aureus	36895	0.12	0.8	1.0	1.7	2.6
S.aureus	43456	0.12	1.0	1.4	2.4	3.6
S.aureus	31236	0.12	0.4	0.8	0.8	1.2
S.aureus	45800	0.25	5.1	5.5	6.3	6.9
S.aureus	45798	0.5	2.6	3.9	5.2	7.8
S.aureus	45798	0.5	6.3	6.6	6.8	6.8
Mean			2.7±2.1	3.2±2.1	4.0±2.2	5.3±3.0

Table 7: *f*AUC96 required for a static, one and two log reduction in viable count at 96h

strain		MIC	static	-1log drop	-2log drop	-3log drop
S.aureus NRS123	46951	0.12	44.3	57.6	69.2	89.1
S.aureus	45796	0.12	9.8	10.3	10.4	10.9
S.aureus	36895	0.12	7.2	7.8	8.7	10.1
S.aureus	43456	0.12	4.7	4.8	5.3	5.4
S.aureus	31236	0.12	4.9	6.1	7.2	8.6
S.aureus	45800	0.25	9.8	10.2	10.2	10.9
S.aureus	45798	0.5	28.8	33.8	41.9	52.6
S.aureus	45798	0.5	9.5	9.8	10.1	10.5
Mean			14.9±14.1	17.6±18.6	20.4±20.4	24.8±30.1

Figure1. Relationship between Cmax/MIC and log reduction in viable count at 24h (all strains)

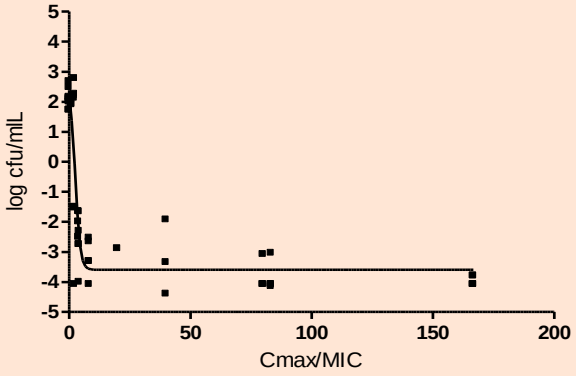


Figure 2: Relationship between AUC/MIC and log reduction in viable count at 24h (all strains)

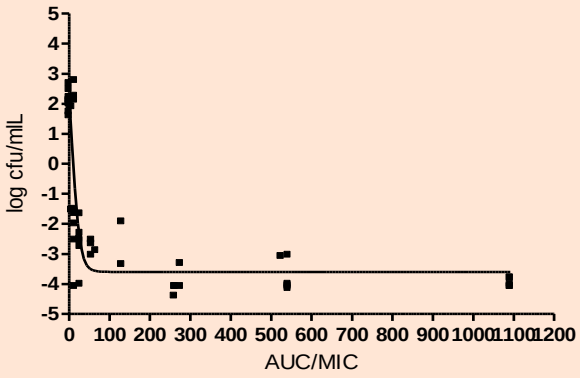
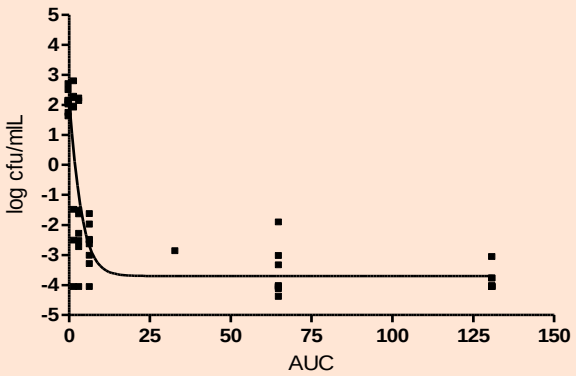


Figure 3: relationship between AUC and log reduction in viable count at 24h (all strains)



Comment [GM1]: could limit of detection be readily aded to each figure? Or at least stated in legend?

Comment [AB2]: Would be nice to show the fitting R-square value or correlation coefficients for each figure