Comparison of Dalbavancin, Oritavancin and Vancomycin Pharmacodynamics using Clinical Targets against ABSSSI Pathogens

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ABSTRACT

Background: Oritavancin (ORI) and dalbavancin (DAL) are newer agents for treatment of ABSSSI; however, vancomycin (VANC) is still frequently used. Since ORI and DAL have not been directly compared to each other in clinical trials, Monte Carlo analysis (MCA) was used to assess potential efficacy differences between these drugs and against VANC for methicillin-susceptible (MSSA), resistant (MRSA), and VANC intermediate (VISA) Staphylococcus aureus, and coagulase negative Staphylococcus (CoNS).

Methods: Multi-compartment pharmacokinetic parameters, current MIC distributions, and clinical pharmacodynamic targets from peer-reviewed literature were used. AUC simulations used population distributions for clearance (a distribution for ORI, derived from CrCl - Cl regressions for DAL and VANC) and volume for: ORI (3 h infusion) 1.2 g single dose; DAL (0.5 h infusion) 1g, then 0.5g 7 days later and a 1.5 g single dose; VANC 1g, 1.5g, and 2g given q12h. Doses of DAL and VANC were adjusted for CrCl (using a distribution of CrCl from our tertiary-care institution). Serum protein binding (PB) values (85% - 90% for ORI and 93% - 97% for DAL) were used to estimate free (f) AUCs for ORI and DAL. Total AUCs were used for VANC. fAUC/MIC clinical targets of ORI (1797, fAUC/MIC 0-72 h), DAL (1013 and 1489 , mean 24 h fAUC/MIC 0-120 h for clinical and microbiological targets, respectively), and 400 (VANC, total AUC24/MIC) were used in the MCA.

Results: Target attainment (TA%) using the clinical targets (DAL 93% PB, ORI 85% PB) were:

Drug	Vancomycin			Dalbavancin		Oritavancin
Dose	1 g q12	1.5 g q12	2 g q12	1g/0.5 g	1.5 g	1.2 g
MSSA	86	97	99	85	96	99
MRSA	85	97	99	85	96	99
CoNS	49	74	94	90	95	100

TA% for VISA was 0%, 1%, and 8% for VANC, DAL, and ORI, respectively. For DAL, microbiologic success TA% was 10-33% lower than for clinical success. TA% was lower when the higher PB values were used (12-50% for DAL and 1-4% for ORI).

Conclusion: Single-dose regimens of DAL and ORI achieved good target attainment (>90%) for MSSA, MRSA, and CoNS. Differences in DAL regimens were likely due to the 0-120h AUC calculation that gives a numeric advantage to the higher dose. VANC TA% was highly dependent on the dosage regimen; VANC doses of 1.5g and 2g were needed to achieve target attainment >90% for MSSA/MRSA and CoNS, respectively. Target attainment was poor for all drugs and regimens against VISA.

BACKGROUND

Due to lack of clinical trial comparison data between two newer anti-infective agents, dalbavancin and oritavancin, Monte Carlo analysis (MCA) was performed against staphylococcal species to assess efficacy of these agents along with the standard of care treatment, vancomycin.

OBJECTIVE

To assess potential clinical efficacy of dalbavancin, oritavancin, and vancomycin against common pathogens in acute bacterial skin and skin structure infections (ABSSSI) using Monte Carlo analysis.

METHODS

Microbiology:
Wild type broth microdilution U.S. MIC distributions were collected for MSSA, MRSA, coagulase-negative Staphylococci (CoNS), and VISA (vancomycin-only) from peer-reviewed literature. MIC distributions of VISA for DAL and ORI were created from MIC_{50}, MIC_{90} and MIC ranges. MIC distributions are displayed in Figures 1-4.

Pharmacokinetic Parameters:
From peer-reviewed pharmacokinetic (PK) literature, we collected the following PK parameters: volume of distribution, serum protein binding (PB) percentage, and creatinine clearance (CrCl) vs. drug clearance regression relationships (DAL and VAN only).

METHODS (cont.)

Using these parameters, a CrCl distribution from our institution (mean ~ 65, range 10 – 120 ml/min), and the dosage regimens in Table 1, we simulated free (f) PK profiles (2-comp. model) for DAL. Using population PK data, we simulated free PK profiles for ORI using a 3-compartment model. Due to literature variability, two PB values (93% and 97% for DAL and 85% and 90% for ORI) were used. Unless otherwise noted, PB throughout the simulations were 93% for DAL and 85% for ORI. For VAN, total AUC distributions were simulated using a CrCl vs. drug clearance regression from peer-reviewed literature and dosage regimens in Table 1.

Dosing Regimens:
For each drug, these dosage regimens were simulated: those in the product label for DAL (normal dose and high dose) and ORI (normal dose) and three typical clinical regimens for VAN. Dosage adjustments for renal dysfunction were made for DAL (Table 1) and VAN (50% of the initial dosage at CrCl 31 – 60 ml/min, 25% at CrCl 15 – 30 ml/min, and 17% at CrCl < 15 ml/min.

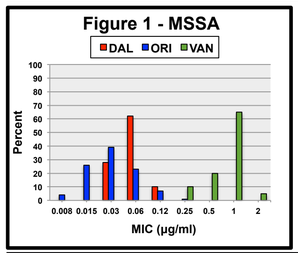
Pharmacodynamic (PD) Targets:
PD targets were gathered from peer-reviewed clinical literature. For DAL [mean $fAUC_{24}$/MIC (from 0 – 120 hr)] targets of ≥ 1013 (clinical success) and 1489 (microbiological success) were used. For ORI ($fAUC_{0\text{-}72}$/MIC), a target of ≥ 1797 (clinical response) was used. For VAN (total AUC_{24}/MIC), a target of ≥ 400 (clinical response) was used.

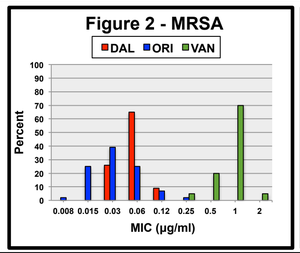
Monte Carlo Analysis (MCA):
MCA was performed using the full distributions of the PK parameters and MICs. Target attainment (TA %) was assessed for each target, dosage regimen, and organism. To assess the impact of protein binding on TA% for DAL and ORI, we used modified targets derived from mean serum PB values for each drug. TA was assessed using susceptibility breakpoints for each agent.

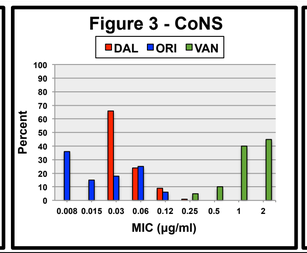
Table 1: Dosing Regimens

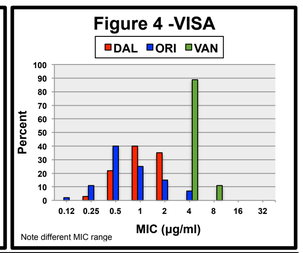
Regimen	CrCl (ml/min)	Dose (mg)	Given on	Infusion Time (hrs)
Dalbavancin				
Normal	≥ 30	1000	Day 1	0.5
		500	Day 8	0.5
	< 30	750	Day 1	0.5
		375	Day 8	0.5
High Dose	≥ 30	1500	Day 1	0.5
	<30	1000	Day 1	0.5
Oritavancin				
Normal	all	1200	Day 1	3
Vancomycin				
1 g q12	Dose adjusted based on percentage in methods	1000	Days 1-14	1
1.5 g q12		1500	Days 1-14	1.5
2 g q12		2000	Days 1-14	2

Microbiologic Activity: MIC Distributions



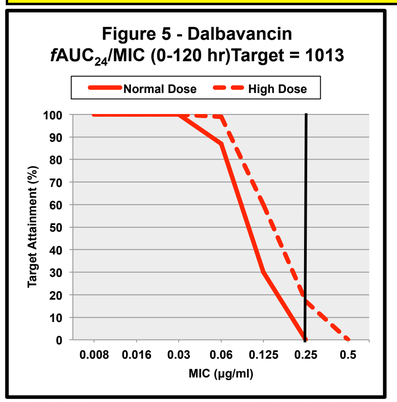


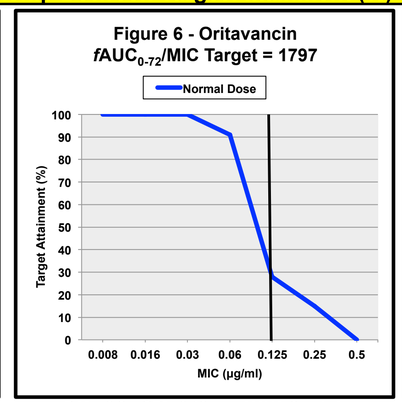


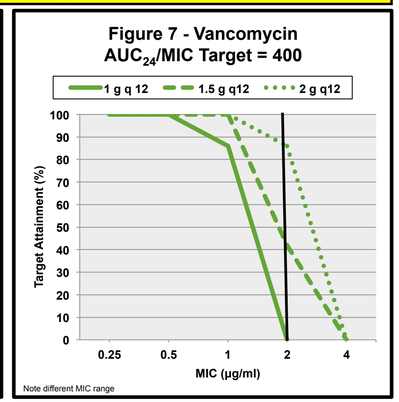


RESULTS

Relationship Between Target Attainment (%) and MIC

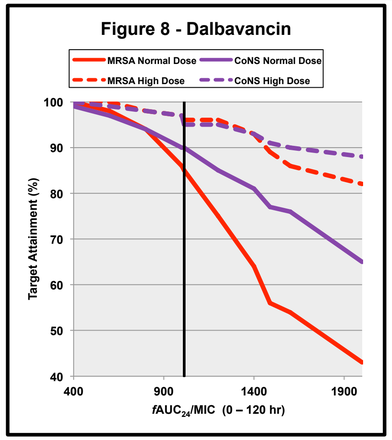


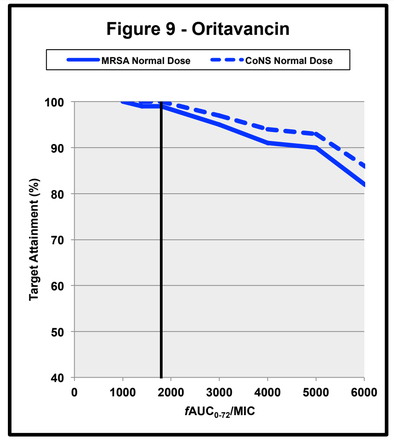


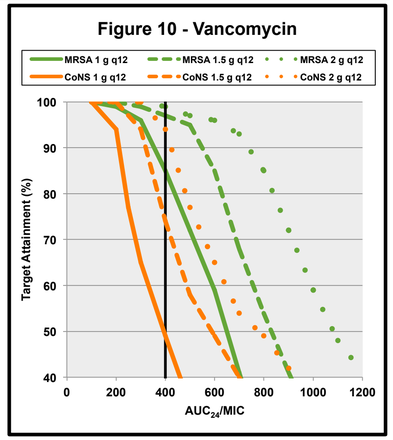


*Vertical line represents susceptibility breakpoint for *S. aureus:* DAL =0.25, ORI =0.125, and VAN=2 µg/ml

Monte Carlo Analysis: Target Attainment (%) vs. AUC/MIC Targets







*MSSA and VISA not shown due to graphing similarities and overlap. Full results in Table 2. ** Vertical line represents clinical target: DAL=1013, ORI =1797, VAN=400.

RESULTS (Cont.)

Monte Carlo Analysis: Target Attainment (%)

Table 2.
Clinical Endpoint Target Attainment (%)

Drug	DAL		ORI	VAN		
Dosing Regimen	Normal	High Dose	Normal	1 g q12	1.5 g q12	2 g q12
Target	1013 $fAUC_{24}$/MIC (0-120h)		1797 $fAUC_{0\text{-}72}$/MIC	400 AUC_{24}/MIC		
MSSA	85	96	99	86	97	99
MRSA	85	96	99	85	97	99
CoNS	90	95	100	49	74	94
VISA	0	1	8	0	0	0

*Green shaded cells represent TA ≥90%
Numerical representation of targets from Figures 8-10

Table 3.
Differences in Target Attainment (%) Due to Protein Binding

Drug	DAL			ORI		
Target	724 $fAUC_{24}$/MIC(0-120 hr)			1498 $fAUC_{0\text{-}72}$/MIC		
PB%	93	97	Difference	85	90	Difference
Dosing Regimen	Normal					
MSSA	95	49	46	99	95	4
MRSA	95	49	46	99	95	4
CoNS	94	74	20	100	99	1
Dosing Regimen	HD					
MSSA	99	78	21			
MRSA	99	78	21			
CoNS	99	87	12			

*Green shaded cells represent TA ≥90%
Difference calculated by subtraction of higher PB% TA from lower PB% TA
Note targets above adjusted based on mean PB %

- For DAL the microbiological endpoint (1489) achieved 10-33% lower target attainment than the clinical endpoint (1013).

DISCUSSION

- With the newer agents with very long half-lives and multi-compartment pharmacokinetics (DAL and ORI), the ideal pharmacodynamic endpoint has not been established. Both the length of the AUC measurement (e.g., 0 – 72 hr vs. mean 24 hr AUC over 120 hr) and the clinical endpoint (clinical success at test of cure vs. clinical response at post-therapy evaluation) were not identical. Thus, direct comparisons between those agents are more difficult. Furthermore, the VAN endpoint was initially established with LRTI.

CONCLUSIONS

- Target attainment was ≥85% for all drugs and regimens for non-VISA *S. aureus* using clinically derived targets. High Dose DAL and higher dosages of VAN were required to achieve >90% TA. For CoNS, TA was ≥90% for DAL and ORI and for only the highest dosage of VAN. As expected, VISA isolates showed poor TA% for all drugs.
- Based on the specific data used in this analysis, current susceptibility breakpoints may need to be reevaluated.
- Due to the higher protein binding of DAL, variability expected in patients would more profoundly affect target attainment.
- Further studies are needed to clarify the ideal pharmacodynamic endpoints for these drugs.