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 (VAN) is still frequently used. Some 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, correcting for differences in binding, and MIC distributions for 1 strain of MSSA, MRSA, and CoNS. Differences in PB, ORI (85% PB) were:

Results:

Dalbavancin simulations used models from our literature variability, two PB values (93% and 97% 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. Differences in TA% for DAL were demonstrated for VAN, total AUC distributions were simulated using a distribution of CrCl from our literature variability, two PB values (93% and 97% for ORI and 1500 (clinical response) was used.

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 C - C1) estimates, target attainment (90% for MSSA, MRSA, and CoNS). Differences in PB, ORI (85% PB) were:

• Using these parameters, a CRI distribution from our institution (mean = 65, range 10 – 120 ml/min), and the dosing regimens in Table 1, were simulated free 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. All other parameters used in this study were those in the product label for DAL (normal dose) and ORI (high dose) for ORI (normal dose) and three typical clinical regimens for VAN. Dosage adjustments for renal dysfunction were made for DAL and VAN, total AUC distributions were simulated using a distribution of CrCl from our literature variability, two PB values (93% and 97% for ORI and 1500 (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 drug, 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.

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

• Target attainment was 83% for all drugs and regimens for MIC/MC 3 (auroux S aureus strains) using clinically derived targets. High Dose DAL and higher dosages of VAN were required to achieve >90% TA. For CoNS, TA was 83% 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 reconsidered.

• Due to the higher protein binding of DAL, variability expected in patients would more likely affect target attainment.

• Further studies are needed to clarify the ideal pharmacodynamic endpoints for these drugs.

Methods (cont.)

Results (Cont.)

• Differences in Target Attainment (%) Due to Protein Binding

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

• 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 (400–700 hr or 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 these agents are more difficult. Furthermore, the clinical endpoint was initially established with LRT.

Conclusions

Background:

• 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.

• Monto Carlo Analysis: Target Attainment (%) vs. MIC/MC Targets

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• Based on the specific data used in this analysis, current susceptibility breakpoints may need to be reconsidered.

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Figure 1 - MSSA

Figure 2 - MRSA

Figure 3 - CoNS

Figure 4 - VISA

Figure 5 - Dalbavancin

Figure 6 - Oritavancin

Figure 7 - Vancomycin

Figure 8 - Dalbavancin

Figure 9 - Oritavancin

Figure 10 - Vancomycin

*Ventral line represents susceptibility breakpoint for each strain. DAL: 1013, ORI: 1797, VAN=400.