Pharmacodynamic profiling of oritavancin dosing regimens for salvage therapy of vancomycin resistant enterococcus endocarditis: semi-mechanistic modelling of rabbit infection data to support human dosing regimens

Andras Farkas, Pharm.D[1,2]; Phillip Villasurda , Pharm.D[3]; Catie Hoffmann, MT [4]; Angela Koo, Pharm.D[2]; George Mckinley, MD[2]

Optimum Dosing Strategies, Bloomingdale, NJ[1] ; Mount Sinai West Hospital, NY, NY[2]; Mount Sinai Beth Israel Hospital, NY, NY[3] ; LabCorp, Nyack, NY[4]

ABSTRACT/REVISED

Background: Oritavancin (ORI) is a glycopeptide antibiotic with a long half-life that is highly active against enterococci with acquired resistance to other available glycopeptides. Its favorable susceptibility profile makes it an attractive option for salvage therapy against endocarditis caused by multi-drug resistant enterococci (MDRE). The aim of our study was to investigate the pharmacodynamics of ORI based on a rabbit model of infection and extrapolate those results to the design of human treatment regimens.

Methods: The pharmacokinetics (PK) and pharmacodynamics (PD) of ORI in a rabbit endocarditis model against MDR *Enterococcus faecalis* was characterized with a semi-mechanistic system and Bayesian approach. Next, the pharmacodynamic model was linked to a human pharmacokinetic model of ORI derived from patients with bacteremia. 500 subjects' Monte Carlo simulations were conducted for daily, every 72 hours, and weekly dosing regimen, while taking into consideration variability in penetration of the vegetation. Probabilities of target attainment (PTAs) for achieving bactericidal targets of ≥ 3 log CFU reduction per gram of vegetation in seven heterogeneous diffusion areas of the cardiac vegetation were calculated after 3, 7, 14, 28 and 42 days of therapy.

Results: The PTAs of ≥ 3 log CFU per gram of vegetation were poor for all regimens evaluated. Mean (SD) PTAs of 31.9% (6.4%), 32.3% (11.1%), 36.4% (11.2%), 39.8% (10.9%), and 41.5% (10.5%) were estimated for the two targets and all regimens combined after 3, 7, 14, 28 and 42 days of therapy. Maximum average PTAs of 42.8%, 47.8%, 50.6%, 53.1%, and 54.2% were estimated for the ≥ 3 log CFU target after 3, 7, 14, 28 and 42 days of therapy using the highest total mgs per week dosing regimen. When evaluated at the same target, there was an average of 12.9% increase in PTAs at 42 days when the weekly dose was divided and administered in daily increments, as opposed to administering the total weekly dose once weekly.

Conclusion: Our experimental design suggests that ORI dosing regimens with established safety profile are likely to provide suboptimal efficacy when treating endocarditis caused by MDRE. Administering the total weekly dose divided into daily doses also showed minimal benefit. Administration of higher weekly doses than studied may be considered to improve bactericidal effect. Efficacy and safety of new regimens should be confirmed in well-controlled clinical trials.

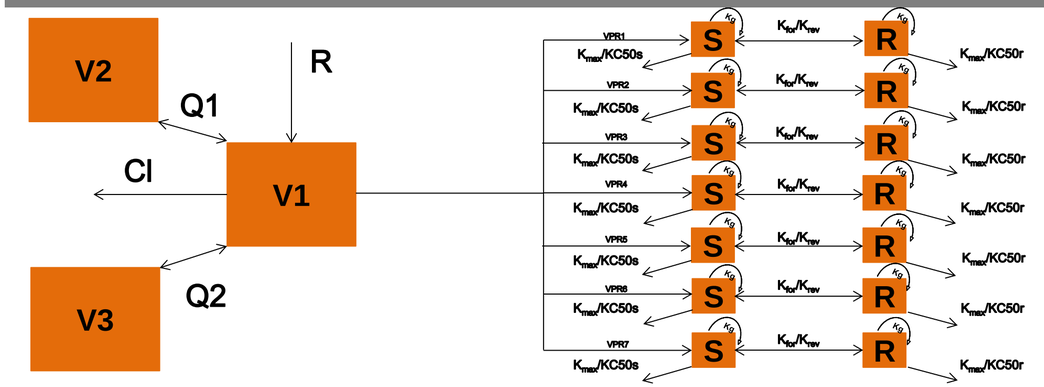
INTRODUCTION AND OBJECTIVES

- Oritavancin is a lipoglycopeptide with activity against MDR gram-positive organisms, including MDRE.
- Variable dosing regimens established in case reports for treatment of MDRE endocarditis.
- Pharmacodynamic properties of oritavancin for the treatment of MDRE endocarditis has not been established in humans.
- The objective of this study was to investigate the pharmacodynamics of ORI based on a rabbit model of infection and extrapolate those results to the design of human treatment regimens.

METHODS

- ORI concentrations and colony counts in cardiac vegetation from a previously published enterococcus rabbit infective endocarditis model were digitized and used in this analysis. [1, 2]
- The R® software application and deSolve package was used to build the structural model for the pharmacokinetic and pharmacodynamic analysis.[3]
- The FME package was utilized to carry out the Bayesian analysis via the Markov Chain Monte Carlo technique using the Metropolis – Hastings algorithm.[4]
- 500 patient Monte Carlo simulation was conducted to generate profiles of bacterial kill in 7 distinct areas of human cardiac vegetation by linking the rabbit pharmacodynamic system to a 3 compartment human population pharmacokinetic model.[5]

METHODS



R represents the infusion rate of ORI, *Cl* is the clearance, *V1* is the volume of the central compartment , *V2-3 are* the volume of the peripheral compartments, *Q1-2* are the inter-compartmental clearance, *VPR1-7* are the penetration ratios into the vegetation, *Popmax* is the maximum total bacterial population size, *Kg* is the apparent growth rate constant, *Kmax* the maximal rate constant of bacterial killing, *KC50S* the antibiotic concentration yielding 50% of *Kmax* for susceptible bacteria, *KC50R* the antibiotic concentration yielding 50% of *Kmax* for resistant bacteria, *Kfor* and *Krev* are the first-order transfer rate constants from the susceptible to the resistant population and vice-versa, *S* and *R* are the population of susceptible and resistant organisms.

Figure 1. Structural mathematical model evaluated in this analysis

RESULTS

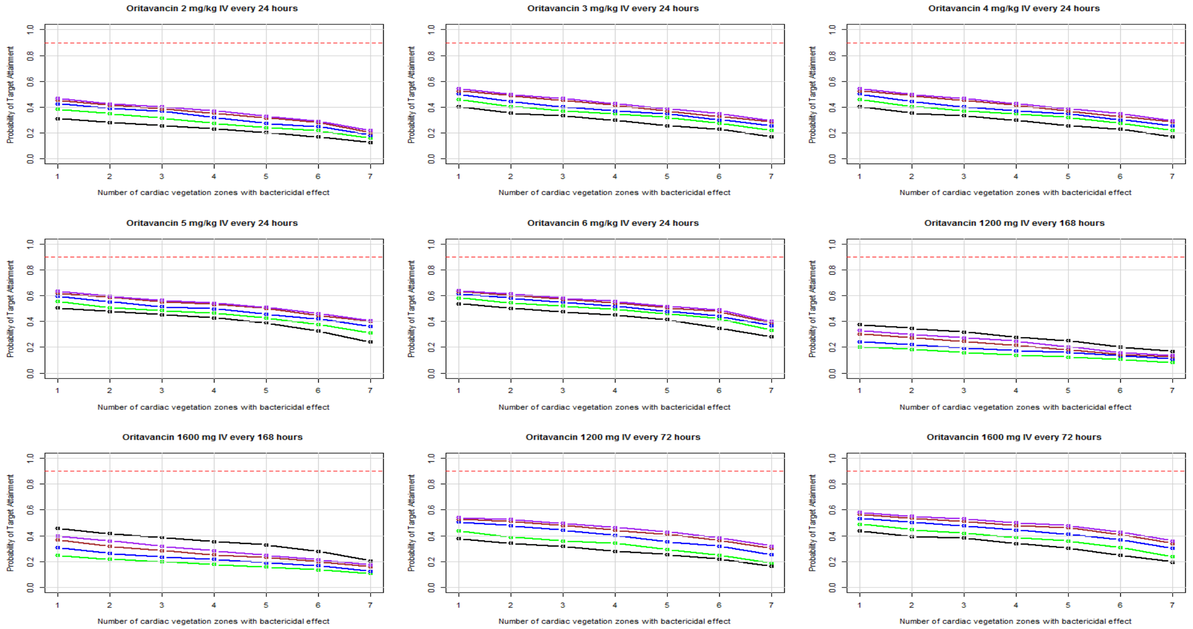


Figure 2 . PTAs of ≥ 3 CFU reduction per gram of vegetation in distinct zones (cumulatively) at 3 (black),, 7 (green), 14 (blue), 28 (brown), and 42 (purple) days

RESULTS

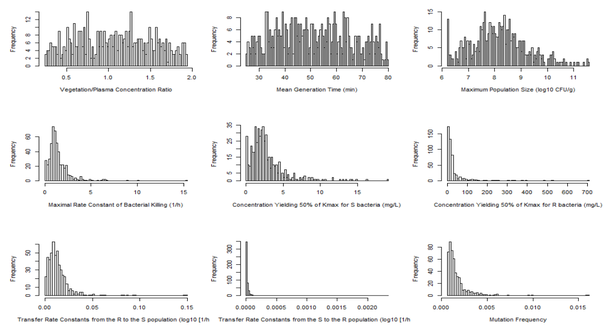


Figure 3 Histograms of estimated pharmacodynamic parameters

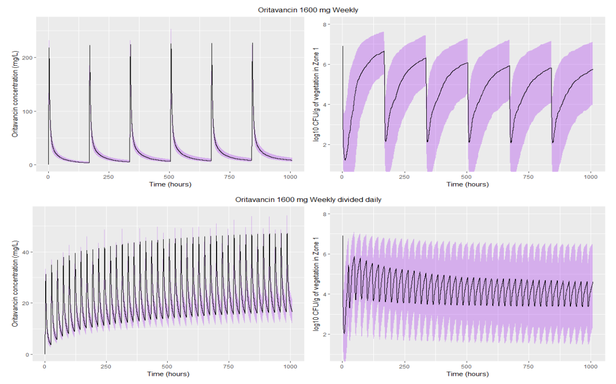


Figure 4. Median (IQR) range of drug levels and CFU/g of vegetation for daily or weekly dose over time

CONCLUSION

ORI dosing regimens with established safety profile in the literature are likely to provide suboptimal efficacy when treating MDRE endocarditis. Daily administration of the same total weekly dose will also be of minimal benefit. Established dosing regimens of ORI should be used with caution for the treatment of MDRE and reserved for those with a lack of treatment options, due to its broad spectrum of activity and likelihood of suboptimal efficacy. Safety and efficacy of higher dosing regimens should be established in well-designed clinical trials.

REFERENCES

1. Antimicrob Agents Chemother. 2000 Nov;44(11):3017
2. http://arohatgi.info/WebPlotDigitizer/
3. http://www.R-project.org/.
4. https://cran.r-project.org/web/packages/FME/index.html
5. Antimicrob. Agents Chemother. Oct,2009;53 (10) 4422

Mount Sinai West

Contact: Andras Farkas, Pharm.D, andras.farkas@mountsinai.org