

Session: EP191 Recent advances in PK/PD: efficacy and toxicity

**Category: 5b. Pharmacokinetics/pharmacodynamics of antibacterial drugs & therapeutic drug monitoring**

25 April 2017, 12:48 - 12:53  
EP0946

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

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**Background:** Oritavancin 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 (MDR) *Enterococcus faecalis*. The aim of our study was to establish the pharmacodynamics of oritavancin based on a rabbit model of infection and extrapolate those results to the design of human treatment regimens.

**Material/methods:** The pharmacokinetics and pharmacodynamics of oritavancin 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 oritavancin derived from patients with bacteremia. 1500 subjects' Monte Carlo simulations were conducted for daily, every 72 hours, and weekly dosing regimens (total dose of 14 to 40 mg/kg/week), while considering differences in penetration into the vegetation. Probabilities of target attainment (PTAs) for achieving targets of < 1 log CFU and < 2 log CFU per gram of vegetation in seven heterogeneous diffusion areas of the cardiac vegetation were calculated to establish expected percentage of patients with fully sterilized vegetations after 3, 7, 14, 28 and 42 days of therapy.

**Results:** The PTAs of < 1 log CFU and < 2 log CFU per gram of vegetation were poor for all regimens evaluated. Mean (SD) PTAs of 1.5% (1.1%), 6.8% (4.7%), 18.1% (8.5%), 36.3% (12.3%), and 48.3% (12.6%) were estimated for the two targets and all regimens combined after 3, 7, 14, 28 and 42 days of therapy. Maximum PTAs of 2%, 10.6%, 25.4%, 47.8%, and 62.8% were estimated for the < 1 log CFU target versus 3.7%, 17.7%, 37.2%, 62.2%, and 72.8% for the < 2 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 2% to 5% 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.

**Conclusions:** Our experimental design suggests that single-agent oritavancin dosing regimens with established safety profile in humans are likely to provide suboptimal efficacy when treating endocarditis caused by MDR Enterococci. Administering the total weekly dose divided into daily doses also showed minimal benefit. Administration of higher weekly doses than studied or longer courses of therapy should be considered to improve sterilizing effect. Efficacy and safety of new regimens should be confirmed in well-controlled clinical trials.