Pharmacodynamic (PD) Activity of Dalbavancin against VISA Staphylococcus aureus (SA) Isolates in the Neutrophilic Murine Thigh Infection Model
A. Lepak and D. R. Andes
University of Wisconsin-Madison, Madison, WI

ABSTRACT

Background: Dalbavancin is a novel lipoglycopeptide with activity against drug-resistant gram-positive pathogens, including beta-lactam resistant isolates, and is currently approved for use in acute bacterial skin and skin structure infections. Previous studies have examined the PD target against a group of SA isolates with a relatively low and narrow MIC range. The aim of this study was to examine the PD targets for a group of isolates with dalbavancin MICs above that observed in clinical populations.

Methods: 7 clinical isolates of SA, including VISA, were selected for this study. MICs were determined using CLSI methodology in the presence of dalbavancin. The PD target against a group of SA isolates with relatively low and narrow MIC range. The study was a 7 d in vivo study. MICs were determined using CLSI methodology in the presence of dalbavancin. The PD target against a group of SA isolates with relatively low and narrow MIC range. The study was a 7 d in vivo study. MICs were determined using CLSI methodology in the presence of dalbavancin. The PD target against a group of SA isolates with relatively low and narrow MIC range. The study was a 7 d in vivo study. MICs were determined using CLSI methodology in the presence of dalbavancin.

Results: MICs to dalbavancin were 0.12-0.5 mg/L. IP administration determined the PD target against 3 MRSA with vancomycin MIC = 2 mg/L and 4 VISA with vancomycin MIC = 4 mg/L were used for this study. All isolates were tested in accordance with CLSI methodology in the presence of P60. When administered IP, AUC/MIC was examined using the Hill sigmoid Emax exposure-response model. Pharmacodynamic studies and analysis: Single-dose plasma PK studies were performed in high-dose subject. Each subject received a single dose of dalbavancin at 2.5, 10, 40, 80, and 160 mg/kg. Plasma PK was determined using non-compartmental method was well described by the PD index AUC/MIC (R2=0.86). A 1-log and 2-log kill was achieved at 2.5 mg/kg and 10 mg/kg respectively. The dose required to produce net static effect (Static Dose, SD) and 1-log kill, 2-log kill was calculated for each isolate. The associated 24 h total drug exposure was determined for all isolates are listed in the table below.

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>24h fAUC/MIC (mg*h/L)</th>
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<tbody>
<tr>
<td>2.5</td>
<td>2.5</td>
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<td>10</td>
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<td>40</td>
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Conclusions: Dalbavancin is a lipoglycopeptide antibiotic with enhanced potency against drug-resistant gram-positive pathogens. It possesses unique PK properties including an extremely long half-life making once weekly administration sufficient for treatment of infections of the skin and soft tissues.

REFERENCES

1) Dalbavancin demonstrated greater potency in vivo against SA isolates with higher MICs than typically noted in wild-type strains including those with VISA phenotype.

2) Free drug AUC/MIC targets for stasis, 1 log kill, and 2 log kill were 27, 50, and 111 mg*h/L respectively.

3) The preclinical data presented in this study suggests drug exposure with the current dosing regimen would provide cidal activity against isolates with higher MICs than the current FDA breakpoint of 0.12 mg/L. Further studies in humans will be necessary to corroborate in-vivo findings.

4) Translation of the steady state kinetics of dalbavancin in patients and the PD targets identified for 2 log kill, 1 log kill, and stasis, the MIC breakpoints would be 1.2 and 2.4 mg/L for 2 log kill, 1 log kill, and net stasis, respectively.

CONCLUSIONS

Figure 3: The 7 d AUC for the currently recommended dose of dalbavancin (1000 mg) in humans is 111.60 mg*h/L. Using protein binding in humans of 93%, the average daily (24 h) free drug AUC over the treatment period is 111.60 mg*h/L. The MIC ceiling would therefore be 1, 2, and 4 mg/L for 2 log kill, 1 log kill, and net stasis, respectively.

Figure 2: The dose-response curves for each of the 7 SA isolates is shown in the Figure 2 below. Each symbol represents the geometric mean ± standard deviation of organism burden in four thighs.

Figure 1: The dose-response curves for each of the 7 SA isolates is shown in the Figure 1 below. Each symbol represents the geometric mean ± standard deviation of organism burden in four thighs.