2516

THE EFFICACY OF DALBAVANCIN IN TREATMENT OF RAT STERNAL MRSA OSTEOMYELITIS

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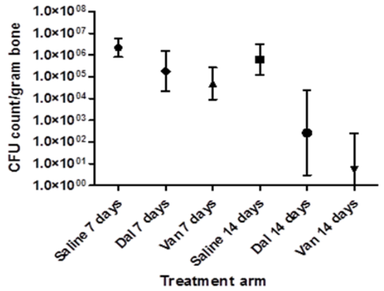
ABSTRACT

Background:
Dalbavancin, a semi-synthetic lipoglycopeptide antibiotic, has been approved by the US FDA for the treatment of acute bacterial skin and skin structure infections in adults. It is characterized by a long plasma half-life which allows for weekly dosing. Thus, dalbavancin may be a good treatment option for patients with deep sternal wound infections due to its improved pharmacokinetic profile and antibacterial activity compared to currently used antibiotics. The primary objective of this study was to evaluate the efficacy of dalbavancin in reducing sternal bone bacterial counts in a rat *S. aureus* deep sternal wound infection model.

Methods:
A mid-sternal wound was surgically induced in anesthetized rats. A clinical strain of MRSA was injected (0.05 mL of $1X10^7$ cfu/rat) into the sternum to establish infection. Rats were treated for 7 days or 14 days with either dalbavancin, given IP 20 mg/kg loading dose followed by 10 mg/kg daily, vancomycin, given IP, 50 mg/kg, q12h, or saline, 0.9% NaCl, given IP once daily. Quantitative cultures of sternum and spleen were determined (cfu/g specimen) using viable counts following serial dilutions and plating on blood agar plates. The antibacterial efficacy of each antibiotic was determined by the reduction in bacterial counts/gram sternum and spleen tissue in each treatment group.

Results:
A total of 84 rats were analyzed for MRSA sternal bone counts:

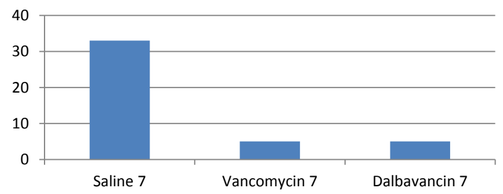
Figure 1: Geometrical mean MRSA cfu/gram of bone with 95% CI



*p values: Dal 7 vs Saline 7 = 0.001; Dal 14 vs Saline 14 = 0.006; Dal 7 vs Van 7 = 0.35; Dal 14 vs Van 14 = 0.53

Systemic dissemination was examined in 58 rats:

Figure 2: Proportion of infected rats with systemic dissemination after 7 days of treatment.



*p values: dalbavancin vs saline = 0.025; dalbavancin vs vancomycin = 1.0

Conclusions:

Treatment with dalbavancin was superior to treatment with saline for 7 days (0.75 log reduction in bone CFU) or 14 days (>3 log reduction in bone CFU) and similar to treatment with vancomycin. Additionally, dalbavancin was also effective in reducing systemic dissemination of MRSA. Dalbavancin is effective in the treatment of MRSA rat sternal osteomyelitis.

METHODS

- Sternal infection was induced with 1X107 cfu/rat of MRSA in male Lewis rats, 10 weeks of age, weighing 250-270 g
- 84 rats were treated for 7 days or 14 days with either:
  - dalbavancin, given IP 20 mg/kg loading dose followed by 10 mg/kg daily, OR
  - vancomycin, given IP, 50 mg/kg, q12h, OR
  - 0.9% NaCl, given IP once daily
- Rats were sacrificed on either day 7 or day 14 of treatment and quantitative cultures of sternum and spleen were determined (cfu/g specimen) using viable counts following serial dilutions and plating on blood agar plates.
- The cfu/g of sternal bone was compared between the treatment groups.
- Dalbavancin levels in bone were measured on Days 4, 6 and 10
- The geometric mean + 95% confidence interval is used for graphical representation, and an unpaired student t test was performed on the log transformed cfu to compare differences between the treatment groups. This approach was chosen based on modern approach to skewed data18, 19. Difference in proportion was tested using chi square. All analyses were performed using GraphPad Prism version 5 (San Diego, CA) and Stata version 12 (College Station, TX). Differences were considered to be statistically significant with a p value of 0.05 or less.

RESULTS

Figure 1: Bacterial Counts in Sternal Bone

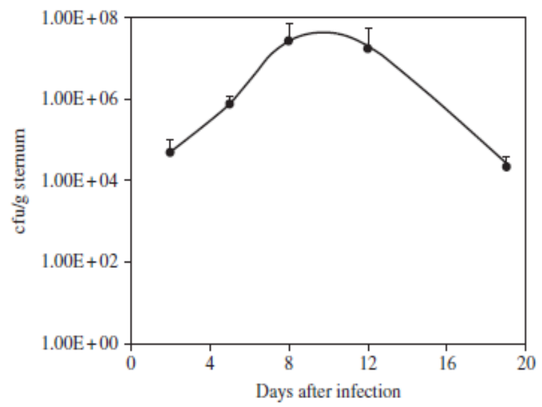
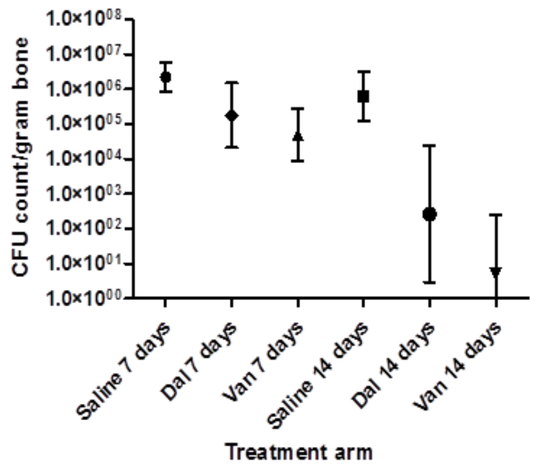
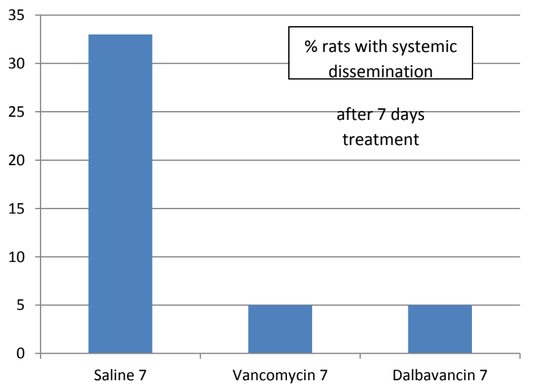


Figure 2: *S. Aureus* Sternal Bone cfu Counts



*p values: Dal 7 vs Saline 7 = 0.001; Dal 14 vs Saline 14 = 0.006; Dal 7 vs Van 7 = 0.35; Dal 14 vs Van 14 = 0.53
Geometrical mean with 95% Confidence Intervals
Dal=Dalbavancin, Van=Vancomycin, CFU=colony forming units

Figure 3: Systemic dissemination

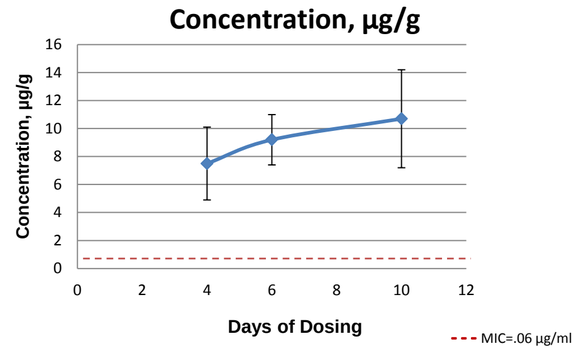


*p values: dalbavancin vs saline = 0.025; dalbavancin vs vancomycin = 1.0

Table 1: Dalbavancin Concentration in Rat Bones

Sample	N	Days of dosing	Concentration, µg/g	Range, µg/g (SD)
Sternum	10	4	9.5	5.7-12.6 (2.7)
	10	4	7.5	4.4 - 12.4 (2.6)
Femur	4	6	9.2	6.8 – 10.9 (1.8)
	4	10	10.7	8.3 – 15.9 (3.5)

Figure 4: Dalbavancin Concentration in Rat Femur



CONCLUSION

- Dalbavancin (using doses mimicking human PK following a single intravenous dose of 1000 mg) is effective in the treatment of MRSA rat sternal osteomyelitis
- Treatment with dalbavancin was superior to treatment with saline for 7 days (0.75 log reduction in bone CFU) or 14 days (>3 log reduction in bone CFU)
- Treatment with dalbavancin for 7 days reduced systemic dissemination of MRSA compared to treatment with saline (5% vs 33%)
- Results were similar to those achieved by treatment with vancomycin

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