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Dalbavancin *In Vitro* Activity Obtained against Gram-positive Clinical Isolates Causing Bone and Joint Infections in USA and European Hospitals (2011 - 2015)

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AMENDED ABSTRACT

Background

Osteomyelitis represents hard-to-treat infections that regularly involves the use of prolonged and systemic antibiotics. Dalbavancin has demonstrated activity against Gram-positive isolates and has been considered as a candidate for osteomyelitis therapy in adults and children. This study evaluates the activity of dalbavancin against pathogens isolated from bone-joint infections (BJI).

Methods

650 *S. aureus*, 118 coagulase-negative staphylococci (CoNS), 115 β-hemolytic streptococci (BHS), 61 *E. faecalis* and 35 viridans group streptococci (VGS) causing BJI were included (2011 - 2015). Bacteria were identified by standard algorithms and MALDI-TOF. Susceptibility testing was performed by CLSI methods (M07-A10); interpretation of MIC results used CLSI (2016) criteria.

Results

S. aureus (65.3%) was the most common pathogen associated with BJI, followed by CoNS (11.9%) and BHS (11.6%; see Table). All *S. aureus* (34.2% MRSA) isolates were susceptible to dalbavancin and vancomycin, while daptomycin and clindamycin showed susceptibility rates of 99.8% and 88.6%, respectively. Dalbavancin MIC results were at least 4-fold lower than these comparators against all *S. aureus*. A total of 61.0% of CoNS were methicillin (oxacillin)-resistant and dalbavancin was the most potent agent, followed by daptomycin and vancomycin. All *E. faecalis* isolates were inhibited by dalbavancin at ≤0.25 µg/mL (FDA breakpoint for susceptibility), except for one vancomycin-resistant (VanA) isolate. High susceptibility rates for ampicillin (98.4%), daptomycin (100.0%) and vancomycin (96.7%) were obtained against *E. faecalis*. Dalbavancin (100.0% susceptible), ceftriaxone ($MIC_{50/90}$, ≤0.06/0.12 µg/mL; 100.0% susceptible) and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 µg/mL; 100.0% susceptible) were the most active drugs against BHS; while dalbavancin (100.0% susceptible) was the most active agent against VGS inhibiting all isolates at ≤0.06 µg/mL. Ceftriaxone, daptomycin and vancomycin were also active (94.3 - 100.0% susceptible) against VGS, whereas clindamycin (85.7% susceptible) had marginal activity.

Conclusion

Dalbavancin demonstrated potent *in vitro* activity against common Gram-positive isolates causing BJI (2011-2015). Dalbavancin appears to be a viable candidate for treatment of BJI/osteomyelitis caused by Gram-positive cocci.

INTRODUCTION

Bone and joint infections (BJI) comprises a series of disorders, including septic arthritis, osteomyelitis, and infections in prosthetics joints. Osteomyelitis is an infection of the bone associated with either hematogenous dissemination or direct inoculation as a consequence of trauma or infection from contiguous tissues. *Staphylococcus aureus* remains the most common pathogen responsible for acute infections, while Gram-negative organisms are usually associated with traumatic infections and chronic presentations. Infection in children occurs less frequently than adults, but it is predominantly a result of bacteremia due to *S. aureus*. The estimated incidence of acute osteomyelitis is about 22 and eight per 100,000 adults and children per year, respectively. Moreover, an increase in incidence of osteomyelitis in children has been observed in the recent years.

Since there is a high incidence of infections caused by community-acquired methicillin-resistant *S. aureus* (MRSA) in the USA, vancomycin needs to be considered for empirical treatment. Dalbavancin was approved in the USA (2014) and Europe (2015) for the treatment of adults with acute bacterial skin and skin structure infections (ABSSSI), and has been considered as a candidate for osteomyelitis therapy in adults and children. Dalbavancin can be administrated in a single dose of 1500 mg or 1000 mg followed by 500 mg a week later for the treatment of ABSSSI. This study evaluates the activity of dalbavancin against pathogens isolated from BJI, including osteomyelitis.

METHODS

Bacterial isolates

A total of 650 *S. aureus*, 118 coagulase-negative staphylococci (CoNS), 115 β-hemolytic streptococci (BHS), 61 *E. faecalis* and 35 viridans group streptococci (VGS) causing BJI were included (2011 - 2015). Isolates were collected from 32 medical sites in the USA and 17 European countries (35 sites), Russia (three sites), Turkey (six sites), Ukraine (one site) and Israel (one site). Isolates were determined to be clinically significant based on local guidelines and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA), as part of the **I**nternational **D**albavancin **E**valuation of **A**ctivity (IDEA) surveillance program. Isolates were initially identified by the participating laboratory and bacterial identifications were confirmed by the reference monitoring laboratory by standard algorithms and supported by MALDI–TOF–MS (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility testing

Isolates were tested for susceptibility by broth microdilution following guidelines in the CLSI M07–A10 document. Testing was performed using reference 96-well panels manufactured by JMI Laboratories (North Liberty, Iowa, USA). Quality assurance was performed by concurrent testing of CLSI–recommended QC reference strains (*S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619). All QC results were within published acceptable ranges. The dalbavancin breakpoints approved by the Food and Drug Administration (FDA) for indicated species were applied (i.e. ≤0.25 µg/ml). Breakpoint criteria for comparator agents were those from the CLSI (M100-S26).

RESULTS

- *S. aureus* (65.3%) was the most common pathogen associated with BJI, followed by CoNS (11.9%) and BHS (11.6%; see **Table 1**). A total of 34.2% of *S. aureus* isolates were methicillin-resistant, while 61.0% of CoNS exhibited this phenotype (**Tables 1** and **2**).
- Most tested agents demonstrated *in vitro* activity against MSSA (≥93.0% susceptible) . Dalbavancin (100.0% susceptible), daptomycin (99.5% susceptible), linezolid (100.0% susceptible) and vancomycin (100.0% susceptible) were the most active against MRSA (**Table 2**).
- Dalbavancin ($MIC_{50/90}$, 0.06/0.06 µg/mL) MIC results were 16-fold lower than those of daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL), vancomycin ($MIC_{50/90}$, 1/1 µg/mL) and linezolid ($MIC_{50/90}$, 1/1 µg/mL) when tested against MRSA (**Table 2**).
- *S. aureus* isolates responsible for BJI in adults and children showed very similar (within 5%) susceptibility rates (**Figure 1**), with the exception of clindamycin (87.1% susceptible in adults and 96.9% in children) and levofloxacin (68.4% susceptible in adults and 86.5% in children).
- Only daptomycin (100.0% susceptible), linezolid (100.0% susceptible) and vancomycin (100.0% susceptible) showed *in vitro* activity against CoNS, and dalbavancin had the lowest MIC_{50} and MIC_{90} results (**Tables 1** and **2**).
- All *E. faecalis* isolates were inhibited by dalbavancin at ≤0.25 µg/mL (FDA breakpoint for susceptibility), except for one vancomycin-resistant (VanA) isolate (**Table 1**). High susceptibility rates for ampicillin (98.4%), daptomycin (100.0%), linezolid (100.0% susceptible) and vancomycin (96.7%) were observed against *E. faecalis* (**Table 2**).
- Dalbavancin ($MIC_{50/90}$, ≤0.03/0.06 µg/mL; 100.0% susceptible), ceftriaxone ($MIC_{50/90}$, ≤0.06/0.12 µg/mL; 100.0% susceptible) and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 µg/mL; 100.0% susceptible) were the most active drugs against BHS (**Table 2**).
- Dalbavancin (100.0% susceptible) was the most active agent against VGS inhibiting all isolates at ≤0.06 µg/mL. Ceftriaxone, daptomycin and vancomycin were also active (94.3 - 100.0% susceptible) against VGS, whereas clindamycin (85.7% susceptible) had marginal activity (**Table 2**).

Table 1. Activity and spectrum of dalbavancin against contemporary Gram-positive isolates causing BJIs in the USA and Europe.

Pathogens[a] (no. tested)	MIC (µg/mL)		Number (cumulative %) inhibited at MIC (µg/mL)[b]				
	50%	90%	≤0.03	0.06	0.12	0.25	>0.25
S. aureus (650)	0.06	0.06	276 (42.5)	327 (92.8)	47 (100.0)		
MSSA (428)	0.06	0.06	186 (43.5)	212 (93.0)	30 (100.0)		
MRSA (222)	0.06	0.06	90 (40.5)	115 (92.3)	17 (100.0)		
CoNS (118)	≤0.03	0.06	72 (61.0)	40 (94.9)	5 (99.2)	1 (100.0)	
E. faecalis (61)	0.06	0.12	24 (39.3)	30 (88.5)	5 (96.7)	1 (98.4)	1 (100.0)
BHS (115)	≤0.03	0.06	103 (89.6)	9 (97.4)	3 (100.0)		
VGS (35)	≤0.03	0.06	31 (88.6)	4 (100.0)			

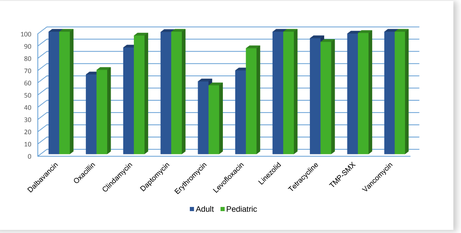
a. MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; CoNS = coagulase-negative staphylococci, BHS = β-hemolytic streptococci, VGS = viridans group streptococci.
b. One vancomycin-resistant (VanA) *E. faecalis* had dalbavancin MIC value of >0.25 µg/mL.

Table 2. Antimicrobial activity of dalbavancin and comparator agents against contemporary Gram-positive isolates causing BJIs in the USA and Europe.

Organism/Group[a] (no.) Antimicrobial agent[b]	MIC (µg/mL): MIC_{50}	MIC_{90}	Range	%Susceptible/%Intermediate/%Resistant[c]:		
MSSA (428)						
Dalbavancin	0.06	0.06	≤0.03 — 0.12	100.0	-	-
Clindamycin	≤0.25	≤0.25	≤0.25 — >2	97.9	0.0	2.1
Daptomycin	0.25	0.5	≤0.12 — 1	100.0	-	-
Erythromycin	0.25	>8	≤0.12 — >8	75.7	4.0	20.3
Levofloxacin	≤0.12	0.5	≤0.12 — >4	93.0	0.2	6.8
Linezolid	1	1	≤0.12 — 2	100.0	-	0.0
Tetracycline	≤0.5	≤0.5	≤0.5 — >8	96.3	0.2	3.5
TMP-SMX	≤0.5	≤0.5	≤0.5 — >4	99.3	-	0.7
Vancomycin	1	1	≤0.12 — 2	100.0	0.0	0.0
MRSA (315)						
Dalbavancin	0.06	0.06	≤0.03 — 0.12	100.0	-	-
Clindamycin	≤0.25	>2	≤0.25 — >2	70.7	0.0	29.3
Daptomycin	0.25	0.5	≤0.12 — 2	99.5	-	-
Erythromycin	>8	>8	≤0.12 — >8	25.7	1.4	73.0
Levofloxacin	4	>4	≤0.12 — >4	29.7	1.4	68.9
Linezolid	1	1	0.25 — 2	100.0	-	0.0
Tetracycline	≤0.5	8	≤0.5 — >8	89.6	0.9	9.5
TMP-SMX	≤0.5	≤0.5	≤0.5 — >4	97.3	-	2.7
Vancomycin	1	1	≤0.12 — 2	100.0	0.0	0.0
CoNS (118)[d]						
Dalbavancin	≤0.03	0.06	≤0.03 — 0.25	-	-	-
Oxacillin	1	>2	≤0.25 — >2	39.0	-	61.0
Clindamycin	≤0.25	>2	≤0.25 — >2	69.5	0.0	30.5
Daptomycin	0.25	0.5	≤0.12 — 1	100.0	-	-
Erythromycin	>8	>8	≤0.12 — >8	45.8	0.0	54.2
Levofloxacin	0.25	>4	≤0.12 — >4	65.3	3.4	31.4
Linezolid	0.5	1	0.25 — 2	100.0	-	0.0
Tetracycline	≤0.5	>8	≤0.5 — >8	83.9	1.7	14.4
TMP-SMX	≤0.5	>4	≤0.5 — >4	78.8	-	21.2
Vancomycin	1	2	≤0.12 — 2	100.0	0.0	0.0
E. faecalis (61)						
Dalbavancin	0.06	0.12	≤0.03 — >2	98.4[e]	-	-
Ampicillin	1	1	≤0.5 — >8	98.4	-	1.6
Daptomycin	1	1	≤0.25 — 2	100.0	-	-
Levofloxacin	1	>4	≤0.5 — >4	72.1	0.0	27.9
Linezolid	1	1	≤0.25 — 2	100.0	0.0	0.0
Tetracycline	>8	>8	≤1 — >8	26.2	1.6	72.1
Vancomycin	1	2	≤0.5 — >16	96.7	0.0	3.3
BHS (115)[f]						
Dalbavancin	≤0.03	0.06	≤0.03 — 0.12	100.0	-	-
Ceftriaxone	≤0.06	0.12	≤0.06 — 0.12	100.0	-	-
Clindamycin	≤0.25	>2	≤0.25 — >2	75.4	0.9	23.7
Daptomycin	0.12	0.25	≤0.06 — 0.5	100.0	-	-
Erythromycin	≤0.12	>4	≤0.12 — >4	61.7	0.9	37.4
Levofloxacin	0.5	1	0.12 — >4	98.3	0.0	1.7
Linezolid	1	1	0.25 — 1	100.0	-	-
Penicillin	≤0.06	≤0.06	≤0.06	100.0	-	-
Tetracycline	>8	>8	≤0.5 — >8	45.6	2.6	51.8
Vancomycin	0.25	0.5	0.12 — 0.5	100.0	-	-
VGS (35)[g]						
Dalbavancin	≤0.03	0.06	≤0.03 — 0.06	100.0	-	-
Ceftriaxone	0.12	1	≤0.06 — 2	94.3	5.7	0.0
Clindamycin	≤0.25	>2	≤0.25 — >2	85.7	0.0	14.3
Daptomycin	0.5	1	≤0.06 — 1	100.0	-	-
Erythromycin	1	>4	≤0.12 — >4	48.6	0.0	51.4
Levofloxacin	1	2	0.25 — >4	94.3	2.9	2.9
Linezolid	0.5	1	0.25 — 1	100.0	-	-
Penicillin	≤0.06	0.25	≤0.06 — 2	85.7	14.3	0.0
Tetracycline	1	>8	≤0.5 — >8	54.3	5.7	40.0
Vancomycin	0.5	1	0.25 — 1	100.0	-	-

a. MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; CoNS = coagulase-negative staphylococci; BHS = β-hemolytic streptococci; VGS = viridans group streptococci.
b. TMP-SMX = Trimethoprim-sulfamethoxazole.
c. Dalbavancin FDA-approved breakpoint for primary indicated species (all ≤0.25 µg/mL). Breakpoint criteria for comparator agents were those from CLSI (2016), as available. "-" breakpoint not available.
d. Includes: *Staphylococcus capitis* (4), *S. caprae* (5), *S. cohnii* (1), *S. epidermidis* (74), *S. haemolyticus* (2), *S. hominis* (5), *S. lugdunensis* (12), *S. pettenkoferi* (1), *S. pseudintermedius* (1), *S. simulans* (3), *S. warneri* (6), *Staphylococcus* spp. (4).
e. 98.4% susceptible when including a vancomycin-resistant isolate (not indicated), or 100.0% susceptible against indicated vancomycin-susceptible *E. faecalis*.
f. Includes: *Streptococcus agalactiae* (55), *S. dysgalactiae* (22), *S. pyogenes* (38).
g. Includes: *Streptococcus anginosus* (8), *S. constellatus* (3), *S. cristatus* (1), *S. gallolyticus* (1), *S. gordonii* (2), *S. mitis/oralis* group (13), *S. parasanguinis* (2), *S. salivarius* (3), *S. sanguinis* (2).

Figure 1. Susceptibility profile of *S. aureus* clinical isolates causing BJIs in the adult (≥18 years old) and pediatric (≤17 years old) populations.



CONCLUSIONS

- Staphylococcal isolates were the most frequent pathogens responsible for BJI in this study population. A total of 38.3% of these isolates were methicillin-resistant, which precludes the use of both commonly used antimicrobial therapies, cefazolin and oxacillin, for such cases.
- Dalbavancin demonstrated potent *in vitro* activity against common Gram-positive isolates causing BJI in the USA and Europe (2011-2015). This *in vitro* characteristic along with prolonged half-life and convenient administration make dalbavancin a promising candidate for treatment of BJI, including osteomyelitis caused by Gram-positive cocci.

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DISCLOSURES

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