Update on Dalbavancin Activity, a Recently Approved Lipoglycopeptide, Tested Against Gram-positive Isolates Causing Documented Skin and Soft tissue Infections in USA and European Hospitals (2011-2013)

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INTRODUCTION

Dalbavancin is a novel lipoglycopeptide with an extended terminal serum half-life of approximately 14 days that allows for a convenient two-dose regimen (1000 mg followed by 500 mg one week later). Dalbavancin was approved in the United States (USA; 2014) and Europe (2015) for the treatment of adults with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of *Staphylococcus aureus*, including methicillin–susceptible (MSSA) and –resistant (MRSA) *S. aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus anginosus* group. A single dose of dalbavancin (1500 mg) versus a two-dose regimen for treating patients with ABSSSI is also under investigation.

During pre-clinical development, dalbavancin has demonstrated potent *in vitro* activity against *S. aureus* (including MRSA), streptococci and vancomycin–susceptible enterococci. *In vitro* activity has also been demonstrated against heterogeneous vancomycin–intermediate (hVISA; MIC range, 0.12 – 0.5 mg/L) and vancomycin–intermediate *S. aureus* (VISA; 0.5 – 2 mg/L), and other Gram–positive isolates less often recovered from human clinical specimens. This report describes dalbavancin *in vitro* activity and potency when tested against a contemporary (2011 – 2013) collection of Gram–positive isolates responsible for SSSI recovered from patients in USA and European medical centres.

MATERIALS AND METHODS

Bacterial isolates. A total of 8,399 isolates from documented SSSI were collected from 29 sites in the USA and 39 sites in the European (Belgium, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Poland, Portugal, Romania, Slovenia, Spain, Sweden, Turkey, United Kingdom and Ukraine), Russian and Israeli regions. 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 SENTRY Antimicrobial Surveillance Program (2011–2013). Isolates were initially identified by the participating laboratory and bacterial identifications 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 dry–form panels manufactured by Thermo Fisher Scientific (Cleveland, Ohio, 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) were applied, as follows: *S. aureus*, ≤0.12 mg/L; *S. anginosus* group, ≤0.12 mg/L; *S. pyogenes* and *S. agalactiae*, ≤0.12 mg/L (also applied for *S. dysgalactiae*). Breakpoint criteria for comparator agents were those from the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

RESULTS

- Dalbavancin showed $MIC_{50/90}$ values of 0.06/0.06 mg/L against *S. aureus* (99.8% susceptible overall), including MRSA. In addition, the $MIC_{50/90}$ values (0.06/0.06 mg/L) for dalbavancin against MRSA isolates from the USA and European region were equivalent (**Tables 1** and **2**).
- When tested against MRSA, dalbavancin ($MIC_{50/90}$, 0.06/0.06 mg/L) MIC results were at least 4-fold lower than those obtained for vancomycin ($MIC_{50/90}$, 1/1 mg/L), daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L) or linezolid ($MIC_{50/90}$, 1/1 mg/L), regardless of geographic region (**Table 2**).
- MRSA isolates from the USA and European region exhibiting elevated vancomycin MIC results (i.e. 2 mg/L) had dalbavancin MIC_{50} results (0.06 mg/L; 93.3 – 93.8% susceptible; **Table 2**) similar to those obtained against MRSA displaying vancomycin MIC values at ≤1 mg/L (dalbavancin MIC_{50} results, 0.06 mg/L; 99.7%; data not shown).
- Daptomycin showed MIC_{50} results (0.5 mg/L; 75.0 – 96.7% susceptible; **Table 2**) against MRSA with elevated vancomycin MIC results (i.e. 2 mg/L) two-fold higher than those obtained against the more susceptible MRSA counterpart group (MIC_{50}, 0.25 mg/L, 99.7 – 100.0% susceptible; data not shown).
- Dalbavancin ($MIC_{50/90}$, ≤0.03/≤0.03 mg/L; 100.0% susceptible), penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 mg/L; 100.0% susceptible) and daptomycin ($MIC_{50/90}$, ≤0.06/≤0.06-0.12 mg/L; 100.0% susceptible) showed highest *in vitro* activities against *S. pyogenes* and *S. dysgalactiae* from the USA and Europe (**Table 2**).
- Dalbavancin ($MIC_{50/90}$, ≤0.03/0.06 mg/L; 97.3 − 97.8% susceptible) and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 mg/L; 100.0% susceptible) had highest *in vitro* activities against *S. agalactiae* from the Europe and USA (**Table 2**).
- *S. anginosus* group isolates were very susceptible to dalbavancin ($MIC_{50/90}$, ≤0.03/≤0.03 mg/L; 100.0% susceptible), as well as penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 – 0.12 mg/L; 96.0 – 97.9% susceptible) and vancomycin ($MIC_{50/90}$, 0.5 – 1/1 mg/L; 100.0% susceptible; **Table 2**).

Table 1. Activity and spectrum of dalbavancin against contemporary *S. aureus* and streptococci causing SSSIs in USA, and European and adjacent regions.

Pathogens[a] (no. tested)	MIC (mg/L)		Number (cumulative %) inhibited at MIC (mg/L)[b]				
	50%	90%	≤0.03	0.06	0.12	0.25	0.5
S. aureus (7,473)	0.06	0.06	2095 (28.0)	**4688 (90.8)**	676 (99.8)	12 (100.0)	2 (100.0)
MSSA (4,495)	0.06	0.06	1239 (27.6)	**2815 (90.2)**	438 (99.9)	3 (100.0)	
MRSA (2,978)	0.06	0.06	856 (28.7)	**1873 (91.6)**	238 (99.6)	9 (99.9)	2 (100.0)
Vancomycin MIC ≤1 mg/L (2,932)	0.06	0.06	853 (29.1)	**1844 (92.0)**	227 (99.7)	8 (100.0)	
Vancomycin MIC = 2 mg/L (46)	0.06	0.12	3 (6.5)	**29 (69.6)**	11 (93.5)	1 (95.7)	2 (100.0)
S. pyogenes (512)	≤0.03	≤0.03	**480 (93.8)**	26 (98.8)	6 (100.0)		
S. agalactiae (283)	≤0.03	0.06	**234 (82.7)**	30 (93.3)	12 (97.5)	7 (100.0)	
S. dysgalactiae (58)	≤0.03	≤0.03	**53 (91.4)**	4 (98.3)	1 (100.0)		
S. anginosus group (73)	≤0.03	≤0.03	**73 (100.0)**				

a. MSSA=methicillin-susceptible *S. aureus*; MRSA=methicillin-resistant *S. aureus*.
b. Dalbavancin modal MIC results are in bold. Underlined percentages represent dalbavancin susceptibility rates using the FDA-approved breakpoint for primary indicated species (all ≤0.12 mg/L; *S. pyogenes* and *S. agalactiae* breakpoint [≤0.12 mg/L] also applied for *S. dysgalactiae*).

Table 2. Antimicrobial activity of dalbavancin and comparator agents against Gram-positive clinical isolates from USA, and European and adjacent regions.

Organism[a]/ Antimicrobial agent (no. USA/Europe)	MIC_{50} and MIC_{90} (mg/L):				%Susceptible/%Intermediate/ %Resistant[b]:	
	USA		Europe		USA	Europe
MRSA (2319/659)						
Dalbavancin	0.06	0.06	0.06	0.06	99.7 / - / -	99.5 / - / -
Vancomycin	1	1	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Teicoplanin	≤2	≤2	≤2	≤2	99.9 / 0.0 / 0.1	99.2 / 0.0 / 0.8
Daptomycin	0.25	0.5	0.25	0.5	>99.9 / 0.0 / <0.1	99.1 / 0.0 / 0.9
Linezolid	1	1	1	1	99.9 / 0.0 / 0.1	99.7 / 0.0 / 0.3
Erythromycin	>16	>16	>16	>16	11.6 / 0.3 / 88.1	33.1 / 0.5 / 66.4
Clindamycin	≤0.25	>2	≤0.25	>2	80.4 / 0.4 / 19.2	68.5 / 0.8 / 30.7
Tetracycline	≤0.25	≤0.25	≤0.25	>8	93.9 / 1.2 / 4.9	83.5 / 0.0 / 16.5
Levofloxacin	4	>4	>4	>4	39.6 / 3.0 / 57.4	18.5 / 1.5 / 80.0
TMP/SMX[c]	≤0.5	≤0.5	≤0.5	≤0.5	98.2 / 0.2 / 1.6	98.2 / 0.3 / 1.5
MRSA, vancomycin MIC = 2 mg/L (30/16)						
Dalbavancin	0.06	0.12	0.06	0.12	93.3 / - / -	93.8 / - / -
Vancomycin	2	2	2	2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Teicoplanin	≤2	≤2	≤2	4	90.0 / 0.0 / 10.0	75.0 / 0.0 / 25.0
Daptomycin	0.5	1	0.5	2	96.7 / 0.0 / 3.3	75.0 / 0.0 / 25.0
Linezolid	1	2	1	2	100.0 / 0.0 / 0.0	93.8 / 0.1 / 6.3
Erythromycin	>16	>16	>16	>16	6.7 / 0.0 / 93.3	31.3 / 0.1 / 68.8
Clindamycin	≤0.25	>2	≤0.25	>2	60.0 / 0.0 / 40.0	60.0 / 0.0 / 40.0
Tetracycline	≤0.25	0.5	≤0.25	>8	90.0 / 6.7 / 3.3	87.5 / 0.0 / 12.5
Levofloxacin	>4	>4	>4	>4	13.3 / 0.0 / 86.7	12.5 / 0.0 / 87.5
TMP/SMX[c]	≤0.5	≤0.5	≤0.5	≤0.5	96.7 / 0.0 / 3.3	100.0 / 0.0 / 0.0
S. pyogenes (289/223)						
Dalbavancin	≤0.03	≤0.03	≤0.03	≤0.03	100.0 / - / -	100.0 / - / -
Penicillin	≤0.06	≤0.06	≤0.06	≤0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Vancomycin	0.25	0.5	0.25	0.5	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Teicoplanin	≤2	≤2	≤2	≤2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Daptomycin	≤0.06	≤0.06	≤0.06	≤0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Linezolid	1	1	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Erythromycin	≤0.12	1	≤0.12	0.5	88.6 / 0.3 / 11.1	89.2 / 0.9 / 9.9
Clindamycin	≤0.25	≤0.25	≤0.25	≤0.25	96.5 / 0.0 / 3.5	97.7 / 0.0 / 2.3
Tetracycline	≤0.25	>8	≤0.25	>8	88.1 / 0.0 / 11.9	71.0 / 0.0 / 29.0
Levofloxacin	0.5	1	0.5	1	93.4 / 6.6 / 0.0	93.3 / 6.7 / 0.0
S. agalactiae (148/135)						
Dalbavancin	≤0.03	0.06	≤0.03	0.06	97.3 / - / -	97.8 / - / -
Penicillin	≤0.06	≤0.06	≤0.06	≤0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Vancomycin	0.5	0.5	0.5	0.5	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Teicoplanin	≤2	≤2	≤2	≤2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Daptomycin	0.25	0.25	0.25	0.25	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Linezolid	1	1	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Erythromycin	1	>16	≤0.12	>16	47.3 / 0.7 / 52.0	67.4 / 1.5 / 31.1
Clindamycin	≤0.25	>2	≤0.25	>2	70.9 / 0.0 / 29.1	83.0 / 0.0 / 17.0
Tetracycline	>8	>8	>8	>8	13.6 / 0.0 / 86.4	14.2 / 1.5 / 84.3
Levofloxacin	0.5	1	0.5	1	98.6 / 1.4 / 0.0	97.0 / 1.5 / 1.5
S. dysgalactiae (11/47)						
Dalbavancin	≤0.03	≤0.03	≤0.03	≤0.03	100.0 / - / -	100.0 / - / -
Penicillin	≤0.06	≤0.06	≤0.06	≤0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Vancomycin	0.25	0.25	0.25	0.25	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Teicoplanin	≤2	≤2	≤2	≤2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Daptomycin	≤0.06	≤0.06	≤0.06	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Linezolid	1	1	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Erythromycin	≤0.12	≤0.12	≤0.12	4	100.0 / 0.0 / 0.0	80.9 / 0.0 / 19.1
Clindamycin	≤0.25	≤0.25	≤0.25	≤0.25	100.0 / 0.0 / 0.0	95.7 / 0.0 / 4.3
Tetracycline	4	32	0.5	>8	36.4 / 9.1 / 54.5	53.2 / 4.2 / 42.6
Levofloxacin	0.5	0.5	0.5	1	100.0 / 0.0 / 0.0	95.7 / 4.3 / 0.0
S. anginosus group (25/48)						
Dalbavancin	≤0.03	≤0.03	≤0.03	≤0.03	100.0 / - / -	100.0 / - / -
Penicillin	≤0.06	0.12	≤0.06	≤0.06	96.0 / 4.0 / 0.0	97.9 / 2.1 / 0.0
Vancomycin	1	1	0.5	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Teicoplanin	≤2	≤2	≤2	≤2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Daptomycin	0.25	0.5	0.25	0.5	- / - / -	- / - / -
Linezolid	0.5	1	1	1	- / - / -	- / - / -
Erythromycin	≤0.12	≤0.12	≤0.12	>16	- / - / -	- / - / -
Clindamycin	≤0.25	≤0.25	≤0.25	>2	96.0 / 0.0 / 4.0	83.3 / 0.0 / 16.7
Tetracycline	0.5	32	0.5	>8	- / - / -	- / - / -
Levofloxacin	0.5	1	0.5	1	- / - / -	- / - / -

a. MRSA = methicillin-resistant *S. aureus*.
b. Dalbavancin FDA-approved breakpoint for primary indicated species (all ≤0.12 mg/L). *S. pyogenes* and *S. agalactiae* breakpoint (≤0.12 mg/L) also applied for *S. dysgalactiae*. Breakpoint criteria for comparator agents were those from EUCAST (2015), as available."-" breakpoint not available.
c. Trimethoprim/sulfamethoxazole.

CONCLUSIONS

- This study evaluated the *in vitro* activities of dalbavancin and comparator agents against a recent collection of Gram-positive clinical isolates implicated in SSSIs, including MRSA, from USA and European hospitals.
- Dalbavancin had *in vitro* potency greater or similar to comparators against indicated species causing SSSI, including *S. aureus* isolates with decreased susceptibility to vancomycin. In addition, no differences in dalbavancin *in vitro* activities were observed between geographic regions.
- Dalbavancin represents an important new addition to the anti-Gram-positive armamentarium, allowing a novel and convenient two-dose regimen.

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REFERENCES

1. Boucher HW, Wilcox M, Talbot GH, Puttagunta S, Das AF, Dunne MW (2014). Once-weekly dalbavancin versus daily conventional therapy for skin infection. *N Engl J Med* 370: 2169-2179.
2. Citron DM, Tyrrell KL, Goldstein EJ (2014). Comparative *in vitro* activities of dalbavancin and seven comparator agents against 41 *Staphylococcus* species cultured from osteomyelitis infections and 18 VISA and hVISA strains. *Diagn Microbiol Infect Dis* 79: 438-440.
3. Clinical and Laboratory Standards Institute (2012). *M07-A9. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; Approved Standard: Ninth edition*. Wayne, PA, USA.
4. Clinical and Laboratory Standards Institute (2015). *M100-S25. Performance standards for antimicrobial susceptibility testing: 25th Informational Supplement.* Wayne, PA, USA
5. Dalvance™ Package Insert (2014). Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021883s000lbl.pdf. Accessed July 2014.
6. EUCAST (2015). Breakpoint tables for interpretation of MICs and zone diameters. Version 5.0, January 2015. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 2015.
7. Jones RN, Flamm RK, Sader HS (2013). Surveillance of dalbavancin potency and spectrum in the United States (2012). *Diagn Microbiol Infect Dis* 76: 122-123.
8. Jones RN, Stilwell MG (2013). Comprehensive update of dalbavancin activity when tested against uncommonly isolated streptococci, *Corynebacterium* spp., *Listeria monocytogenes*, and *Micrococcus* spp. (1357 strains). *Diagn Microbiol Infect Dis* 75: 304-307.