Potency of Dalbavancin Tested Against 37,258 Gram-positive Cutaneous Pathogens from USA Medical Centers (2006-2009)

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AMENDED ABSTRACT

Background: Dalbavancin (DALB) is a highly potent investigational lipoglycopeptide undergoing Phase 3 clinical development for acute bacterial skin and skin structure infections (ABSSSI). An in vitro evaluation of contemporary (2006-2009) activity was completed against USA Gram-positive pathogens, including species that predominate in ABSSSI, using validated reference broth microdilution methods (CLSI; M07-A8, 2009).

Methods: A total of 9,064-10,006 strains/year (2006-2009) were tested by a broth microdilution test validated against the CLSI susceptibility (S) method, which includes addition of 0.002% polysorbate-80 to minimize DALB binding to panel plastic surfaces. Organisms from 75 hospitals (all 9 USA Census Regions) in 37 states and DC were sampled in five organism groups: *S. aureus* (SA; 22,425 strains, 55% MRSA), coagulase-negative staphylococci (CoNS; 4,637 strains, 73% MR), β-hemolytic streptococci (BHS; 2,623 strains), viridans group streptococci (VGS; 1,112 strains) and enterococci (ENT; 6,461 strains).

Results: Among 22,425 SA, the DALB $MIC_{50/90}$ was 0.06/0.12 µg/ml and was the same for the MRSA subset (Table). DALB CoNS activity was comparable to SA (MIC_{90}, 0.12 µg/ml), and was even more potent against BHS (MIC_{90}, ≤0.03 µg/ml) and VGS (MIC_{90}, 0.06 µg/ml). All MIC values for *S. pyogenes* were ≤0.12 µg/ml. Among these isolates, only a single CoNS strain had DALB MIC >0.5 µg/ml. Among ENT, activity of DALB vs. *E. faecalis* was similar to staphylococci; however, as expected, VanA isolates (more frequent in *E. faecium*) were considerably less susceptible. Based on MIC_{50} DALB was ≥16-fold more active than vancomycin and linezolid against all groups of Gram-positive pathogens.

Abstract Table

Pathogen group (no. tested)	DALB MIC distribution (no. strains)							MIC (µg/ml)	
	≤0.03	0.06	0.12	0.25	0.5	1	≥2	50%	90%
SA (22,425)	3,917	16,085	2,323	119	1	-	-	0.06	0.12
MSSA (10,070)	1,811	7,137	1,072	50	-	-	-	0.06	0.12
MRSA (12,355)	2,106	8,928	1,251	69	1	-	-	0.06	0.12
CoNS (4,637)	1,843	2,077	590	113	11	1	-	0.06	0.12
BHS (2,623)	2,419	153	42	9	-	-	-	≤0.03	≤0.03
VGS (1,112)	982	112	17	1	-	-	-	≤0.03	0.06
ENT (6,461)	1,529	2,438	600	106	69	81	1,638	0.06	>4

Conclusions: DALB MIC_{90} values against SA, the MRSA subset and *S. pyogenes* were ≤0.12 µg/ml. DALB demonstrates consistently broad and potent in vitro activity against a current (2006-2009) collection of Gram-positive organisms from the USA including the organisms most prevalent in ABSSSI.

INTRODUCTION

Dalbavancin (also known as BI397, MDL 63,399, A-A1, VER001) is an investigational semisynthetic lipoglycopeptide with an elimination half-life allowing once weekly dosing with initial reports of high clinical success and safety in Phase 2 and 3 trials. The spectrum of dalbavancin most closely resembles that of teicoplanin, however it has greater potency against some organism groups. The compound is derived from a natural glycopeptide (A-40,926) produced by a 3,3-dimethylaminopropyl amide substitution on the peptide carboxyl group. Such modifications of existing structures of Gram-positive-active antimicrobial agents have been necessary to address emerging resistances to glycopeptides, as well as fostering the development of novel structures such as the oxazolidinones, streptogramin combinations and other classes

In vitro international resistance surveillance programs for dalbavancin were initiated as early as 2002. The 2006-2009 results for the United States (USA) are presented here. A total of 37,258 Gram-positive cocci were tested, using validated reference methods of the Clinical and Laboratory Standards Institute (CLSI). Results from other regions (Europe, Asia-Pacific, Latin America) and a worldwide collection of staphylococci numbering more than 100,000 organisms have been presented elsewhere (ECCMID, 2011).

MATERIALS AND METHODS

Bacterial species tested: All 37,258 Gram-positive pathogens were isolated in USA medical centers over the following years: 2006 (9,352 strains), 2007 (10,006 strains), 2008 (9,064 strains), and 2009 (8,826 strains). A total of 37 states and the District of Columbia were sampled, encompassing all 9 USA Census Regions. At least 31.5% of the strains came from bacteremias with the other common sites of infection being skin and skin structure, and the lower respiratory tract (pneumonia). The distribution of organisms was: *S. aureus* (22,425 strains; 55.1% methicillin-resistant [MRSA]), coagulase-negative staphylococci (CoNS; 4,637 strains, 86.2% methicillin-resistant), β-hemolytic streptococci (2,623 strains; 36.4% *S. pyogenes* and 49.0% *S. agalactiae*), viridans group streptococci (1,112 strains), and enterococci (6,461 strains).

Susceptibility testing: The MIC results were generated by the reference CLSI method (M07-A8, 2009) with concurrent quality control (QC) guided by CLSI document M100-S21 (2011). All QC results were within range for dalbavancin (Anderegg et al., 2003) and multiple comparison agents.

The method used was a dry-form product (SensiTitre panels; TREK Diagnostic, Cleveland, Ohio, USA) validated by Jones et al., (2004) as being comparable to the CLSI M07-A8 method. The accuracy was very high having the same results in 76.2% of MIC comparisons and 98.6% ± one doubling dilution step using a collection of 429 organisms. Reproducibility was also assessed (± one doubling dilution) at 100.0%. Reference dalbavancin MIC values in this cited study were tested with a 0.002% polysorbate-80 surfactant supplement to minimize drug binding to panel plastics.

RESULTS

- This comprehensive sample of important Gram-positive pathogens (37,258 strains) from 75 hospitals in the USA was tested against dalbavancin and selected comparators by reference methods (2006-2009; see Tables 1 and 2)
- Table 1 illustrates the potent dalbavancin activity against *S. aureus* ($MIC_{50/90}$, 0.06/0.12 µg/ml) and CoNS ($MIC_{50/90}$, 0.06/0.12 µg/ml), regardless of methicillin susceptibility patterns. All *S. aureus* were inhibited by ≤0.5 µg/ml of dalbavancin with a clear modal MIC at 0.06 µg/ml. Only one strain of *S. aureus* had a MIC at 0.5 µg/ml.
- Dalbavancin was four-fold more active than daptomycin, 16-fold more potent than vancomycin and linezolid when tested against *S. aureus* isolates (22,425 strains, see Tables 1 and 2) from these USA medical centers.
- Dalbavancin was very active against β-hemolytic ($MIC_{50/90}$, ≤0.03/≤0.03 µg/ml) and viridans group ($MIC_{50/90}$, ≤0.03/0.06 µg/ml) streptococci; all USA streptococcal isolates were inhibited at ≤0.25 µg/ml (Tables 1 and 2).
- Among enterococci, reduced susceptibility to dalbavancin was encountered among *E. faecium* isolates, where vancomycin resistance, in particular the VanA phenotype is most prevalent, and less frequently among *E. faecalis* (Table 1). The MIC_{90} of dalbavancin for *E. faecalis* was 0.12 µg/ml.
- Various comparison agents tested between 2006 and 2009 exhibited evolving resistance patterns (Table 2, see footnotes d, f, g, h and i), including daptomycin, levofloxacin, linezolid and vancomycin.

Table 1. Dalbavancin MIC distributions for 37,258 Gram-positive pathogens isolated from patients in USA hospitals from 2006-2009.

Organism/resistance subgroup (no. tested)[a]	Dalbavancin MIC (µg/ml) distributions (%)							MIC (µg/ml)	
	≤0.03	0.06	0.12	0.25	0.5	1	≥2	50%	90%
S. aureus									
All (22,425)	17.5	71.6	10.4	0.5	<0.1[b]	-	-	0.06	0.12
MSSA (10,070)	18.0	70.9	10.7	0.5	-	-	-	0.06	0.12
MRSA (12,355)	17.1	72.3	10.1.	0.6	<0.1[b]	-	-	0.06	0.12
CoNS									
All (4,637)	39.8	44.8	12.7	2.4	0.2	<0.1	-	0.06	0.12
MS (1,242)	47.3	41.3	10.1	1.0	0.2	<0.1	-	0.06	0.12
MR (3,395)	37.0	46.1	13.7	3.0	0.3	<0.1	-	0.06	0.12
β-hemolytic streptococci									
All (2,623)	92.2	5.8	1.6	0.3	-	-	-	≤0.03	≤0.03
S. pyogenes (956)	98.1	1.8	0.1	-	-	-	-	≤0.03	≤0.03
S. agalactiae (1,284)	86.6	9.7	3.0	0.7	-	-	-	≤0.03	0.06
Viridans group streptococci									
All (1,112)	88.3	10.1	1.5	<0.1	-	-	-	≤0.03	0.06
Enterococcus spp.									
All (6,461)	23.7	37.7	9.3	1.6	1.1	1.3	25.3	0.06	>4
E. faecalis (3,972)	34.8	53.4	7.2	0.5	<0.1	<0.1	4.0	0.06	0.12
E. faecium (2,253)	4.0	10.1	11.5	3.3	3.0	3.5	64.6	4	>4

a. MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; MS = methicillin-susceptible; MR = methicillin-resistant.
b. One strain only.

Table 2. Comparative potencies of selected agents and dalbavancin tested against USA clinical isolates (2006-2009).

Organism (no. tested)	Antimicrobial agent	MIC (µg/ml)		% susceptible:[a]	
		50%	90%	CLSI	EUCAST
S. aureus (22,425)	Dalbavancin	0.06	0.12 (0.5)[b]	-[c]	-
	Daptomycin	0.25	0.5	99.9[d]	99.9
	Teicoplanin	≤2	≤2	100	99.7
	Vancomycin	1	1	>99.9[d]	>99.9
	Oxacillin	>2	>2	44.9	44.9
	Erythromycin	>2	>2	34.1	34.3
	Clindamycin	≤0.25	>2	76.9	76.5
	Levofloxacin	≤0.5	>4	55.5	55.5
	Tetracycline	≤2	≤2	95	94.3
	TMP/SMX[e]	≤0.5	≤0.5	98.2	98.2
	Linezolid	1	2	>99.9[d]	>99.9
CoNS (4,637)	Dalbavancin	0.06	0.12 (1)[b]	-[c]	-
	Daptomycin	0.25	0.5	99.7[f]	99.7
	Teicoplanin	2	4	97.6	90.6
	Vancomycin	1	2	>99.9[f]	99.6
	Oxacillin	>2	>2	26.8	26.8
	Erythromycin	>2	>2	31.5	31.8
	Clindamycin	≤0.25	>2	64.5	63.3
	Levofloxacin	4	>4	43.5	43.5
	Tetracycline	≤2	>8	86.5	85
	TMP/SMX[e]	≤0.5	>2	62.2	62.2
	Linezolid	1	1	98.6[f]	98.6
β-hemolytic streptococci (2,623)	Dalbavancin	≤0.03	≤0.03 (0.25)[b]	-[c]	-
	Daptomycin	0.12	0.25	100	100
	Teicoplanin	≤2	≤2	-	>99.9
	Vancomycin	0.5	0.5	100	100
	Penicillin	0.03	0.06	100	100
	Erythromycin	≤0.25	>2	69	69
	Clindamycin	≤0.25	>2	85.7	86.2
	Levofloxacin	≤0.5	1	98.7[g]	95.7
	Tetracycline	>8	>8	45.9	45.9
	TMP/SMX[e]	≤0.5	≤0.5	-	98.2
	Linezolid	1	1	100	100
Viridans gr. streptococci (1,112)	Dalbavancin	≤0.03	0.06 (0.25)[b]	-[c]	-
	Daptomycin	0.25	0.5	99.7[h]	-
	Teicoplanin	≤2	≤2	-	99.6
	Vancomycin	0.5	1	99.9[h]	100
	Penicillin	0.06	1	73.7	81.2
	Erythromycin	1	>2	45.1	-
	Clindamycin	≤0.25	0.5	89.2	90.5
	Levofloxacin	1	2	91.4[h]	-
	Tetracycline	≤2	>8	61.2	-
	Linezolid	1	1	100	-
Enterococci (6,461)	Dalbavancin	0.06	>4 (>4)[b]	-[c]	-
	Daptomycin	1	2	99.9[i]	-
	Teicoplanin	≤2	>16	71.6	71.2
	Vancomycin	1	>16	70.1	70.1
	Ampicillin	≤1	>16	67	66.6
	Q/D[d]	>2	>2	32.6	37.6
	Levofloxacin	>4	>4	45.3	-
	Linezolid	1	2	99.1[i]	99.3

a. Susceptibility criteria published in 2011 by CLSI and EUCAST.
b. Highest dalbavancin MIC in parentheses (one occurrence for *S. aureus*).
c. - = no published criteria.
d. *S. aureus* had 25 strains with daptomycin MICs at 2 or 4 µg/ml; 7 strains with linezolid MICs at ≥8 µg/ml; and 4 strains with vancomycin MICs at 4 µg/ml.
e. TMP/SMX = trimethoprim/sulfamethoxazole (TMP concentration of a 1:19 ratio test) and Q/D = quinupristin/dalfopristin.
f. CoNS had 12 strains with daptomycin MICs at 2 or 4 µg/ml; 67 strains with linezolid MICs at ≥8 µg/ml; and 18 strains with vancomycin MICs at 4 or 8 µg/ml.
g. β-hemolytic streptococci had 34 strains with levofloxacin MICs at ≥4 µg/ml (only 5 were *S. pyogenes*).
h. Viridans group streptococci had 3 strains with daptomycin MICs at 2 µg/ml; 96 strains with levofloxacin MICs at ≥4 µg/ml; and only 1 strain with vancomycin MIC at 2 µg/ml.
i. Enterococci had 10 strains with daptomycin MICs at ≥8 µg/ml; and 57 strains with linezolid MICs at ≥4 µg/ml (intermediate or resistant).

CONCLUSIONS

- USA Gram-positive pathogen collection (2006-2009) of 37,258 organisms showed remarkable susceptibility of Gram-positive skin pathogens to dalbavancin with MIC_{90} results of 0.12 µg/ml for *S. aureus* and ≤0.03 µg/ml for β-hemolytic streptococci. MIC_{90}s for other streptococcal species, CoNS, and *E. faecalis* ranged from ≤0.03 to 0.12 µg/ml. Only the *E. faecium* isolates, which included a large proportion of vancomycin-non-susceptible (mainly VanA) strains, had reduced susceptibility to dalbavancin (MIC_{90} >4 µg/ml).
- Among staphylococci, dalbavancin MIC values above 0.25 µg/ml were rare (<0.1% for *S. aureus* and 0.3% for CoNS). No dalbavancin MIC values above 0.25 µg/ml were observed for streptococci.
- Dalbavancin MIC values for USA Gram-positive organisms have remained stable in surveillance programs over the last seven years (2003-2009) of monitoring (see references and Tables 1 and 2). As dalbavancin continues in Phase 3 clinical trials for severe cutaneous infections, resistance surveillance should be extended to monitor sustained activity.

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