Dalbavancin Activity and Spectrum Evaluated Against a Contemporary (2007-2009) Worldwide Collection of Staphylococci (62,590 strains)

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ABSTRACT

Objectives: To update the in vitro profile of dalbavancin (DALB), an investigational lipoglycopeptide, for its anti-staphylococcal potency and spectrum via the testing of a collection of clinical isolates from 2006-2009. A total of 62,590 staphylococci were evaluated (14,492-17,604/year) from the Asia-Pacific region (11,692 strains), Europe (16,001), Latin America (6,711) and North America (28,186).

Methods: All organisms were susceptibility (S) tested by CLSI (M07-A8, 2009) reference MIC methods in a central laboratory design. *Staphylococcus* species from 21 countries (201 medical centers) were sampled as follows: *S. aureus* (SA: 50,271 strains; 44.5% MRSA), and coagulase-negative staphylococci (CoNS; 12,373, 76.4% methicillin-resistant [R], 23 species). DALB MIC results were determined in validated panels equivalent to reference polysorbate-80 (0.002%) containing broth media. All QC results were within published ranges (CLSI M100-S21, 2011). Most isolates came from blood (63.0%), lower respiratory or acute bacterial skin and skin structure infection (ABSSSI) sources.

Results: DALB was highly active against SA ($MIC_{50/90}$, 0.06/0.12 mg/L). Methicillin S or R did not influence DALB activity (Table) and DALB potency remained stable across the monitored time interval (2006-2009). All SA and 99.8% of CoNS were inhibited at ≤0.5 mg/L, only 30 CoNS had DALB MIC values at 1 or 2 mg/L (a number comparable to daptomycin, data not shown). DALB was 16- and four-fold more potent than vancomycin and daptomycin, respectively. The susceptibility rates of comparator agents were not superior to DALB against staphylococci e.g. daptomycin (99.8-99.9%), vancomycin (>99.9%), linezolid (99.3-99.9%), teicoplanin (70.8-99.4%) and cotrimoxazole (61.3-95.4%). No variations in DALB activity by geographic region were observed.

Pathogen (no. tested)	Cum. % inhibited at DALB MIC (mg/L): ≤0.03	0.06	0.12	0.25	0.5	1	2
S. aureus							
All (50,217)	17.3	88.3[a]	99.5	>99.9	100.0	-	-
MRSA (22,330)	16.8	87.0	99.4	>99.9	100.0	-	-
MSSA (27,887)	17.8	89.3	99.6	100.0	-	-	-
CoNS							
All (12,373)	38.0	80.7[a]	95.9	99.4	99.8	>99.9	100.0
MR (9,453)	35.0	78.4	95.1	99.3	99.7	>99.9	100.0
MS (2,920)	47.6	88.3	98.6	99.9	>99.9	100.0	-

a. Modal DALB MIC values compared favorably to 1 mg/L for vancomycin (16-fold greater) and 0.25 mg/L for daptomycin (four-fold greater).

Conclusions: DALB activity updated with contemporary staphylococcal strains worldwide through 2009 shows sustained potent inhibition and a modal MIC value at only 0.06 mg/L. This level of potency was many-fold greater than currently available glycopeptides or lipopeptide-class agents, thus warranting renewed clinical investigations for several indications where multidrug-R staphylococci may be prevalent.

INTRODUCTION

Dalbavancin (BI-397, MDL 63,399, A-A1, VER001) is a semisynthetic glycopeptide derivative of the natural glycopeptide A40926 produced by 3,3-dimethylaminopropyl amide substitution on the peptide carboxyl group. It is similar to other lipoglycopeptides in its mechanism of activity, binding to the terminal alanyl-D-alanine of nascent peptidoglycan chains and thus interfering with bacterial cell wall biosynthesis and resulting in cell death. Previous studies have demonstrated the potent activity of dalbavancin against aerobic and anaerobic Gram-positive organisms, including such clinically relevant strains as methicillin-resistant (MR) staphylococci, penicillin-resistant *Streptococcus pneumoniae* and vancomycin-resistant enterococci (*vanB* phenotypes).

Since *Staphylococcus* spp., *Enterococcus* spp., and *Streptococcus* spp. are major causes of both community-acquired and nosocomial infections, dalbavancin could be an effective agent. During the past decade, numerous studies have documented increasing rates of resistance among Gram-positive species, including MR among staphylococci, vancomycin resistance among enterococci, and penicillin and/or erythromycin resistance among streptococci. Acquisition of additional resistance mechanisms and virulence factors by these pathogens has resulted in the spread of multidrug-resistant (MDR) clones that have been detected globally, thereby compromising empirical and directed therapies. The increase in prevalence of resistant organisms and the resulting increases in morbidity and mortality has resulted in the need for development of new antimicrobials with activity against these pathogens. Therefore, we update earlier in vitro studies on dalbavancin with a summary of 2006-2009 worldwide surveillance results against the staphylococci (62,590 strains).

MATERIALS AND METHODS

Bacterial isolates: A total of 62,590 staphylococci were tested during 2006, 2007, 2008 and 2009 from 201 medical centers in 21 nations. These organisms were from North America (28,186 strains; 2 countries); Latin America (6,711 strains; 4 countries); Europe (16,001 strains; 13 countries); and the Asia-Pacific region (11,692 strains; 12 countries. The largest staphylococcal samplings came from the United States (USA; 27,062 strains), Brazil (3,204 strains), Japan (3,153 strains) and France (3,085 strains). The distribution of the forwarded strains by year was 2006 (15,455 strains), 2007 (17,601 strains), 2008 (15,042 strains) and 2009 (14,492 strains); averaging 15,648 staphylococci per year. The sources of these infection isolates were: bloodstream infections (63.0%), lower respiratory tract (13.2%) and skin and soft tissue or wound infections (23.8%).

The species tested were *Staphylococcus aureus* (50,217 strains) of which 44.5% were MRSA; and 12,373 coagulase-negative staphylococci (CoNS; 23 different species, dominantly *S. epidermidis*) of which 76.4% were resistant to methicillin.

Susceptibility testing: The MIC results were generated by the reference-quality Clinical and Laboratory Standards Institute method (CLSI M07-A8, 2009) with concurrent quality control (QC) guided by CLSI document M100-S21 (2011). All QC results were within ranges 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 were tested with a 0.002% polysorbate-80 surfactant supplement to minimize drug binding to panel plastics.

RESULTS

- *S. aureus* was very susceptible to dalbavancin ($MIC_{50/90}$, 0.06/0.12 mg/L) regardless of methicillin susceptibility (Table 1), and the highest MIC was only 0.5 mg/L for this organism collection (2006-2009). This potency versus *S. aureus*, was four- and eight-fold greater than daptomycin and vancomycin, respectively (Table 2) and 16-fold more active than linezolid.

- CoNS species were equally susceptible to dalbavancin ($MIC_{50/90}$, 0.06/0.12 mg/L), but 0.2% of isolates had MIC values at either 1 or 2 mg/L (Tables 1 and 3). Methicillin resistance (MR) did not negatively influence dalbavancin activity (Table 1), although MR-CoNS were the greatest contributor (28 of 30 strains) of isolates with higher dalbavancin MIC results (≥1 mg/L).

- Across all staphylococci tested, 65.4% of dalbavancin MIC values were at 0.06 mg/L (Table 1 and Figure 1), and 98.8% of *S. aureus* and CoNS were inhibited at ≤0.12 mg/L.

- Coverage of MRSA by comparison agents at CLSI/EUCAST breakpoints were: daptomycin (99.9/99.9%), teicoplanin (100.0/98.8%), vancomycin (>99.9/>99.9%), quinupristin/dalfopristin (99.7/99.7%), TMP/SMX (99.6/91.6%) and linezolid (>99.9/>99.9%). Mupirocin high-level resistance was detected at a rate of 2.4%.

Table 1. Dalbavancin MIC distributions for 62,590 staphylococci collected worldwide (2006-2009).

Organisms/ subset (no. tested)	no. (cum. % inhibited) by MIC in mg/L: ≤0.06	0.06	0.12	0.25	0.5	1	2
S. aureus							
All (50,217)	8,702 (17.3)	35,627 (88.3)	5,655 (99.5)	229 (>99.9)	4 (100.0)	-	-
MSSA (27,887)	4,952 (17.8)	19,960 (89.3)	2,874 (99.6)	101 (100.0)	-	-	-
MRSA (22,330)	3,750 (16.8)	15,667 (87.0)	2,781 (99.4)	128 (>99.9)	4 (100.0)	-	-
CoNS[a]							
All (12,373)	4,701 (38.0)	5,286 (80.7)	1,880 (95.9)	433 (99.4)	43 (99.8)	23 (>99.9)	7 (100.0)
MS (2,920)	1,389 (47.6)	1,188 (88.3)	301 (98.6)	38 (99.9)	2 (>99.9)	2 (100.0)	-
MR (9,453)	3,312 (35.0)	4,098 (78.4)	1,579 (95.1)	395 (99.3)	41 (99.7)	21 (>99.9)	7 (100.0)

a. CoNS = coagulase-negative staphylococci, MR = methicillin-resistant, MS = methicillin-susceptible, MRSA = methicillin-resistant *S. aureus*, and MSSA = methicillin-susceptible *S. aureus*.

Table 2. Comparative activity of dalbavancin and 13 other agents tested against *S. aureus* strains (50,217 strains), 2006-2009.

Organism subset (no. tested)	Antimicrobial agent	MIC (mg/L) 50%	90%	Range	% susceptible:[a] CLSI	EUCAST
All (50,217)	Dalbavancin	0.06	0.12	≤0.03-0.5	-[b]	-[b]
	Daptomycin	0.25	0.5	≤0.06-4	>99.9	>99.9
	Teicoplanin	≤2	≤2	≤2-8	100.0	99.4
	Vancomycin	1	1	≤0.12-4	>99.9	>99.9
	Oxacillin	0.5	>2	≤0.25->2	55.5	55.5
	Erythromycin	>2	>2	≤0.25->2	48.1	48.4
	Clindamycin	≤0.25	>2	≤0.25->2	76.7	76.2
	Q/D[c]	0.5	0.5	≤0.25->2	99.8	99.8
	Levofloxacin	≤0.5	>4	≤0.5->4	60.9	60.9
	Gentamicin	≤2	>8	≤2->8	87.5	87.0
	Tetracycline	≤2	>8	≤2->8	87.5	87.0
	TMP/SMX[c]	≤0.5	≤0.5	≤0.5->2	95.4	95.4
	Linezolid	2	2	≤0.06->8	>99.9	>99.9
	Mupirocin	≤4	≤4	≤4->256	98.4[d]	98.4[d]
MSSA (27,887)	Dalbavancin	0.06	0.12	≤0.03-0.25	-[b]	-[b]
	Daptomycin	0.25	0.5	≤0.06-4	>99.9	>99.9
	Teicoplanin	≤2	≤2	≤2-8	100.0	99.9
	Vancomycin	1	1	≤0.12-4	>99.9	>99.9
	Erythromycin	≤0.25	>2	≤0.25->2	76.5	76.9
	Clindamycin	≤0.25	≤0.25	≤0.25->2	95.3	94.8
	Q/D[c]	≤0.25	0.5	≤0.25->2	99.9	99.9
	Levofloxacin	≤0.5	≤0.5	≤0.5->4	92.4	92.4
	Gentamicin	≤2	≤2	≤2->8	96.4	96.1
	Tetracycline	≤2	>8	≤2->8	93.7	93.3
	TMP/SMX[c]	≤0.5	≤0.5	≤0.5->2	98.5	98.5
	Linezolid	2	2	≤0.06-4	100.0	100.0
	Mupirocin	≤4	≤4	≤4->256	99.0[d]	99.0[d]
MRSA (22,330)	Dalbavancin	0.06	0.12	≤0.06-0.5	-[b]	-[b]
	Daptomycin	0.25	0.5	≤0.06-4	99.9	99.9
	Teicoplanin	≤2	≤2	≤2-8	100.0	98.8
	Vancomycin	1	1	≤0.12-4	>99.9	>99.9
	Erythromycin	>2	>2	≤0.25->2	12.5	12.7
	Clindamycin	≤0.25	>2	≤0.25->2	53.4	53.0
	Q/D[c]	0.5	1	≤0.25->2	99.7	99.7
	Levofloxacin	>4	>4	≤0.5->4	21.7	21.7
	Gentamicin	≤2	>8	≤2->8	76.2	75.7
	Tetracycline	≤2	>8	≤2->8	79.8	79.1
	TMP/SMX[c]	≤0.5	≤0.5	≤0.5->2	91.6	91.6
	Linezolid	1	2	0.12->8	>99.9	>99.9
	Mupirocin	≤4	≤4	≤4->256	97.6[d]	97.6[d]

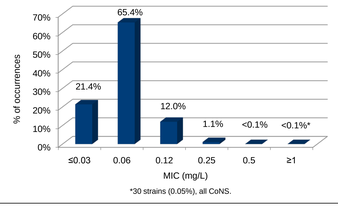
a. Year 2011 breakpoint criteria of CLSI and EUCAST.
b. - = no interpretive criteria.
c. Q/D = quinupristin/dalfopristin and TMP/SMX = trimethoprim/sulfamethoxazole (1:19 ratio, TMP concentration only).
d. High-level resistance breakpoint at ≤256 mg/L as susceptible.

Table 3. Comparative activity of dalbavancin and 13 other agents tested against CoNS strains (12,373 strains), 2006-2009.

Organism subset (no. tested)	Antimicrobial agent	MIC (mg/L) 50%	90%	Range	% susceptible:[a] CLSI	EUCAST
All (12,373)	Dalbavancin	0.06	0.12	≤0.03-2	-[b]	-[b]
	Daptomycin	0.25	0.5	≤0.06-4	99.8	99.8
	Teicoplanin	≤2	4	≤2->16	97.6	70.8
	Vancomycin	1	2	≤0.12-8	>99.9	99.4
	Oxacillin	>2	>2	≤0.25->2	23.6	23.6
	Erythromycin	>2	>2	≤0.25->2	34.0	34.2
	Clindamycin	≤0.25	>2	≤0.25->2	65.9	64.2
	Q/D[c]	≤0.25	0.5	≤0.25->2	99.1	99.1
	Levofloxacin	4	>4	≤0.5->4	43.2	43.2
	Gentamicin	≤2	>8	≤2->8	61.1	55.5
	Tetracycline	≤2	>8	≤2->8	85.3	82.8
	TMP/SMX[c]	≤0.5	>2	≤0.5->2	61.5	61.5
	Linezolid	1	1	≤0.06->8	99.3	99.3
	Mupirocin	≤4	>256	≤4->256	81.3[d]	81.3[d]
MS-CoNS (2,920)	Dalbavancin	0.06	0.12	≤0.03-1	-[b]	-[b]
	Daptomycin	0.25	0.5	≤0.06-4	99.7	99.7
	Teicoplanin	≤2	4	≤2-16	99.4	85.4
	Vancomycin	1	2	≤0.12-4	100.0	99.7
	Erythromycin	≤0.25	>2	≤0.25->2	64.5	63.7
	Clindamycin	≤0.25	≤0.25	≤0.25->2	92.8	91.9
	Q/D[c]	≤0.25	≤0.25	≤0.25->2	99.8	99.8
	Levofloxacin	≤0.5	4	≤0.5->4	86.0	86.0
	Gentamicin	≤2	≤2	≤2->8	95.5	94.4
	Tetracycline	≤2	8	≤2->8	89.4	88.1
	TMP/SMX[c]	≤0.5	>2	≤0.5->2	88.0	88.0
	Linezolid	1	1	≤0.06->8	99.8	99.8
	Mupirocin	≤4	≤4	≤4->256	94.2[d]	94.2[d]
MR-CoNS (9,453)	Dalbavancin	0.06	0.12	≤0.03-2	-[b]	-[b]
	Daptomycin	0.25	0.5	≤0.06-4	99.8	99.8
	Teicoplanin	≤2	8	≤2->16	97.1	66.3
	Vancomycin	2	2	≤0.12-8	>99.9	99.3
	Erythromycin	>2	>2	≤0.25->2	24.6	24.7
	Clindamycin	≤0.25	>2	≤0.25->2	57.6	55.6
	Q/D[c]	≤0.25	0.5	≤0.25->2	98.8	98.8
	Levofloxacin	4	>4	≤0.5->4	30.0	30.0
	Gentamicin	4	>8	≤2->8	50.4	43.5
	Tetracycline	≤2	>8	≤2->8	84.0	81.2
	TMP/SMX[c]	2	>2	≤0.5->2	53.0	53.0
	Linezolid	1	1	≤0.06->8	99.2	99.2
	Mupirocin	≤4	>256	≤4->256	77.3[d]	77.3[d]

a. Year 2011 breakpoint criteria of CLSI and EUCAST
b. - = no interpretive criteria
c. Q/D = quinupristin/dalfopristin and TMP/SMX = trimethoprim/sulfamethoxazole (1:19 ratio, TMP concentration only)
d. High-level resistance breakpoint at ≤256 mg/L as susceptible.

Figure 1. MIC distribution for dalbavancin tested against all staphylococci (62,590 strains; 2006-2009) worldwide.



*30 strains (0.05%), all CoNS.

CONCLUSIONS

- Dalbavancin anti-staphylococcal activity remains stable (MIC_{90}, 0.12 mg/L) worldwide when compared to previously published surveillance reports dating from 2003 in the USA and Europe (Jones et al., 2005).
- Dalbavancin was equally potent (MIC_{90} values at 0.12 mg/L) against *S. aureus* and CoNS, as well as methicillin-susceptible or resistant isolates (Table 1).
- Dalbavancin international surveillance programs should be sustained as this novel lipoglycopeptide continues Phase 3 clinical development for complicated skin and soft tissue infections.

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