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Worldwide Assessment of Dalbavancin Activity and Spectrum (2002)

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ABSTRACT

Background

Continuing appearance of new resistance (R) mechanisms and the increased frequency of existing R, requires the development of alternative antimicrobial agents. Dalbavancin (DAL) is an amide glycopeptide derivative of A40926 with an extended elimination half-life. A large collection of clinical strains were tested to establish DAL spectrum and potency.

Methods

DAL and over 20 comparators were tested against 6,339 recent (2002) clinical isolates from the Americas and Europe using NCCLS (M7-A6) susceptibility (S) testing methods. The characteristics of this collection were: oxacillin (OXA)-R *S. aureus* (SA) = 39% and CoNS = 80%; VRE = 10% and PEN-non-S *S. pneumoniae* = 28%.

Results

Species distribution and MIC data for these highly represented species.

	DAL MIC (µg/ml):			
Organism (no. tested)	50%	90%	Range	% ≤ 1 µg/ml
S. aureus (2,992)	0.06	0.06	≤0.015-0.5	100.0
S. pneumoniae (1,396)	≤0.015	0.03	≤0.015-0.06	100.0
Coag.-neg. staphylococci (774)	0.03	0.06	≤0.015-0.5	100.0
Enterococci (753)	0.03	0.12	≤0.015->32	92.6
β-streptococci (234)	≤0.015	0.06	≤0.015-0.25	100.0
viridans group streptococci (134)	≤0.015	0.03	≤0.015-0.06	100.0

OXA- or macrolide-R had no effect on DAL potency among staphylococci or streptococci. DAL MIC for some VRE (20 *E. faecalis*, 55 *E. faecium*) were low (27%; ≤1 µg/ml), similar to the teicoplanin-S rate. DAL activity did not vary by species between strains isolated in North America, Europe or Latin America. Fifty-six tested strains (8 *Bacillus* spp. 11 *Corynebacterium* spp., *G. morbillarum*, 8 *L. monocytogenes*, 2 *Micrococcus* spp., 16 *S. bovis*) not cited in the Table had DAL MIC_{90} ranging from 0.03 - 0.12 µg/ml; highest MIC at 0.25 µg/ml. DAL MICs were lower than those of available glycopeptides.

Conclusions

This DAL activity survey indicates that this glycopeptide has significant activity, superior to available agents in the class, and the potency was uniform among continents. Some VRE were inhibited by very low concentrations of DAL. Further clinical development seems warranted.

INTRODUCTION

Increasing antimicrobial resistance among bacterial pathogens such as *S. aureus*, coagulase negative staphylococci (CoNS) and enterococci has prompted attempts to develop new antimicrobial agents active against multi-drug resistant Gram positive pathogens. The effectiveness of the glycopeptides (vancomycin and teicoplanin) has diminished due to the emergence and dissemination of new resistance mechanisms. Enterococcal isolates with the VanA phenotype and multi-drug-resistant staphylococcal isolates are increasingly being recognized worldwide. Novel Gram-positive active compounds such as linezolid, Synercid®, newer quinolones, and telithromycin (a ketolide) have been developed recently; however, resistance to these agents has been reported among several species.

Dalbavancin (formerly BI-397) is a dimethylaminopropyl amide derivative of the glycopeptide MDL 62479. Earlier dalbavancin studies showed promising results against frequently isolated Gram-positive pathogens without regard to other resistance markers. In addition, *in vivo* studies have shown that dalbavancin effectively reduced bacterial loads in mouse models of septicaemia, endocarditis and lung infection in immunocompetent as well as neutropenic mice. Dalbavancin also showed an extended elimination serum half-life allowing once-daily dosing in animal models and early Phase II trials have proven clinical efficacy in cutaneous infections when dosed once-weekly.

In the present study we evaluated the spectrum and potency of dalbavancin against a large collection of recent clinical isolates from around the globe.

MATERIALS AND METHODS

Bacterial Isolates

Isolates were collected from more than 70 medical centers in North and South America and in Europe for the year 2002. A total of 6,339 Gram-positive isolates were evaluated and included: *S.aureus* (2,992; 39.3% resistant to oxacillin), CoNS (774; 79.7% resistant to oxacillin), *S. pneumoniae* (1,396; 28.6% non-susceptible to penicillin), enterococci (749; 10.0% resistant to vancomycin), β-haemolytic streptococci (234), viridans group streptococci (134), *Listeria* (18), *S. bovis* (16), other Gram-positive species (22). The isolates were sent to a central monitor (Jones Microbiology Institute, North Liberty, Iowa) for confirmation of species identification and reference susceptibility testing.

Susceptibility Testing

Minimum inhibitory concentrations (MICs) were determined by the broth microdilution method described by the NCCLS. Dalbavancin was provided by Vicuron Pharmaceuticals, Inc. (King of Prussia, PA, USA) as laboratory grade powder. Powders for comparator antimicrobial agents were obtained from the respective manufacturers or purchased from Sigma (St. Louis, MO, USA). Validated dry-form panels for susceptibility testing were manufactured by Trek Diagnostics (Cleveland, OH, USA). Mueller-Hinton broth was used as a growth medium to determine MICs of non-fastidious organisms. Mueller-Hinton broth was supplemented with 2 - 5% lysed horse blood to test streptococci, *Listeria* spp. and *Corynebacterium* spp. Susceptibility and resistance breakpoints used for other antibiotics were established by the NCCLS. Breakpoints are not yet available for dalbavancin. Quality control of test procedures and reagents was monitored through routine testing of the following ATCC strains: *S. aureus* 29213, *E. faecalis* 29212, and *S. pneumoniae* 49619.

RESULTS

- The most frequently isolated pathogens were: *S. aureus* (2,992 isolates, 47%), *S. pneumoniae* (1,396 isolates, 22%), CoNS (774 isolates, 12%) and enterococci (753 isolates, 11.8%).
- All the organism groups tested except *Enterococcus* spp. were inhibited at ≤ 0.5 µg/ml of dalbavancin, and >98% of all organisms tested were inhibited at ≤ 0.12 mg/ml (Table 1).
- Dalbavancin was the most potent by weight compound against *S. aureus* and it was equally active against oxacillin-susceptible and -resistant *S. aureus* (MIC_{90}, 0.06 µg/ml for both). The highest dalbavancin MIC detected was 0.5 µg/ml (one strain) and among the comparators, only vancomycin was active against all oxacillin-resistant *S. aureus* strains (MIC_{90}, 2 µg/ml).
- CoNS also showed very low dalbavancin MIC values (MIC_{90}, 0.06 µg/ml) and all isolates were inhibited at ≤ 0.5 µg/ml. Vancomycin (MIC_{90}, 2 µg/ml) and linezolid (MIC_{90}, 1 µg/ml) were active against 100% of strains at the susceptible breakpoint, but resistance to teicoplanin (MIC_{90}, 4 µg/ml; 97.6% susceptible) and quinupristin/dalfopristin (MIC_{90}, 0.5 µg/ml; 99.4% susceptible) was detected among oxacillin-resistant isolates.
- Dalbavancin was the most active compound against *E. faecalis* (MIC_{90}, 0.06 µg/ml). However, vancomycin-resistant strains showed higher dalbavancin MIC values (MIC_{90}, 32 µg/µl) when compared to vancomycin-susceptible strains (MIC_{90}, 0.06 µg/ml).
- *E. faecium* strains were also very susceptible to dalbavancin (MIC_{90}, 0.12 µg/ml), but vancomycin-resistant *E. faecium* strains showed high MIC results for dalbavancin (MIC_{90}, 32 µg/ml) and most of the antimicrobial agents evaluated.
- Dalbavancin was highly active against both penicillin-susceptible and -non-susceptible *S. pneumoniae* strains (MIC_{90}, 0.03 µg/ml). All the isolates were inhibited at ≤ 0.25 µg/ml of dalbavancin. Dalbavancin was eight- and 128-fold more potent than ceftriaxone against penicillin-susceptible (MIC_{90}, 0.25 µg/ml) and -non-susceptible (MIC_{90}, 1 µg/ml) strains, respectively.
- β-haemolytic streptococci were highly susceptible to dalbavancin (MIC_{90} 0.06 µg/ml) and most antimicrobial agents tested, except for clindamycin (5.7% resistant) and erythromycin (17.6% resistant).
- All viridans group streptococci were inhibited at ≤ 0.06 µg/ml of dalbavancin, and its activity was not affected by resistance to penicillin (MIC_{90}, 0.03 µg/ml for both penicillin-susceptible and -non-susceptible strains) or erythromycin.
- Dalbavancin was active against all strains of less commonly isolated pathogens tested, including *S. bovis*, *Bacillus* spp., *Corynebacterium* spp. and *Listeria* spp. Dalbavancin MICs ranged from ≤ 0.015 to 0.25 µg/ml against these pathogens.

Figure 1: Cumulative % of Dalbavancin MICs among Staphylococci (3,766 isolates), Streptococci (1,780 isolates) and Enterococci (753 isolates)

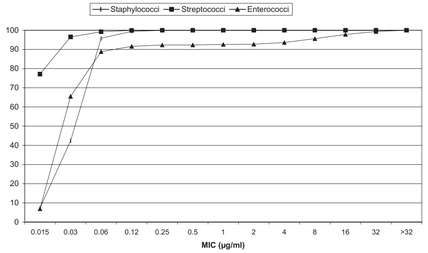

Table 1. Dalbavancin MIC Distribution for 6,336 Organisms Collected Worldwide in 2002

	Occurrences (cumulative %) at MIC in µg/ml:												
Organism (no.tested)	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
S. aureus													
Oxacillin-susceptible(1,815)	15(0.8)	581(32.8)	1,180(97.9)	37(99.9)	2(100.0)	-	-	-	-	-	-	-	-
Oxacillin-resistant (1,177)	11(0.9)	366(32.2)	745(95.3)	51(99.7)	3(99.9)	1(100.0)	-	-	-	-	-	-	-
CoNS													
Oxacillin- susceptible (157)	63(40.1)	73(86.6)	17(97.5)	3(99.4)	1(100.0)	-	-	-	-	-	-	-	-
Oxacillin-resistant (617)	187(30.4)	299(79.0)	72(90.6)	45(97.8)	12(99.8)	2(100.0)	-	-	-	-	-	-	-
E. faecalis													
Vancomycin-susceptible (586)	44(7.5)	411(77.8)	128(99.5)	1(99.7)	1(99.8)	-	-	-	1(100.0)	-	-	-	-
Vancomycin-resistant(20)	1(5.0)	-	3(20.0)	4(40.0)	-	-	-	1(45.0)	1(50.0)	1(55.5)	1(60.0)	6(90.0)	2(100.0)
E. faecium													
Vancomycin-susceptible (77)	4(5.2)	19(29.9)	38(79.2)	13(96.1)	2(98.7)	-	-	-	1(100.0)	-	-	-	-
Vancomycin-resistant(51)	-	4(7.8)	1(9.8)	1(11.8)	2(15.7)	1(17.6)	1(19.6)	-	4(21.5)	14(54.9)	15(84.3)	5(94.1)	3(100.0)
Enterococcus spp.[a] (19)	3(15.8)	7(52.6)	6(84.2)	2(94.7)	-	-	-	-	-	-	1(100.0)	-	-
S. pneumoniae													
Penicillin-susceptible (996)	749(75.2)	227(98.0)	20(100.0)	-	-	-	-	-	-	-	-	-	-
Penicillin-non-susceptible(400)	344(86.0)	50(98.5)	5(99.8)	1(100.0)	-	-	-	-	-	-	-	-	-
-haemolytic strept. (234)	181(77.4)	27(88.9)	13(94.4)	11(99.1)	2(100.0)	-	-	-	-	-	-	-	-
vir. gr. streptococci													
Penicillin- susceptible (104)	70(67.3)	28(94.2)	6(100.0)	-	-	-	-	-	-	-	-	-	-
Penicillin-non-susceptible(30)	22(73.3)	8(100.0)	-	-	-	-	-	-	-	-	-	-	-
S. bovis (16)	7(43.8)	6(81.3)	3(100.0)	-	-	-	-	-	-	-	-	-	-
Bacillus spp. (8)	1(12.5)	7(100.0)	-	-	-	-	-	-	-	-	-	-	-
Corynebacterium spp. (11)	1(9.1)	3(36.4)	3(63.6)	3(90.9)	1(100.0)	-	-	-	-	-	-	-	-
Listeria spp. (18)	-	6(33.3)	11(94.4)	1(100.0)	-	-	-	-	-	-	-	-	-

a. Includes *E. durans* (one strain), *E. raffinosus* (one strain), *E. casseliflavus* (three strains), *E. avium* (four strains), *E. gallinarium* (four strains), *Enterococcus* spp. (two strains), and group D streptococci(four strains).

Table 2. Antimicrobial Aactivity of Dalbavancin and Comparator Agents Tested Against 6,339 Strains of Gram-positive Bacteria Collected Worldwide in 2002

	MIC (µg/ml)			% by category:	
Organism/antimicrobial agent (no. tested)	50%	90%	Range	Susceptible	Resistant
S. aureus					
Oxacillin-susceptible (1,815)					
Dalbavancin	0.06	0.06	≤0.015-0.25	-[a]	-
Penicillin	4	32	≤0.016->32	17.2	32.8
Chloramphenicol	8	8	≤2->16	96.9	0.4
Tetracycline	≤4	≤4	≤4->8	94.8	4.4
Levofloxacin	0.12	0.5	≤0.03->4	93.2	5.0
Vancomycin	1	1	0.25-2	100.0	0.0
Teicoplanin	0.5	1	≤0.12-2	100.0	0.0
Quinupristin/Dalfopristin	0.25	0.5	≤0.06-2	100.0	0.0
Linezolid	2	2	0.5-4	100.0	-
Oxacillin-resistant (1,177)					
Dalbavancin	0.06	0.06	≤0.015-0.5	-	-
Penicillin	32	>32	≤0.016->32	0.5	94.5
Chloramphenicol	8	16	≤2->16	78.1	7.2
Tetracycline	≤4	>8	≤4->8	85.4	14.0
Levofloxacin	>4	>4	0.06->4	11.1	65.7
Vancomycin	1	2	0.25-2	100.0	0.0
Teicoplanin	0.5	2	≤0.12-16	99.8	0.0
Quinupristin/Dalfopristin	0.5	1	≤0.06->8	99.7	0.2
Linezolid	2	2	≤0.25-16	99.9	-
Coagulase-neg. staphylococci					
Oxacillin-susceptible (157)					
Dalbavancin	0.03	0.06	≤0.015-0.25	-	-
Penicillin	0.5	2	≤0.016-16	35.0	65.0
Chloramphenicol	4	8	≤2-8	100.0	0.0
Tetracycline	≤4	>8	≤4->8	85.8	14.2
Levofloxacin	0.25	4	≤0.03->4	87.9	8.3
Vancomycin	1	2	0.5-2	100.0	0.0
Teicoplanin	1	4	≤0.12-16	98.7	0.0
Quinupristin/Dalfopristin	0.12	0.25	≤0.06-1	100.0	0.0
Linezolid	1	1	≤0.25-2	100.0	-
Oxacillin-resistant (615)					
Dalbavancin	0.03	0.06	≤0.015-0.5	-	-
Penicillin	8	32	≤0.016->32	4.1	95.9
Chloramphenicol	4	>16	≤2->16	87.9	11.7
Tetracycline	≤4	>8	≤4->8	83.9	16.1
Levofloxacin	4	>4	0.06->4	40.2	42.6
Vancomycin	1	2	≤0.12-4	100.0	0.0
Teicoplanin	2	4	≤0.12->16	97.9	0.5
Quinupristin/Dalfopristin	0.25	0.5	≤0.06->8	99.3	0.2
Linezolid	1	1	≤0.25-2	100.0	-
E. faecalis					
Vancomycin-susceptible (586)					
Dalbavancin	0.03	0.06	≤0.015-4	-	-
Penicillin	4	8	1->32	96.9	3.1
Chloramphenicol	8	>16	≤2->16	81.7	17.2
Doxycycline	>4	>4	≤0.5->4	44.3	55.7[b]
Levofloxacin	1	>4	0.25->4	58.5	40.8
Teicoplanin	≤0.12	0.5	≤0.12-2	100.0	0.0
Quinupristin/Dalfopristin	8	>8	0.25->8	0.5	94.4
Linezolid	1	2	≤0.25-4	99.8	0.0
Gentamicin (high-level)	≤500	>1000	≤500->1000	66.4	33.6
Vancomycin-resistant (20)					
Dalbavancin	4	32	≤0.015->32	-	-
Penicillin	4	16	2->32	80.0	20.0
Chloramphenicol	8	>16	4->16	55.0	35.0
Doxycycline	2	>4	≤0.5->4	55.0	45.0[b]
Levofloxacin	>4	>4	1->4	5.0	95.0
Teicoplanin	>16	>16	≤0.12->16	30.0	70.0
Quinupristin/Dalfopristin	>8	>8	4->8	0.0	100.0
Linezolid	1	2	0.5-2	100.0	0.0
Gentamicin (high-level)	>1000	>1000	≤500->1000	25.0	75.0
E. faecium					
Vancomycin-susceptible (77)					
Dalbavancin	0.06	0.12	≤0.015-4	-	-
Penicillin	>32	>32	0.5->32	23.4	70.1
Chloramphenicol	8	16	≥2->16	89.6	1.3
Doxycycline	≤0.5	>4	≤0.5->4	76.6	23.4[b]
Levofloxacin	>4	>4	0.25->4	32.5	61.0
Teicoplanin	0.5	0.5	≤0.12-4	100.0	0.0
Quinupristin/Dalfopristin	1	2	0.25-8	62.3	7.8
Linezolid	2	2	≤0.25-2	100.0	0.0
Gentamicin (high-level)	≥500	>1000	≤500->1000	85.5	14.5
Vancomycin-resistant (51)					
Dalbavancin	8	32	0.03->32	-	-
Penicillin	>32	>32	2->32	2.0	96.1
Chloramphenicol	8	8	≥2->16	92.2	3.9
Doxycycline	>4	>4	≤0.5->4	40.8	59.2[b]
Levofloxacin	>4	>4	1->4	2.0	98.0
Teicoplanin	>16	>16	0.25->16	13.7	68.6
Quinupristin/Dalfopristin	1	1	0.25-8	96.0	4.0
Linezolid	2	2	0.5->16	98.0	2.0
Gentamicin (high-level)	≥500	>1000	≤500->1000	54.9	45.1
S. pneumoniae (1,396)					
Penicillin-susceptible (996)					
Dalbavancin	≤0.015	0.03	≤0.015-0.06	-	-
Amoxicillin/Clavulanate	≤0.06	2	≤0.06-16	99.9	0.1
Ceftriaxone	0.015	0.25	≤0.008-4	99.4	0.1
Vancomycin	0.25	0.5	≤0.06-1	100.0	0.0
Clindamycin	≤0.06	0.5	≤0.06->8	93.9	5.7
Erythromycin	≤0.25	2	≤0.25->32	87.8	10.9
Quinupristin/Dalfopristin	0.25	0.5	≤0.06-1	100.0	0.0
Linezolid	1	1	≤0.25-2	100.0	-
Levofloxacin	1	1	≤0.03->4	98.8	1.2
Penicillin-non-susceptible (400)					
Dalbavancin	≤0.015	0.03	≤0.015-0.25	-	-
Amoxicillin/Clavulanate	1	4	≤0.06-16	89.7	5.8
Ceftriaxone	0.5	1	≤0.008-8	95.7	2.3
Vancomycin	0.25	0.5	≤0.06-2	99.8	-
Clindamycin	≤0.06	>8	≤0.06->8	69.3	29.5
Erythromycin	2	>32	≤0.06->32	37.5	60.0
Quinupristin/Dalfopristin	0.5	0.5	≤0.06-1	100.0	0.0
Linezolid	1	1	≤0.25-2	100.0	-
Levofloxacin	1	1	0.12->4	98.5	1.5
viridans gr. streptococci(134)					
Penicillin-susceptible (104)					
Dalbavancin	≤0.015	0.03	≤0.015-0.06	-	-
Penicillin	0.03	0.12	≤0.016-0.12	100.0	0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25-2	99.0	0.0
Vancomycin	0.5	1	≤0.12-1	100.0	0.0
Erythromycin	≤0.06	>8	≤0.06->8	70.2	26.0
Quinupristin/Dalfopristin	0.5	1	≤0.06-2	99.0	0.0
Linezolid	1	1	≤0.25-2	100.0	-
Levofloxacin	1	2	≤0.03->4	97.1	2.9
Penicillin-non-susceptible (30)					
Dalbavancin	≤0.015	0.03	≤0.015-0.03	-	-
Ceftriaxone	0.5	2	≤0.25-8	80.0	7.0
Vancomycin	0.5	0.5	0.25-1	100.0	0.0
Erythromycin	1	>8	≤0.06->8	36.7	56.7
Quinupristin/Dalfopristin	0.5	1	0.12-1	100.0	0.0
Linezolid	1	1	≤0.25-1	100.0	0.0
Levofloxacin	1	2	0.5->4	100.0	0.0
β-haemolytic streptococci(234)					
Dalbavancin	≤0.015	0.06	≤0.015-0.25	-	-
Penicillin	≤0.016	0.06	≤0.016-0.12	100.0	0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0	0.0
Vancomycin	0.25	0.5	≤0.12-1	100.0	0.0
Clindamycin	≤0.06	≤0.06	≤0.06->8	94.3	5.7
Erythromycin	≤0.06	2	≤0.06->8	81.5	17.6
Quinupristin/Dalfopristin	0.25	0.5	≤0.06-1	100.0	0.0
Linezolid	1	1	≤0.25-2	100.0	-
Levofloxacin	0.5	1	0.06->4	97.9	2.1

a. - = No breakpoint has been established by the NCCLS.
b. Includes intermediate and resistant strains.

CONCLUSIONS

- Dalbavacin showed excellent *in vitro* potency against a wide spectrum of Gram-positive pathogens collected.
- Dalbavancin activity did not vary by species between strains isolated in North America, Europe and South America.
- Dalbavancin activity was not affected by oxacillin resistance among staphylococci or by penicillin resistance among streptococci.
- Strains with dalbavancin MICs (> 0.5 µg/ml) were detected only for the genus Enterococcus, mainly among *E. faecium* having a Van A phenotype.

SELECTED REFERENCES

Candiani G, Abbondi M, Borgonovi M, Romanò G , Parenti F. *In vitro* and *in vivo* antibacterial activity of BI 397, a new semisynthetic glycopeptide antibiotic. *Journal of Antimicrobial Chemotherapy* 1999; 44:179-192.

Goldstein EJC, Citron DM, Merriam CV, Warren Y, Tyrrell K, Fernandez HT. *In vitro* activities of dalbavancin and nine comparator agents against anaerobic gram-positive species and Corynebacteria. *Antimicrobial Agents and Chemotherapy* 2003; 47:1968-1971.

Jones RN, Biedenbach DJ, Johnson DM, Pfaller MA. *In vitro* evaluation of BI 397, a novel glycopepetide antimicrobial agent. *Journal of Chemotherapy* 2001; 13:244-254.

National Committee for Clinical Laboratory Standards. (2003). *MIC testing. Performance standards for antimicrobial susceptibility testing (M100-S13).* Wayne, PA:NCCLS.

National Committee for Clinical Laboratory Standards. (2003). *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, M7-A6.* Wayne, PA:NCCLS.

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