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Evaluations of Dalbavancin Activity and Spectrum Tested Against European Isolates

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ABSTRACT

Background: Ongoing development of novel resistances (R) and the increased frequency of currently characterized R, requires the search for alternative antimicrobials. Dalbavancin (DAL, formerly BI397) is an amide glycopeptide derivative of A40926 with an extended elimination half-life enabling once weekly dosing. A large collection of clinical strains were tested to establish DAL spectrum and potency against European isolates.

Methods: DAL and over 20 comparators were tested against 2,886 recent (year 2002) clinical isolates from Europe using NCCLS (M7-A6) susceptibility (S) testing methods. The characteristics of this collection were: oxacillin (OXA)-R *S. aureus* = 31.1% and Coagulase-negative staphylococci (CoNS) = 79.0%; vancomycin-resistant enterococci (VRE) = 2.6-8.8% and PEN-non-susceptible pneumococci = 27.6%. Some fastidious Gram-negative species, *H. influenzae* (HI; 725) and *M. catarrhalis* (MCAT; 238) were also tested.

Results: Species distribution and MIC data for these highly represented Gram-positive species.

	DAL MIC (mg/L)		
Organism (no. tested)	50%	90%	Range
S. aureus (599)	0.06	0.06	≤0.016-0.25
Coag.-neg. staphylococci (247)	0.03	0.06	≤0.016-0.25
Enterococci (195)	0.03	0.06	≤0.016->32
S. pneumoniae (726)	≤0.016	0.03	≤0.016-0.25
β-streptococci (67)	≤0.016	0.03	≤0.016-0.12
viridans group streptococci (65)	≤0.016	0.03	≤0.016-0.06

OXA- or macrolide-R had no effect on DAL potency among staphylococci or streptococci. DAL results for VRE were most similar to the teicoplanin-S rates overall (active against VanB strains). Twenty-four tested strains (*Bacillus spp., Corynebacterium spp., L. monocytogenes, Micrococcus spp., S. bovis*) not cited in the Table had a combined DAL MIC_{90} of 0.12 mg/L; highest MIC at 0.25 mg/L. DAL MICs were lower than those of available glycopeptides by four- to >16-fold. HI (MIC_{90}, 32 mg/L) and MCAT (MIC_{90}, 4 mg/L) were less DAL-S.

Conclusions: This DAL activity survey indicates that this new glycopeptide has significant Gram-positive activity (96.9 - 100.0% inhibited at ≤ 1 mg/L), superior to available agents in the class, and the potency was similar for European isolates when compared to prior experience in other geographic areas. Further clinical development seems warranted.

INTRODUCTION

Dalbavancin (formerly BI-397) is a dimethylaminopropyl amide derivative of the glycopeptide A40926. Our earlier dalbavancin studies showed promising results against commonly isolated resistant Gram-positive pathogens. In addition, *in vivo* studies have shown that dalbavancin effectively reduced bacterial counts in models of septicemia, endocarditis and lung infection in immunocompetent as well as neutropenic animals. Dalbavancin also demonstrated an extended serum elimination half-life. Phase II trials have proven clinical efficacy in cutaneous and bloodstream infections when dalbavancin was dosed once-weekly as compared to a standard of practice.

Increasing antimicrobial resistance among bacterial pathogens such as *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS) and enterococci has prompted attempts to develop new antimicrobial agents active against multi-drug resistant Gram-positive organisms. The effectiveness of currently available 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, including VISA and VRSA are increasingly being recognized worldwide. Novel Gram-positive-active compounds such as linezolid, quinupristin/dalfopristin, newer fluoroquinolones, and telithromycin (a ketolide) have been developed; however, resistance to these agents has already been reported among several Gram-positive species.

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

MATERIALS AND METHODS

Bacterial Isolates. Clinical isolates were collected from more than 25 medical centers in Europe for the year 2002. A total of 1,918 Gram-positive isolates were evaluated and included: *S.aureus* (599; 31.1% resistant to oxacillin), CoNS (247; 79.0% resistant to oxacillin), *S. pneumoniae* (726; 27.6% non-susceptible to penicillin), enterococci (190; 3.7% resistant to vancomycin), β-haemolytic streptococci (67), viridans group streptococci (65), *Listeria* spp. (5), *S. bovis* (6), other Gram-positive species (13). A total of 963 additional fastidious Gram-negative organisms (*Haemophilus influenzae* and *Moraxella catarrhalis*) were also tested by NCCLS reference methods to determine potency and possible activity against these respiratory tract pathogens. The isolates were sent to a central monitor (Jones Microbiology Institute, North Liberty, Iowa, USA) 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, 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 were established by the NCCLS. 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

- Dalbavancin inhibited all Gram-positive organisms at ≤ 0.25 mg/L, except *Enterococcus* spp. (Table 1) [Dalbavancin is not active against VanA enterococci.]

Table 1. Antimicrobial activity of dalbavancin and eight other agents tested against 1739 strains from European medical centers (2002).

	MIC (mg/L)			% by category:[a]	
Organism/antimicrobial agent (no. tested)	50%	90%	Range	Susceptible	Resistant
S. aureus (599)					
Dalbavancin	0.06	0.06	≤0.016-0.25		-[b]
Teicoplanin	0.5	2	≤0.12-16	99.7	0.0
Vancomycin	1	1	0.25-2	100.0	0.0
Oxacillin	0.5	>8	≤0.06->8	68.9	31.1
Erythromycin	8	>32	0.12->8	63.4	36.2
Clindamycin	0.12	>8	≤0.06->8	81.7	18.2
Quinupristin/Dalfopristin	0.25	0.5	≤0.06->8	99.3	0.5
Levofloxacin	0.25	>4	≤0.03->4	68.2	19.4
Linezolid	2	2	0.5-4	100.0	-
Coagulase-neg. staphylococci (247)					
Dalbavancin	0.03	0.06	≤0.016-0.25		-
Teicoplanin	2	4	≤0.12->16	97.9	0.4
Vancomycin	1	2	0.5-2	100.0	0.0
Oxacillin	8	>8	≤0.06->8	21.0	79.0
Erythromycin	>8	>8	≤0.06->8	34.5	65.1
Clindamycin	0.12	>8	≤0.06->8	70.5	29.5
Quinupristin/Dalfopristin	≤0.25	0.5	≤0.25->8	98.9	0.7
Levofloxacin	4	>4	≤0.03->4	44.5	35.1
Linezolid	1	1	≤0.25-2	100.0	-
E. faecium (35)					
Dalbavancin	0.06	0.12	≤0.016->32		-
Teicoplanin	0.25	0.5	≤0.12->16	93.0	7.0
Vancomycin	1	2	0.25->16	91.2	7.0
Ampicillin	>16	>16	≤2->16	24.6	75.4
Chloramphenicol	8	16	≤2->16	84.2	7.0
Levofloxacin	>4	>4	≤0.5->4	28.1	63.2
Gentamicin	≤500	>1000	≤500->1000	68.4	31.6
Quinupristin/Dalfopristin	1	2	0.25->2	64.9	3.5
Linezolid	2	2	≤0.25-2	100.0	0.0
β-haemolytic streptococci (67)					
Dalbavancin	≤0.016	0.03	≤0.016-0.12		-
Teicoplanin	≤0.12	≤0.12	≤0.12	-	-
Vancomycin	0.25	0.5	≤0.12-1	100.0	-
Penicillin	≤0.016	0.06	≤0.016-0.12	100.0	-
Erythromycin	≤0.06	8	≤0.06->8	85.1	13.5
Clindamycin	≤0.06	≤0.06	≤0.06->8	92.0	8.0
Quinupristin/Dalfopristin	0.25	0.5	≤0.06-1	100.0	0.0
Levofloxacin	0.5	1	0.06->4	98.7	1.3
Linezolid	1	1	≤0.25-2	100.0	-
viridans gr. streptococci (65)					
Dalbavancin	≤0.016	0.03	≤0.016-0.06		-
Teicoplanin	≤0.12	1	≤0.12-1	-	-
Vancomycin	0.5	1	≤0.12-1	100.0	-
Penicillin	0.06	1	≤0.016-8	75.3	5.2
Erythromycin	≤0.06	>8	≤0.06->8	55.8	32.5
Clindamycin	≤0.06	>8	≤0.06->8	77.9	18.2
Quinupristin/Dalfopristin	0.5	1	≤0.25-1	100.0	0.0
Levofloxacin	1	1	≤0.03->4	97.4	2.6
Linezolid	1	1	≤0.25-2	100.0	-
S. pneumoniae (726)					
Dalbavancin	≤0.016	0.03	≤0.016-0.25		-
Teicoplanin	≤0.12	≤0.12	≤0.12-0.5	-	-
Vancomycin	0.25	0.5	≤0.12-2	100.0	-
Penicillin	≤0.03	2	≤0.03-4	72.4	13.7
Erythromycin	≤0.25	8	≤0.25->8	70.4	18.0
Clindamycin	≤0.06	>8	≤0.06->8	81.2	18.1
Quinupristin/Dalfopristin	≤0.25	0.5	≤0.25-1	100.0	0.0
Levofloxacin	1	1	0.12->4	98.8	1.2
Linezolid	1	1	≤0.25-2	100.0	-

a. Interpretative criteria of the NCCLS [2003].
b. No breakpoint has been established by the NCCLS [2003].

- Resistance rates to oxacillin were relatively high among *S. aureus* (31.1%) and isolates with reduced susceptibility to quinupristin/dalfopristin (MIC_{90}, 0.5 mg/L; 99.3% susceptible) and teicoplanin (MIC_{90}, 2 mg/L; 99.7% susceptible) were detected.
- Dalbavancin was equally active against oxacillin-susceptible and -resistant *S. aureus* (MIC_{90}, 0.06 mg/L for both) and was the most potent compound tested by weight against all staphylococci isolates.
- CoNS also appeared highly susceptible to dalbavancin (MIC_{90}, 0.06 mg/L) as well as to vancomycin (MIC_{90}, 2 mg/L) and linezolid (MIC_{90}, 1 mg/L). However, resistance to teicoplanin (97.9% susceptible) and quinupristin/dalfopristin (98.9% susceptible) was detected.
- Dalbavancin was very active against enterococci strains (MIC_{90}, 0.06 mg/L for *E. faecalis* and 0.12 mg/L for *E. faecium*).
- β-haemolytic and viridans group streptococci were highly susceptible to dalbavancin (MIC_{90}, 0.03 mg/L for both) and its activity was not affected by penicillin-resistance in the viridans group streptococci.
- Dalbavancin was highly active against both penicillin-susceptible and -nonsusceptible *S. pneumoniae* strains (MIC_{90}, 0.03 mg/L).
- Dalbavancin was active against all strains of less commonly isolated Gram-positive pathogens including *S. bovis*, *Bacillus* spp., *Corynebacterium* spp., and *Listeria* spp. Dalbavancin MICs ranged from ≤ 0.016 to 0.25 mg/L against these pathogens (Table 2).
- Dalbavancin showed only moderate *in vitro* activity against *M. catarrhalis* (MIC_{90}, 4 mg/L) and *H. influenzae* (MIC_{90}, 32 mg/L) isolates.

Table 2. Activity of dalbavancin against eight additional bacterial groups including *H. influenzae* and *M. catarrhalis* (987 total strains).

	Occurrences at MIC (mg/L):											
Organism (no. tested)	≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
Gram-positive organisms													
Bacillus cereus (1)	-	1	-	-	-	-	-	-	-	-	-	-	-
Corynebacterium spp. (5)[a]	-	1	2	1	1	-	-	-	-	-	-	-	-
Enterococcus spp. (5)[b]	1	1	2	1	-	-	-	-	-	-	-	-	-
Listeria monocytogenes (5)	-	2	2	1	-	-	-	-	-	-	-	-	-
Micrococcus luteus (2)	-	1	1	-	-	-	-	-	-	-	-	-	-
Streptococcus bovis (6)	2	2	2	-	-	-	-	-	-	-	-	-	-
Gram-negative organisms													
H. influenzae (725)	-	-	-	-	-	-	-	-	1	53	366	242	63
M. catarrhalis (238)	-	-	-	-	-	-	2	89	136	11	-	-	-

a. Includes *C. amycolatum* (one strain), *C. jeikeium* (one strain), and *Corynebacterium* spp. NOS (three strains).
b. Includes *E. durans* (one strain), *E. gallinarum* (two strains), and *Enterococcus* spp. NOS (two strains).

Table 3. MIC distributions for dalbavancin when tested against commonly isolated Gram-positive pathogens from European medical centers.

	Cum. % inhibited at MIC (mg/L):												
Pathogen (no. tested)	≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
S. aureus (599)	0.7	35.2	94.0	99.8	100.0	-	-	-	-	-	-	-	-
CoNS (247)	32.8	83.4	93.9	99.2	100.0	-	-	-	-	-	-	-	-
Enterococci (195)	9.7	70.8	91.8	96.4	96.9	96.9	96.9	97.4[a]	97.9[a]	98.5[a]	98.5	98.5	100.0[a]
S. pneumoniae (726)	78.1	97.5	99.9	99.9	100.0	-	-	-	-	-	-	-	-
β-*haemolytic* streptococci (67)	82.1	92.5	97.0	100.0	-	-	-	-	-	-	-	-	-
viridans group streptococci (65)	72.3	93.8	100.0	-	-	-	-	-	-	-	-	-	-
Organisms from Table 2 (24)	12.5	45.8	83.3	95.8	100.0	-	-	-	-	-	-	-	-

a. vanA genotypes of *E. faecalis* and *E. faecium*.

CONCLUSIONS

- Dalbavancin showed excellent *in vitro* potency and spectrum against commonly occurring species of Gram-positive pathogens collected in European medical centers.
- Dalbavancin activity was not affected by oxacillin-resistance among staphylococci nor by penicillin-resistance among streptococci.
- Strains with elevated dalbavancin MICs were detected only for the genus *Enterococcus*, among *E. faecium* having a VanA phenotype (Table 3). Among antimicrobials tested, only linezolid was active against all enterococci.
- This dalbavancin activity survey indicates that this new glyco- peptide has significant Gram-positive activity superior to available agents in the class.
- Dalbavancin potency was similar for European isolates when compared to prior experience in other geographic areas.
- Further clinical development seems warranted.

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14th European Congress of Clinical Microbiology and Infectious Diseases
Prague / Czech Republic, May 1-4, 2004