# 2276 Activity and Spectrum Evaluation of Dalbavancin, A Novel "Glycopeptide" Class Antimicrobial

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## **Abstract**

The continued evolution of resistant (R) Gram-positive (G+) species requires expanded research to develop new molecular entities. Dalbavancin (DALBA) is a novel derivative of MDL62,476 and it was tested against a world-wide collection of R G+ strains. Methods: 630 contemporary (1998-2000) G+ strains were selected for testing by NCCLS MIC procedures versus DALBA, vancomycin (VANCO), teicoplanin(TEICO), and 8 other antimicrobials. Cidal action was assessed by killing curves (VANCO control) and the optimal disk content determined. Results: DALBA curves (VANCO control) and the optimal disk content determined. **Hesuits:** DALBA spectrum was similar to that of other glycopeptides; MIC $_{90}$  of  $\leq$ 0.5 µg/ml for all isolates with the exception of VANCO-R enterococci (Van A; MIC $_{90}$ , 32 µg/ml). DALBA was more potent than VANCO or TEICO against S. aureus (MIC $_{90}$ , 0.25 µg/ml; 2 - 8-fold),  $\beta$ -haem streptococci (MIC90,  $\leq$ 0.03 µg/ml;  $\geq$ 16-fold), viridans gr streptococci (MIC90,  $\leq$ 0.03  $\mu$ g/ml;  $\leq$ 32-fold), and Corynebacterium spp. including C. jeikelium (MIC90,  $\leq$ 0.03 - 0.06  $\mu$ g/ml; 8 - >16-fold). DALBA was also more active than quinupristin/dalfopristin against all G+ organisms tested with the exception of oxa-susc S. aureus, against which it had equal activity. DALBA has little activity against H. influenzae or other G- organisms (MIC $_90$ s,  $\geq$  64  $\mu g/mI$ ). DALBÁ like other glycopeptides (VANCO), exhibited predominant bacteriostatic activity against tested strains, but was cidal against some tested S. pneumoniae. Testing conditions with blood or protein containing media elevated DALBA MICs and the 30-mg disk was acceptable for further test development. Conclusions: These data demonstrate DALBA activity as superior to marketed glycopeptides. PK data published elsewhere suggests that DALBA may be dosed less frequently than TEICO and the results of initial studies in humans are awaited with interest, especially when treating TEICO-R CoNS (DALBA-susceptible).

## Introduction

Dalbavancin (formerly BI397) is a semisynthetic derivative of the glycopeptide MDL 62,476, and has the same antimicrobial mechanism of action as teicoplanin and similar agents. Early in vitro studies demonstrated that, compared to vancomycin and teicoplanin, dalbavancin possessed superior antimicrobial activity against several groups of Grampositive bacteria, with favorable pharmacokinetic properties permitting once-daily dosing in animal models of infection 1,2.

This study compares the antimicrobial activities of dalbavancin and a range of the most commonly used antimicrobial agents against a representative sample of Gram-positive pathogens, including isolates with resistance to glycopeptides,  $\beta$ -lactams, macrolides-lincosamides-streptogramins (MLSB) and fluoroguinolones.

## **Materials and Methods**

A total of 1,061 bacterial strains, selected from contemporary (1998-2000) surveillance studies of the University of Iowa College of Medicine (Iowa City, Iowa), were chosen. The pathogens (number of strains) tested included: *S. aureus* (155), CoNS (67), *S. pneumoniae* (114), *b*-haemolytic streptococci (99; 5 serotypes), viridans group streptococci (108), enterococcal strains (56), *Bacillus* spp. (12), and *Corynebacterium* spp. including *C. jeikeium* (19). Also tested were *Haemophilus influenzae* (97), Enterobacteriaceae (291) and non-fermenter Gram negative bacilli (43). All were tested against the following comparison antimicrobial agents (obtained from their respective manufacturers): vancomycin, teicoplanin, erythromycin, clindamycin, quinupristin/dalfopristin, penicillin, ampicillin, amoxicillin, oxacillin, ceftriaxone, cefepime, tetracycline, ciprofloxacin, levofloxacin, and trimethoprim/sulfamethoxazole. Dalbavancin was obtained from Versicor, Inc. (Fremont, CA).

MIC values were determined using the National Committee for Clinical Laboratory Standards (NCCLS) M7-A5 microdilution broth method using suggested susceptibility and resistance breakpoints<sup>3</sup>.

The effect on dalbavancin MIC results of modifying standardized test conditions or media was determined<sup>4</sup>.

For development of disk diffusion methodology, dalbavancin disk concentrations (15-, 30-, and 60-µg) were replicate tested vs. *S. aureus* ATCC 25923, *S. aureus* ATCC 29213, and *E. faecalis* ATCC 29212.

The bactericidal activity of dalbavancin was determined using kill-curves performed against six Gram-positive organisms, including *S. aureus* (MSSA and MRSA), *S. epidermidis*, *E. faecalis* and *E. faecium* (VRE). Bactericidal action was defined as a  $\geq 3 \log 2$  decrease in the initial inoculum measured at 24 hours.

			MIC (μg/		
rganism (no. tested)	Antimicrobial agent	50%	90%	Range	% susce
Oxsuscept. (51)	Dalbavancin	0.12	0.25	0.06-0.5	-
	Vancomycin Teicoplanin	1	1	0.5-2 0.25-2	100.0 100.0
	Erythromycin	0.5	>8	0.25->8	70.6
	Clindamycin	0.12 0.25	0.12 0.25	≤0.06->8 ≤0.06-2	96.1 98.0
	Quinupristin/Dalfopristin Penicillin	2	32	≤0.06-2 ≤0.015->32	23.5
	Ampicillin Oxacillin	2 0.25	>16 1	≤0.12->16 0.12-2	25.5 100.0
	Ceftriaxone	2	4	1-4	100.0
	Tetracycline	≤4	≤4	≤4->8	96.1
	Ciprofloxacin Trimeth./Sulfa.	≤0.25 ≤0.5	0.5 ≤0.5	≤0.25->2 ≤0.5	94.1 100.0
Oxresist. (104)	Dalbavancin	0.12	0.25	0.06-1	-
	Vancomycin Teicoplanin	1	2	0.5-2 ≤0.12-4	100.0 100.0
	Erythromycin	>8	>8	0.25->8	5.8
	Clindamycin Quinupristin/Dalfopristin	>8 0.5	>8 1	≤0.06->8 0.12-8	23.1 97.1
	Penicillin	32	>32	≤0.015->32	0.0
	Ampicillin	>16	>16	1->16	0.0
	Oxacillin Ceftriaxone	>8 >32	>8 >32	8->8 8->32	0.0
	Tetracycline	≤4	>8	≤4->8	67.3
	Ciprofloxacin Trimeth./Sulfa. ≤0.5	>2 >1	>2 ≤0.5->1	≤0.25->2 78.8	6.7
oagulase-negative st			_0.0 + 1	70.0	
Oxsuscept. (16)	Dalbavancin	0.12	0.12	≤0.03-0.25	-
	Vancomycin Teicoplanin	1	2 8	0.5-2 ≤0.12-16	100.0 93.8
	Erythromycin	0.25	>8	0.25->8	68.8
	Clindamycin	≤0.06	0.12	≤0.06-0.12 0.12-0.25	100.0
	Quinupristin/Dalfopristin Penicillin	0.25 0.25	2	0.12-0.25 ≤0.015-8	100.0 56.3
	Ampicillin	≤0.12	2	≤0.12-4	56.3
	Oxacillin Ceftriaxone	0.12 2	0.25 4	0.12-0.25 0.5-8	100.0 100.0
	Tetracycline	≤4	>8	≤4->8	81.3
	Ciprofloxacin Trimeth./Sulfa.	≤0.25 ≤0.5	1 ≤0.5	≤0.25->2 ≤0.5->1	93.8 93.8
Oxresist. (51)	Dalbavancin	0.12	0.25	0.06-1	-
	Vancomycin	2	2	0.5-4	100.0
	Teicoplanin Erythromycin	4 1 >8	6 0. >8 0.	25->16 12->8	88.2 9.8
	Clindamycin	>8	>8	≤0.06->8	39.2
	Quinupristin/Dalfopristin Penicillin	0.25 16	1 >32	0.12-4 0.12->32	90.2 2.0
	Ampicillin	16	>32	0.12->32	2.0
	Oxacillin	>8	>8	0.5->8	0.0
	Ceftriaxone Tetracycline	32 ≤4	>32 >8	4->32 ≤4->8	0.0 72.5
	Ciprofloxacin	>2	>2	≤0.25->2	35.3
. pneumoniae (114)	Trimeth./Sulfa.	>1	>1	≤0.5->1	41.2
. priedmoniae (114)	Dalbavancin	≤0.03	≤0.03	≤0.03-0.06	-
	Vancomycin	0.5	0.5	≤0.12-1	100.0
	Teicoplanin Erythromycin	≤0.12 ≤0.25	≤0.12 >32	≤0.12 ≤0.25->32	100.0 51.8
	Clindamycin	≤0.25	>2	≤0.25->2	84.2
	Quinupristin/Dalfopristin Penicillin	0.25 0.25	0.5 2	≤0.06-2 ≤0.015->4	99.1 38.6
	Amoxicillin	0.5	2	≤0.06->8	90.7
	Ceftriaxone Cefepime	0.25 0.25	1	0.015-4 ≤0.06-2	70.0 71.1
	Tetracycline	0.25 ≤2	>16	≤0.06-2 ≤2->16	53.5
	Levofloxacin	1	>4	0.06->4	86.8
-haem. streptococci <sup>t</sup>	Trimeth./Sulfa.	2	>4	≤0.5->4	43.0
р-пает. эпергососсі	Dalbavancin	≤0.03	≤0.03	≤0.03-0.12	
	Vancomycin	0.5	0.5	0.25-1	100.0
	Teicoplanin Erythromycin	≤0.12 ≤0.06	£0.12 >8	≤0.12-0.25 ≤0.06->8	100.0 83.9
	Clindamycin	≤0.06	0.5	≤0.06->8	89.8
	Quinupristin/Dalfopristin Penicillin	0.25 ≤0.015	0.5 0.06	≤0.06-1 ≤0.015-0.12	100.0 100.0
	Amoxicillin	≤0.06	≤0.06	≤0.06-0.25	100.0
	Ceftriaxone Cefepime	≤0.25	≤0.25 ≤0.12	≤0.25	100.0 100.0
	Tetracycline	≤0.12 ≤2	≥0.12 >8	≤0.12-1 ≤2->8	60.6
	Levofloxacin	0.5	1	0.25->2	100.0
ridans group strepto	Trimeth./Sulfa.	≤0.5	≤0.5	≤0.5	100.0
	Dalbavancin	≤0.03	≤0.03	≤0.03-0.06	-
	Vancomycin	0.5	1	0.25-2	100.0
	Teicoplanin Erythromycin	≤0.12 0.25	≤0.12 4	≤0.12-2 ≤0.06->32	100.0 51.9
	Clindamycin	0.03	0.12	≤0.06->8	91.7
	Quinupristin/Dalfopristin Penicillin	0.5 0.25	1 8	≤0.06-2 ≤0.015->16	99.1 47.2
	Ampicillin	0.25 ≤2	16	≤0.015->16 4-16	
	Ceftriaxone	≤0.25	2	≤0.25-8	89.9
	Cefepime Tetracycline	0.25 ≤2	4 16	≤0.12->8 ≤2->16	95.4 74.8
	Levofloxacin	1	2	≤0.5->4	95.7
	Trimeth./Sulfa.	≤0.5	4	≤0.25-8	70.4

Organism (== t==t==1)	Antimiarabiel	E00/	MIC (μg/	9/ 04/	
Organism (no. tested)	Antimicrobial agent	50%	90%	Range	% suscept. <sup>a</sup>
Enterococi Vanco-suscept. (28) <sup>d</sup>	Dalbavancin Vancomycin	0.12	0.5	≤0.03-1 0.25-2	100.0
	Teicoplanin Erythromycin Clindamycin	0.25 4 >8	0.5 >8 >8	0.12-1 ≤0.06->8 ≤0.06->8	100.0 32.1 -
	Quinupristin/Dalfopristin Penicillin Ampicillin	8 2 2 >32	>8 >32 >16 >32	0.25->8 ≤0.015->32 ≤0.12->16	21.4 82.1 85.7
	Ceftriaxone Cefepime Tetracycline Ciprofloxacin	>16 ≤4 2	>16 >8 >2	≤0.25->32 ≤0.12->16 ≤4->8 ≤0.25->2	57.1 46.4
Vancoresist. (28) <sup>e</sup>	Trimeth./Sulfa.  Dalbavancin  Vancomycin	≤0.5 16 >16	>2 32 >16	≤0.5->1 0.25-32 >16	75.0 - 0.0
	Teicoplanin Erythromycin Clindamycin	>16 >8 >8	>16 >8 >8	0.25->16 2->8 0.12->8	3.6 0.0
	Quinupristin/Dalfopristin Penicillin Ampicillin	1 >32 >16	>8 >32 >16	0.25->8 2->32 1->16	71.4 21.4 21.4
	Ceftriaxone Cefepime Tetracycline Ciprofloxacin	>32 >16 >8 >2	>32 >16 >8 >2	>32 >16 ≤4->8 0.5->2	46.4 3.6
Bacillus spp. (12)	Trimeth./Sulfa.  Dalbavancin Vancomycin Teicoplanin Erythromycin Clindamycin	2 0.12 1 ≤0.12 0.5 1	>2 0.25 1 2 >8 >8	≤0.05->2 ≤0.03-2 ≤0.12-1 ≤0.12-4 0.12->8 0.5->8	28.6 - 100.0 100.0 -
	Quinupristin/Dalfopristin Penicillin Ampicillin Oxacillin Ceftriaxone Tetracycline	1 4 1 8 16 ≤4	2 16 16 >8 >32 ≤4	0.5-8 ≤0.015-32 ≤0.12->16 0.12->8 ≤0.25->32 ≤4	83.3 - - - 41.7 100.0
	Ciprofloxacin Trimeth./Sulfa	≤0.25 ≤0.5	≤0.25 2	≤0.25-0.5 ≤0.5->2	100.0 66.7
C. jeikeium (8)	Dalbavancin Vancomycin Teicoplanin Erythromycin	0.06 0.5 1 8		≤0.03-0.12 0.5-1 0.5-2 4->8	-
	Clindamycin Quinupristin/Dalfopristin Penicillin	>8 0.25 >32	-	>8 0.12-0.5 >32	-
	Ampicillin Oxacillin Ceftriaxone	>16 >8 >32	-	>16 >8 >32	-
	Tetracycline Ciprofloxacin	£4 >2 >2	-	≤4->8 >2 >2	-
Corynebact. spp. (11)	Trimeth./Sulfa.  Dalbavancin	>2 ≤0.03 0.25	- ≤0.03 0.5	>2 ≤0.03-0.12 0.25-0.5	-
	Vancomycin Teicoplanin Erythromycin	0.5 >8	0.5 >8	≤0.12-1 ≤0.06->8	-
	Clindamycin Quinupristin/Dalfopristin Penicillin	>8 0.25 0.25	>8 0.5 8	≤0.06->8 ≤0.06-1 ≤0.015->32	-
	Ampicillin Oxacillin	1 4	>16 >8	≤0.12->16 0.5->8	-
	Ceftriaxone Tetracycline Ciprofloxacin	1 ≤4 >2	32 ≤4 >2	≤0.25->32 ≤4->8 ≤0.25->2	-
	Trimeth./Sulfa.	>2	>2 >2	≤0.25->2 ≤0.5->2	-

## Results

- Dalbavancin demonstrated excellent activity against a wide range of Grampositive pathogens with MIC<sub>90</sub>s of ≤0.5 µg/ml (Table 1).
- Dalbavancin MIC<sub>90</sub>s were 4- to ≥32-fold (average, 8-fold) lower than those for vancomycin for all vancomycin-susceptible strains tested. A similar pattern was seen when compared to teicoplanin.
- Vancomycin-resistant enterococci of the Van A phenotype were also resistant to dalbavancin (MIC  $_{90}=32\mu g/ml).$
- Dalbavancin was more active than quinupristin/dalfopristin against all tested Gram-positive species with the exception of oxacillin-susceptible S. aureus, against which it was equipotent (MIC $_{90} = 0.25 \, \mu g/mI$ ).
- MIC<sub>90</sub>s for dalbavancin were ≤0.03 µg/ml against S. pneumoniae, β-haemolytic streptococci and viridans group streptococci.

In addition to the susceptibility data shown in Table 1:

- $\bullet$  The MIC  $_{90}$  of dalbavancin against  $\emph{H. influenzae}$  (97 strains) was  $64\mu g/ml.$
- As expected, dalbavancin did not display clinically useful activity against any of the Enterobacteriaceae or non-fermenter Gram-negative bacilli tested

Testing conditions	Median	Mode	90%	Range
pH				
6.0	0.12	0.12	0.25	0.06-0.25
7.2	0.12	0.12	0.25	0.06-0.25
8.0	0.12	0.12	0.25	0.06-0.5
Media				
5% Sheep Blood MHA	0.25	0.25	0.25	0.06-0.5
Chocolate MHA	2	2	4	1-4
BHI Agar	0.12	0.12	0.25	0.06-0.5
Brucella Blood Agar	0.12	0.12	0.5	0.03-2
Incubation				
Ambient air	0.12	0.12	0.25	0.06-0.25
5% CO2	0.25	0.25	0.25	0.12-0.5
Anaerobic	0.12	0.12	0.25	0.06-0.5
Inoculum Size				
10 <sup>2</sup> CFU/spot	0.25	0.25	0.25	0.06-0.5
10 <sup>3</sup> CFU/spot	0.25	0.25	0.25	0.03-0.5
10 <sup>4</sup> CFU/spot	0.25	0.25	0.25	0.03-0.5
10 <sup>5</sup> CFU/spot	0.25	0.25	0.5	0.25-1

#### Regulte

- pH of the test media had little effect on dalbavancin activity (Table 2).
- Medium supplements of red blood cells and lysed-cell components (proteins) elevate the dalbavancin MICs
- Incubation environments had little influence on dalbavancin potency
- A modest inoculum effect was observed with a minority of strains at the highest tested concentration of 10<sup>5</sup> CFU/spot.
- In a separate experiment, dalbavancin disk concentrations (15-, 30-, and 60-µg) were replicate-tested vs. S. aureus ATCC 25923, S. aureus ATCC 29213, and E. faecalis ATCC 29212.
- Zone diameters remained small indicating limited diffusion in agar of this high molecular weight glycopeptide and/or drug binding to media proteins.
- Zone diameters did not significantly increase for concentrations >30  $\mu g$ .
- Further development of disk diffusion methods should not utilize disk contents exceeding 30-μg.
- Killing curves indicate that, at 4X and 8X MIC, dalbavancin is rapidly bactericidal against S. pneumoniae, but bacteriostatic against the remaining organisms tested.
- Results were identical to those noted for vancomycin.

## **Summary and Conclusions**

- Dalbavancin demonstrated potent activity against oxacillin-susceptible and -resistant strains of *S. aureus*, CoNS, and all streptococci tested, including *S. pneumoniae*, b-haemolytic streptococci, viridans group streptococci, and vancomycin-susceptible enterococci.
- Activity was also excellent against Bacillus spp., Corynebacterium spp., and C. jeikeium.
- Dalbavancin showed no useful activity against selected Gram-negative organisms.
- The activity of dalbavancin against all the tested Gram-positive organisms was equal, or superior to that observed for vancomycin, teicoplanin and quinupristin/dalfopristin.
- · More studies are needed to define the clinical role of dalbavancin.
- This study confirms the promise of dalbavancin, demonstrated in an earlier study by Candiani et al.<sup>1</sup>. Pharmacokinetics data reported in human studies (See Poster # 951, Leighton, et. al.) suggest dalbavancin may be effective in the treatment of Gram-positive infections when dosed at extended treatment intervals.

## References

- 1. Candiani, et. al. (1999) J Antimicrob Chemother 44:179.
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