

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 spectrum was similar to that of other glycopeptides; MIC₉₀ of ≤0.5 µg/ml for all isolates with the exception of VANCO-R enterococci (Van A; MIC₉₀, 32 µg/ml). DALBA was more potent than VANCO or TEICO against *S. aureus* (MIC₉₀, 0.25 µg/ml; 2 - 8-fold), β-haem streptococci (MIC₉₀, ≤0.03 µg/ml; ≥16-fold), viridans gr streptococci (MIC₉₀, ≤0.03 µg/ml; ≥32-fold), and *Corynebacterium* spp. including *C. jeikeium* (MIC₉₀, ≤0.03 - 0.06 µg/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 (MIC₉₀s, ≥ 64 µg/ml). DALBA 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 Gram-positive 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, β-lactams, macrolides-lincosamides-streptogramins (MLSB) and fluoroquinolones.

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 breakpoints³.

The effect on dalbavancin MIC results of modifying standardized test conditions or media was determined⁴.

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 ≥3 log2 decrease in the initial inoculum measured at 24 hours.

TABLE 1. Comparative antimicrobial activity of Dalbavancin					
MIC (µg/ml)					
Organism (no. tested)	Antimicrobial agent	50%	90%	Range	% suscept. ^a
<i>S. aureus</i> Ox.-suscept. (51)	Dalbavancin	0.12	0.25	0.06-0.5	-
	Vancomycin	1	1	0.5-2	100.0
	Teicoplanin	1	1	0.25-2	100.0
	Erythromycin	0.5	>8	0.25->8	70.6
	Clindamycin	0.12	0.12	≤0.06->8	96.1
	Quinupristin/Dalfopristin	0.25	0.25	≤0.06-2	98.0
	Penicillin	2	32	≤0.015->32	23.5
	Ampicillin	2	>16	≤0.12->16	25.5
	Oxacillin	0.25	1	0.12-2	100.0
	Ceftriaxone	2	4	1-4	100.0
	Tetracycline	≤4	≤4	≤4->8	96.1
	Ciprofloxacin	≤0.25	0.5	≤0.25->2	94.1
	Trimeth./Sulfa.	≤0.5	≤0.5	≤0.5	100.0
	Dalbavancin	0.12	0.25	0.06-1	-
	Vancomycin	1	2	0.5-2	100.0
	Teicoplanin	1	4	≤0.12-4	100.0
	Erythromycin	>8	>8	0.25->8	5.8
	Clindamycin	>8	>8	≤0.06->8	23.1
	Quinupristin/Dalfopristin	0.5	1	0.12-8	97.1
	Penicillin	32	>32	≤0.015->32	0.0
Ox.-resist. (104)	Ampicillin	>16	>16	1->16	0.0
	Oxacillin	>8	>8	8->8	0.0
	Ceftriaxone	>32	>32	8->32	0.0
	Tetracycline	≤4	>8	≤4->8	67.3
	Ciprofloxacin	>2	>2	≤0.25->2	6.7
	Trimeth./Sulfa. ≤0.5	>1	≤0.5->1	78.8	
Coagulase-negative staphylococci Ox.-suscept. (16)	Dalbavancin	0.12	0.12	≤0.03-0.25	-
	Vancomycin	1	2	0.5-2	100.0
	Teicoplanin	1	8	≤0.12-16	93.8
	Erythromycin	0.25	>8	0.25->8	68.8
	Clindamycin	≤0.06	0.12	≤0.06-0.12	100.0
	Quinupristin/Dalfopristin	0.25	0.25	0.12-0.25	100.0
	Penicillin	0.25	2	≤0.015-8	56.3
	Ampicillin	≤0.12	2	≤0.12-4	56.3
	Oxacillin	0.12	0.25	0.12-0.25	100.0
	Ceftriaxone	2	4	0.5-8	100.0
	Tetracycline	≤4	>8	≤4->8	81.3
	Ciprofloxacin	≤0.25	1	≤0.25->2	93.8
	Trimeth./Sulfa.	≤0.5	≤0.5	≤0.5->1	93.8
	Dalbavancin	0.12	0.25	0.06-1	-
	Vancomycin	2	2	0.5-4	100.0
	Teicoplanin	4	6	0.25->16	88.2
	Erythromycin	>8	>8	12->8	9.8
	Clindamycin	>8	>8	≤0.06->8	39.2
	Quinupristin/Dalfopristin	0.25	1	0.12-4	90.2
Ox.-resist. (51)	Penicillin	16	>32	0.12->32	2.0
	Ampicillin	16	>16	0.25->16	2.0
	Oxacillin	>8	>8	0.5->8	0.0
	Ceftriaxone	32	>32	4->32	0.0
	Tetracycline	≤4	>8	≤4->8	72.5
	Ciprofloxacin	>2	>2	≤0.25->2	35.3
	Trimeth./Sulfa.	>1	>1	≤0.5->1	41.2
<i>S. pneumoniae</i> (114)	Dalbavancin	≤0.03	≤0.03	≤0.03-0.06	-
	Vancomycin	0.5	0.5	≤0.12-1	100.0
	Teicoplanin	≤0.12	≤0.12	≤0.12	100.0
	Erythromycin	≤0.25	>32	≤0.25->32	51.8
	Clindamycin	≤0.25	>2	≤0.25->2	84.2
	Quinupristin/Dalfopristin	0.25	0.5	≤0.06-2	99.1
	Penicillin	0.25	2	≤0.015->4	38.6
	Amoxicillin	0.5	2	≤0.06->8	90.7
	Ceftriaxone	0.25	1	0.015-4	70.0
	Cefepime	0.25	1	≤0.06-2	71.1
	Tetracycline	≤2	>16	≤2->16	53.5
	Levofloxacin	1	>4	0.06->4	86.8
	Trimeth./Sulfa.	2	>4	≤0.5->4	43.0
β-haem. streptococci^b (99)	Dalbavancin	≤0.03	≤0.03	≤0.03-0.12	--
	Vancomycin	0.5	0.5	0.25-1	100.0
	Teicoplanin	≤0.12	≤0.12	≤0.12-0.25	100.0
	Erythromycin	≤0.06	>8	≤0.06->8	83.9
	Clindamycin	≤0.06	0.5	≤0.06->8	89.8
	Quinupristin/Dalfopristin	0.25	0.5	≤0.06-1	100.0
	Penicillin	≤0.015	0.06	≤0.015-0.12	100.0
	Amoxicillin	≤0.06	≤0.06	≤0.06-0.25	100.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0
	Cefepime	≤0.12	≤0.12	≤0.12-1	100.0
	Tetracycline	≤2	>8	≤2->8	60.6
	Levofloxacin	0.5	1	0.25->2	100.0
	Trimeth./Sulfa.	≤0.5	≤0.5	≤0.5	100.0
viridans group streptococci^c (108)	Dalbavancin	≤0.03	≤0.03	≤0.03-0.06	-
	Vancomycin	0.5	1	0.25-2	100.0
	Teicoplanin	≤0.12	≤0.12	≤0.12-2	100.0
	Erythromycin	0.25	4	≤0.06->32	51.9
	Clindamycin	0.03	0.12	≤0.06->8	91.7
	Quinupristin/Dalfopristin	0.5	1	≤0.06-2	99.1
	Penicillin	0.25	8	≤0.015->16	47.2
	Ampicillin	≤2	16	4-16	-
	Ceftriaxone	≤0.25	2	≤0.25-8	89.9
	Cefepime	0.25	4	≤0.12->8	95.4
	Tetracycline	≤2	16	≤2->16	74.8
	Levofloxacin	1	2	≤0.5->4	95.7
	Trimeth./Sulfa.	≤0.5	4	≤0.25-8	70.4
	Dalbavancin	≤0.03	≤0.03	≤0.03-0.12	--
	Vancomycin	0.5	0.5	0.25-1	100.0
	Teicoplanin	≤0.12	≤0.12	≤0.12-0.25	100.0
	Erythromycin	≤0.06	>8	≤0.06->8	83.9
	Clindamycin	≤0.06	0.5	≤0.06->8	89.8
	Quinupristin/Dalfopristin	0.25	0.5	≤0.06-1	100.0
	Penicillin	≤0.015	0.06	≤0.015-0.12	100.0
	Amoxicillin	≤0.06	≤0.06	≤0.06-0.25	100.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0
	Cefepime	≤0.12	≤0.12	≤0.12-1	100.0
	Tetracycline	≤2	>8	≤2->8	60.6
	Levofloxacin	0.5	1	0.25->2	100.0
	Trimeth./Sulfa.	≤0.5	≤0.5	≤0.5	100.0

a. Breakpoints as published by the NCCLS [2001]³ where available. No criteria are available for Dalbavancin.

b. From serogroup A (41 strains), B (32 strains), C (10 strains), F (6 strains) and G (10 strains).

c. Includes: *S. argininosus* (2 strains), *S. constellatus* (2 strains), *S. intermedius* (5 strains), *S. mitis* (19 strains), *S. mutans* (1 strain), *S. oralis* (4 strains), *S. parvus* (7 strains), *S. uberis* (1 strain), and viridans group streptococci NOS (66 strains).

d. Synergy rates were as follows: gentamicin at 67.9% and streptomycin at 64.3%.

e. Synergy rates showed the following: gentamicin at 35.7% and streptomycin at 14.3%.

TABLE 1. Comparative antimicrobial activity of Dalbavancin, continued.					
MIC (µg/ml)					
Organism (no. tested)	Antimicrobial agent	50%	90%	Range	% suscept. ^a
Enterococci					
Vanco-suscept. (28) ^d	Dalbavancin	0.12	0.5	≤0.03-1	-
	Vancomycin	1	2	0.25-2	100.0
	Teicoplanin	0.25	0.5	0.12-1	100.0
	Erythromycin	4	>8	≤0.06->8	32.1
	Clindamycin	>8	>8	≤0.06->8	-
	Quinupristin/Dalfopristin	8	>8	0.25->8	21.4
	Penicillin	2	>32	≤0.015->32	82.1
	Ampicillin	>2	>16	≤0.12->16	85.7
	Ceftriaxone	>32	>32	≤0.25->32	-
	Cefepime	>16	>16	≤0.12->16	-
	Tetracycline	≤4	>8	≤4->8	57.1
	Ciprofloxacin	2	>2	≤0.25->2	46.4
	Trimeth./Sulfa.	≤0.5	>2	≤0.5->1	75.0
Vanco.-resist. (28) ^e	Dalbavancin	16	32	0.25-32	-
	Vancomycin	>16	>16	>16	0.0
	Teicoplanin	>16	>16	0.25->16	3.6
	Erythromycin	>8	>8	2->8	0.0
	Clindamycin	>8	>8	0.12->8	-
	Quinupristin/Dalfopristin	1	>8	0.25->8	71.4
	Penicillin	>32	>32	2->32	21.4
	Ampicillin	>16	>16	1->16	21.4
	Ceftriaxone	>32	>32	>32	-
	Cefepime	>16	>16	>16	-
	Tetracycline	>8	>8	≤4->8	46.4
	Ciprofloxacin	>2	>2	0.5->2	3.6
	Trimeth./Sulfa.	2	>2	≤0.05->2	28.6
Bacillus spp. (12)					
Dalbavancin	0.12	0.25	≤0.03-2	-	
Vancomycin	1	1	≤0.12-1	100.0	
Teicoplanin	≤0.12	2	≤0.12-4	100.0	
Erythromycin	0.5	>8	0.12->8	-	
Clindamycin	1	>8	0.5->8	-	
Quinupristin/Dalfopristin	1	2	0.5-8	83.3	
Penicillin	4	16	≤0.015-32	-	
Ampicillin	1	16	≤0.12->16	-	
Oxacillin	8	>8	0.12->8	-	
Ceftriaxone	16	>32	≤0.25->32	41.7	
Tetracycline	≤4	≤4	≤4	100.0	
Ciprofloxacin	≤0.25	≤0.25	≤0.25-0.5	100.0	
Trimeth./Sulfa	≤0.5	2	≤0.5->2	66.7	
<i>C. jeikeium</i> (8)					
Dalbavancin	0.06	-	≤0.03-0.12	-	
Vancomycin	0.5	-	0.5-1	-	
Teicoplanin	1	-	0.5-2	-	
Erythromycin	8	-	4->8	-	
Clindamycin	>8	-	>8	-	
Quinupristin/Dalfopristin	0.25	-	0.12-0.5	-	
Penicillin	>32	-	>32	-	
Ampicillin	>16	-	>16	-	
Oxacillin	>8	-	>8	-	
Ceftriaxone	>32	-	>32	-	
Tetracycline	≤4	-	≤4->8	-	
Ciprofloxacin	>2	-	>2	-	
Trimeth./Sulfa.	>2	-	>2	-	
Corynebact. spp. (11)					
Dalbavancin	≤0.03	≤0.03	≤0.03-0.12	-	
Vancomycin	0.25	0.5	0.25-0.5	-	
Teicoplanin	0.5	0.5	≤0.12-1	-	
Erythromycin	>8	>8	≤0.06->8	-	
Clindamycin	>8	>8	≤0.06->8	-	
Quinupristin/Dalfopristin	0.25	0.5	≤0.06-1	-	
Penicillin	0.25	8	≤0.015->32	-	
Ampicillin	1	>16	≤0.12->16	-	
Oxacillin	4	>8	0.5->8	-	
Ceftriaxone	1	32	≤0.25->32	-	
Tetracycline	≤4	≤4	≤4->8	-	
Ciprofloxacin	>2	>2	≤0.25->2	-	
Trimeth./Sulfa.	>2	>2	≤0.5->2	-	