E-2009

Comparative Activity of Dalbavancin Tested Against 7,771 Isolates from the USA and Europe (2003)

RN Jones, HS Sader, TR Fritsche, M Stilwell
The JONES Group/JMI Laboratories, North Liberty, IA

Phone: 319-665-3370
Fax: 319-665-3371
Email: Ronald-Jones@JMIlabs.com

ABSTRACT

Background: Dalbavancin (DAL) is a bactericidal dimethylaminopropyl amide derivative of another glycopeptide, A40926. An extended serum elimination half-life allows once-weekly dosing for therapy of Gram-positive infections including resistant (R) phenotypes (MRSA, Van B VRE, DRSP); strains from a USA and Europe (EU) surveillance protocol were sampled in 2003. **Methods:** A total of 7,771 Gram-positive isolates (3,698 from USA and 4,073 from EU [13 countries]) were tested by reference NCCLS methods (M7-A6) against DAL and 10 comparators. Species were analyzed by R phenotypes (oxacillin [OXA]-, vancomycin [VAN]-, penicillin [PEN]-R). **Results:** DAL and other glycopeptides were very active versus staphylococci (n=4648) with DAL 16- to 32-fold more potent than VAN (MIC_{90}s 0.06 and 2 µg/ml, respectively) and the highest DAL MIC observed for staphylococci was only 0.5 µg/ml. 2 - 3% of teicoplanin MICs were elevated for CoNS. MRSA rates were greater (31.6%) in the USA than EU (26.1%). Quinupristin/dalfopristin (Q/D)-R (MIC, ≥ 2 µg/ml; 0.1 - 0.5%) was documented in EU > USA. DAL (MIC_{50}, 0.03 - 0.06 µg/ml) was active against enterococci, but not Van-A phenotypes. VRE rates were EU (8.3%) and USA (35.9%) in this enhanced R collection. Streptococci (DAL MIC_{90}, 0.016 - 0.03 µg/ml) were generally most S to glycopeptides (100.0%), Q/D (98.6 - 100.0%) and linezolid (LZD; 100.0%); but DAL was 16-fold more active than Q/D or LZD. DAL MIC_{90} values for other species were: *Bacillus* spp. (0.12 mg/ml), *Corynebacterium* spp. (0.12 µg/ml), *Listeria* spp. (0.06 µg/ml) and *Micrococcus* spp. (0.03 mg/ml). All VAN-S and VanB VRE had DAL MICs at ≤ 0.5 mg/ml. VanA strain DAL MICs ranged from 0.5 - > 16 µg/ml (median MIC, 8 µg/ml). DAL MIC values were not influenced by geographic region or R phenotypes (except for VanA). **Conclusions:** DAL, a long-acting glycopeptide, exhibits potent activity (≥ 16-fold greater) compared to other Gram-positive agents in this high volume international survey. DAL spectrum includes all important Gram-positive pathogens and nearly all R phenotypes.[a]

INTRODUCTION

Antimicrobial resistance among bacterial pathogens such as *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS) and enterococci has been rapid and prompted attempts to develop new antimicrobial agents active against multidrug-resistant Gram-positive pathogens. Glycopeptides (vancomycin, teicoplanin) have been the mainstay in the treatment of Gram-positive infections, particularly those caused by enterococci and oxacillin-resistant *S. aureus* (ORSA), as well as against multidrug-resistant staphylococcal isolates (MDR). The worldwide emergence of vancomycin-resistant enterococci (VRE), starting in 1988, has limited the effectiveness of glycopeptides against these organisms. However, glycopeptides continue to be a mainstay against. Vancomycin-intermediate *S. aureus* (VISA) has been sporadically reported from various parts of the world, and rare vancomycin-resistant isolates (VRSA) recently appeared in the US. Novel Gram-positive-active compounds such as daptomycin, linezolid, streptogramin combinations (quinupristin/dalfopristin [Q/D]), newer quinolones, and telithromycin (a ketolide) have been developed and are now considered the "last resort" for therapy of many serious Gram-positive infections; however, resistance to these agents has also been detected among several species, including linezolid-resistant ORSA, VRE or viridans group streptococci.

Dalbavancin (formerly BI-397) is a novel bactericidal lipoglycopeptide, a dimethylaminopropyl amide derivative of the natural glycopeptide, A40926. Early dalbavancin in vitro studies showed promising results against frequently isolated Gram-positive pathogens without regard to other resistance markers except VanA. Dalbavancin has advantages over clinically used glycopeptides because of coverage of vancomycin-resistant VanB enterococci and teicoplanin-resistant CoNS. The anti-streptococcal activity of dalbavancin, including penicillin-resistant *S. pneumoniae* and α-haemolytic species, is similar to that of teicoplanin, but more potent than vancomycin.

In addition, *in vivo* animal studies have shown that dalbavancin effectively reduced bacterial loads in models of septicemia, endocarditis, and lung infection in immunocompetent and neutropenic mice. Dalbavancin also exhibited an extended serum elimination half-life allowing single dose or once-daily dosing in the animal infection models and weekly doses in Phase II and III human trials. In one of the first efficacy studies, dalbavancin was well-tolerated, and a regimen of two once-weekly doses eradicated staphylococcal and streptococcal pathogens and was clinically effective in the treatment of deep skin and soft tissue infections with a performance superior to the current standards-of-care including vancomycin. Summaries of three SSTI Phase III clinical trials of dalbavancin showed favorable clinical outcome results when compared to cephalosporin, linezolid and glycopeptide comparator agents.

In the study presented here, we evaluated the spectrum and potency of dalbavancin against a large collection of contemporary (2003) clinical isolates from North America (USA and Canada) and Europe (13 countries) using the reference MIC method of National Committee for Clinical Laboratory Standards (M7-A6, 2003).

MATERIALS AND METHODS

Bacterial isolates. Isolates were collected from more than 50 medical centers in North America (NA) and Europe (EU). A total of 7,771 Gram-positive organisms were evaluated which included (no. for NA/EU): *S. aureus* (1,540/1,877 strains, 31.6/26.1% oxacillin-resistant); CoNS (395/836 strains, 78.2/75.5% oxacillin-resistant); *Streptococcus pneumoniae* (320/362 strains, 38.7/29.3% non-susceptible to penicillin); enterococci (1,171/734 strains, 35.9/8.3% VRE); β-haemolytic streptococci (175/170 strains); viridans group streptococci (66/74 strains, 30.3/29.7% penicillin-non-susceptible); *Bacillus* spp. (10/3 strains); *Corynebacterium* spp. (10/4 strains); *Listeria* monocytogenes (5/6 strains); and *Micrococcus* spp. (6/7 strains).

Minimum inhibitory concentration (MIC) determinations. MICs were determined by the broth microdilution method described by the National Committee for Clinical Laboratory Standards (NCCLS). Dalbavancin was provided by Vicuron Pharmaceuticals, Inc. (King of Prussia, PA) as laboratory grade powder. Powders for comparator antimicrobial agents were obtained from their respective manufacturers or purchased from Sigma Chemical Co. (St. Louis, MO, USA). Validated dry-form panels for susceptibility testing were manufactured by TREK Diagnostics/Sensititre (Cleveland, OH, USA). Dalbavancin and 10 comparator agents were tested, including penicillin or oxacillin or ampicillin, vancomycin, teicoplanin, quinupristin/dalfopristin, linezolid, levofloxacin, chloramphenicol (enterococci only), erythromycin, clindamycin, ceftriaxone, gentamicin and trimethoprim/sulfamethoxazole (not enterococci). Mueller-Hinton broth was used as a growth medium to determine MIC values of non-fastidious organisms.

Mueller-Hinton broth was supplemented with 2 - 5% lysed horse blood to test streptococci, *Listeria* spp., and *Corynebacterium* spp. Susceptibility tests and categorical breakpoints used were those established by the NCCLS. A susceptibility breakpoint for dalbavancin has not been established. Quality control (QC) of test procedures and reagents was monitored via concurrent testing of the following ATCC strains: *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619. All QC values were within published NCCLS ranges for comparator agents and for dalbavancin within those limits suggested in a publication by Anderegg et al and recently approved by NCCLS.

RESULTS

- The most commonly tested Gram-positive cocci tested against dalbavancin were: *S. aureus* (3,417) > enterococci (1,905) > CoNS (1,231) > *S. pneumoniae* (682) > other streptococci (485), regardless of region (North America or Europe).
- Against staphylococci, dalbavancin activity ($MIC_{50/90}$, 0.03/0.06 µg/ml) was uniform between *S. aureus* and CoNS, as well as between regions (**Table 1**). Dalbavancin was 32-fold more active than vancomycin and 64-fold more active than linezolid.
- Streptococci were inhibited by very low concentrations of dalbavancin (MIC_{90}, 0.016 - 0.03 µg/ml) and inter-regional variations were not significant (**Table 1**).
- Dalbavancin was more potent than vancomycin or linezolid against *S. pneumoniae* (32- to 64-fold), β-haemolytic streptococci (16- to 64-fold) and viridans group streptococci (32-fold). Dalbavancin was at least equivalent to penicillin against penicillin-susceptible streptococcal isolates and more potent against peniciln-resistant strains.
- Dalbavancin activity varied against enterococci. The dalbavancin MIC_{50} for vancomycin-susceptible strains was 0.03 - 0.06 µg/ml. Its potency was ≥ 32-fold greater than vancomycin or linezolid (**Table 1**).
- Dalbavancin MICs were higher for vancomycin-resistant enterococci (**Table 2**), because of the VanA isolates within the tested population.
- **Table 2** illustrates that oxacillin resistance in staphylococci (*S. aureus* or CoNS) and penicillin resistance in *S. pneumoniae* did not influence the dalbavancin MIC results.
- Uncommonly isolated species (*Bacillus* spp., *Corynebacterium* spp., *L. monocytogenes, Micrococcus* spp.) of Gram-positive organisms were also inhibited by low concentrations of dalbavancin; MIC_{90} range 0.03 - 0.12 µg/ml (all inhibited at ≤ 0.25 µg/ml; see **Table 3**).
- **Table 4** lists the dalbavancin MIC distributions by geographic region versus four groups of Gram-positive cocci. Distributions were nearly identical between regions and all staphylococci and *S. pneumoniae* were inhibited by ≤ 0.5 µg/ml of dalbavancin. Only the enterococcal strains showed higher dalbavancin MICs, for the VRE subset.

Table 1. In vitro activity of dalbavancin and 10 selected comparison agents tested by NCCLS reference methods against 7,720 Gram-positive organisms isolated in 2003 from patient infections in North America and Europe.

	Europe		North America	
Organism/antimicrobial agent	$MIC_{50/90}$	% susceptible[a]	$MIC_{50/90}$	% susceptible[a]
S. aureus (no. tested)	(1,877)		(1,540)	
Dalbavancin	0.03/0.06	-	0.03/0.06	-
Vancomycin	1/1	100.0	1/1	100.0
Teicoplanin	≤2/≤2	99.9	≤2/≤2	100.0
Linezolid	2/2	99.9	2/2	100.0
Q/D[b]	0.5/0.5	99.7	0.5/0.5	99.9
Oxacillin	0.5/>8	73.9	0.5/>8	68.4
Erythromycin	0.25/>8	67.7	0.5/>8	50.3
Clindamycin	0.12/>8	84.3	0.12/>8	72.6
Levofloxacin	0.25/>4	73.5	0.25/>4	66.2
Gentamicin	≤2/>8	86.0	≤2/≤2	94.9
TMP/SMX[b]	≤0.5/≤0.5	94.8	≤0.5/≤0.5	94.7
CoNS (no. tested)[c]	(836)		(395)	
Dalbavancin	0.03/0.06	-	0.03/0.06	-
Vancomycin	1/2	100.0	1/2	100.0
Teicoplanin	≤2/4	97.1	≤2/8	97.0
Linezolid	1/1	100.0	1/1	100.0
Q/D[b]	≤0.25/0.5	99.5	≤0.25/0.5	99.7
Oxacillin	2/>8	24.5	2/>8	22.8
Erythromycin	>8/>8	39.8	>8/>8	34.7
Clindamycin	≤0.06/>8	69.3	0.12/>8	64.3
Levofloxacin	2/>4	54.8	2/>4	51.5
Gentamicin	4/>8	55.3	≤2/>8	75.7
TMP/SMX[b]	≤0.5/>2	52.6	≤0.5/>2	60.0
Enterococci (no. tested)[d]	(734)		(1,171)	
Dalbavancin	0.03/0.12	-	0.06/16	-
Vancomycin	1/2	91.7	2/>16	64.1
Teicoplanin	≤2/≤2	94.1	≤2/>16	70.2
Linezolid	2/2	100.0	2/2	99.6
Q/D[b]	>2/>2	19.5	>2/>2	33.5
Ampicillin	2/>16	82.3	2/>16	65.7
Erythromycin	>8/>8	5.9	>8/>8	6.6
Chloramphenicol	8/>16	76.0	8/>16	87.2
Levofloxacin	1/>4	58.9	>4/>4	34.8
Gentamicin-HL[b]	≤500/>1000	68.3	≤500/>1000	64.9
Tetracycline	>8/>8	36.9	>8/>8	35.7
β-streptococci (no. tested)	(170)		(175)	
Dalbavancin	≤0.008/0.016	-	≤0.008/0.03	-
Vancomycin	0.25/0.5	100.0	0.5/0.5	100.0
Teicoplanin	≤2/≤2	100.0	≤2/≤2	100.0
Linezolid	1/1	100.0	1/1	100.0
Q/D[b]	≤0.25/0.5	100.0	≤0.25/0.5	100.0
Penicillin	≤0.016/0.06	100.0	0.03/0.06	100.0
Erythromycin	≤0.06/2	86.5	≤0.06/4	79.3
Clindamycin	≤0.06/≤0.06	94.7	≤0.06/≤0.06	93.1
Levofloxacin	0.5/1	100.0	0.5/1	100.0
Ceftriaxone	≤0.25/≤0.25	100.0	≤0.25/£0.25	100.0
TMP/SMX[b]	≤0.5/≤0.5	98.2	≤0.5/≤0.5	96.0
S. pneumoniae (no. tested)	(362)		(320)	
Dalbavancin	0.016/0.016	-	0.016/0.016	-
Vancomycin	0.25/0.5	100.0	0.25/0.5	100.0
Teicoplanin	≤2/≤2	100.0	≤2/≤2	100.0
Linezolid	1/1	100.0	1/1	100.0
Q/D[b]	≤0.5/≤0.5	100.0	≤0.5/≤0.5	99.7
Penicillin	≤0.3/2	70.7	≤0.3/4	61.3
Erythromycin	≤0.25/>32	72.6	≤0.25/>32	68.4
Clindamycin	≤0.25/2	82.6	≤0.25/>2	84.9
Levofloxacin	1/2	99.7	1/2	100.0
Ceftriaxone	0.25/1	97.0	0.25/1	96.6
TMP/SMX[b]	≤0.5/4	71.5	≤0.5/>4	64.4
viridans gr. streptococci (no. tested)	(74)		(66)	
Dalbavancin	0.016/0.03	-	≤0.008/0.03	-
Vancomycin	0.5/1	100.0	0.5/1	100.0
Teicoplanin	≤2/≤2	100.0	≤2/≤2	100.0
Linezolid	1/1	100.0	1/1	100.0
Q/Db	0.5/1	98.6	0.5/1	100.0
Penicillin	0.06/2	70.3	0.06/1	69.7
Erythromycin	0.25/>8	51.4	≤0.06/4	54.5
Clindamycin	≤0.06/>8	81.1	≤0.06/≤0.06	95.5
Levofloxacin	1/2	98.6	1/2	98.5
Gentamicin	≤0.25/2	89.2	≤0.25/1	92.4
TMP/SMX[b]	≤0.5/>2	78.4	≤0.5/>2	84.8

a. NCCLS interpretive criteria [2004], where available. Dalbavancin has no established breakpoints.
b. Q/D = quinupristin/dalfopristin; TMP/SMX = trimethoprim/sulfamethoxazole; gentamicin-HL = high-level resistance screen (≤500 mg/ml = susceptible).
c. CoNS = coagulase-negative staphylococci.
d. Includes: *E. faecalis* (1,295 strains), *E. faecium* (537 strains), *E. casseliflavus* (10 strains), *E. gallinarum* (25 strains), *E. avium* (six strains), *E. durans* (10 strains), *E. hirae* (three strains), *E. mundtii* (two strains) and 16 other enterococcal species isolates.

Table 2. Distribution of dalbavancin MICs by geographic area and resistance phenotype (7,235 strains isolated in 2003).

	$MIC_{50/90}$ (µmg/ml)		
Organism/resistance phenotype (no. tested	Europe	North America	Both continents
S. aureus, oxacillin-susceptible (2,441)	0.03/0.06	0.06/0.06	0.03/0.06
oxacillin-resistant (976)	0.03/0.06	0.03/0.06	0.03/0.06
CoNS, oxacillin-susceptible (295)	0.03/0.06	0.03/0.06	0.03/0.06
oxacillin-resistant (936)	0.03/0.06	0.03/0.06	0.03/0.06
S. pneumoniae, penicillin-susceptible (452)	0.016/0.03	0.016/0.03	0.016/0.03
penicillin-intermediate (107)	0.016/0.016	0.016/0.016	0.016/0.016
penicillin-resistant (123)	0.016/0.016	0.016/0.016	0.016/0.016
Enterococci, vancomycin-susceptible (1,424)	0.03/0.06	0.03/0.06	0.03/0.06
vancomycin-resistant (481)	4/>16	8/16	8/>16

Table 3. Dalbavancin MIC results for rarely isolated Gram-positive species.

	Dalbavancin MIC (µg/ml)		
Organism (no. tested)	50%	90%	Range
Bacillus spp. (13)	0.03	0.12	0.016-0.25
Corynebacterium spp. (14)	0.06	0.12	0.016-0.25
Listeria monocytogenes (11)	0.06	0.06	0.03-0.06
Micrococcus spp. (13)	0.016	0.03	≤0.008-0.03
All strains (51)	0.03	0.12	≤0.008-0.25

Table 4. Dalbavancin MIC distributions for key Gram-positive pathogens indexed by geographic region of the sample.

	Occurrences at each MIC:							
	S. aureus		CoNS		*S. pneumoniae*		Enterococci	
Dalbavancin MIC (µg/ml)	EU	N. Am.	EU	N. Am.	EU	N. Am.	EU	N. Am.
≤0.008	1	1	7	5	92	119	7	4
0.016	40	15	216	57	236	170	45	33
0.03	972	755	440	216	34	30	343	420
0.06	826	740	100	84		1	233	296
0.12	36	26	53	24			58	59
0.25	2	3	19	6			7	8
0.5			1	3			3	16
1							4	17
2							2	20
4							10	38
8							6	106
≥16							16	159
(Total)	(1,877)	(1,540)	(836)	(345)	(362)	(320)	(734)	(1,171)

CONCLUSIONS

- Dalbavancin demonstrates wide, potent activity against Gram-positive species; 16- to 64-fold greater than currently available glycopeptides or oxazolidinones. Results were similar to those of a similar survey conducted in 2002.
- Dalbavancin MICs are higher for some VRE (VanA phenotypes).
- These in vitro features for dalbavancin were similar in Europe and North America although the VRE rates were greater in the USA.
- Recent clinical trial success (Phase II and III) for dalbavancin used once weekly demonstrates potential use in cutaneous infections and expanded applications appear warranted at a global level.

REFERENCES

Anderegg TR, Biedenbach DJ, Jones RN. (2003). Initial quality control evaluations for susceptibility testing of dalbavancin (BI 397), an investigational glycopeptide with Gram-positive activity. *Journal of Clinical Microbiology* 4:2795-2796.

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

Centers for Disease Control and Prevention. (2002). *Staphylococcus aureus* resistant to vancomycin: United States, 2002. *Morbidity and Mortality Weekly Report* 51:565-567.

Chang S, Sievert DM, Hageman JC, Boulton ML, Tenover FC, Downes FP, Shah S, Rudrik JT, Pupp GR, Brown WJ, Cardo D, Fridkin SK. (2003). Infection with vancomycin-resistant *Staphylococcus aureus* containing the vanA resistance gene. *New England Journal of Medicine* 348:1342-1347.

Goldstein BP, Candiani GP, Arain TM, Romanò G, Ciciliato I, Berti M, Abbondi M, Scotti R, Marini M, Ripamonti F, Resconi A, Denaro M (1995). Antimicrobial activity of MDL 63,246, a new semisynthetic glycopeptide antibiotic. *Antimicrobial Agents and Chemotherapy* 39:1580-1585.

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

Gonzales RD, Schreckenberger PC, Graham MB, Kelkar W, DenBesten K, Quinn JP. (2001). Infections due to vancomycin-resistant *Enterococcus faecium* resistant to linezolid (letter). *Lancet* 357:1179.

Jones RN, Streit JM, Fritsche TR. (2003). Validation of commercial dry-form broth microdilution panels and test reproducibility for susceptibility testing of dalbavancin, a new very long-acting glycopeptide. *International Journal of Antimicrobial Agents* (in press).

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

Mutnick AH, Enne V, Jones RN. (2003). Linezolid resistance since 2001: SENTRY Antimicrobial Surveillance Program. *The Annals of Pharmacotherapy* 37:769-774.

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

National Committee for Clinical Laboratory Standards. (2004). *MIC testing. Performance standards for antimicrobial susceptibility testing (M100-S14)*. Wayne, PA:NCCLS.

Seltzer E, Goldstein B, Dorr M-B, Dowell J, Perry M, Henkel T. (2003). Dalbavancin: Phase II demonstration of efficacy of a novel, weekly dosing regimen in skin and soft tissue infection, Abstr. 0143. *Clinical Microbiology and Infection* 9(Suppl 1):22.

Woodford N. (2003). Novel agents for the treatment of resistant Gram-positive infections. *Expert Opinion of Investigational Drugs* 12:117-137.