Dalbavancin Surveillance Results for European Gram-positive Species in a Contemporary (2006-2009) Sample of 23,825 Strains

1129

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ECCMID 2011
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ABSTRACT

Objectives: To assess the in vitro activity of dalbavancin (DALB) for in vitro potency and breadth of spectrum against Gram-positive cocci (3 genera) isolated in European medical centers between 2006 and 2009. Reference MIC susceptibility (S) testing methods (CLSI, M07-A8, 2009) and EUCAST breakpoints were applied to comparator antimicrobials.

Methods: A total of 23,825 strains were tested as follows: *S. aureus* (SA; 11,658 strains, 27.3% MRSA), coagulase-negative staphylococci (CoNS; 4,343 strains, 77.5% oxacillin-resistant [R]), *Enterococcus* spp. (4,982 strains; 525 strains were vancomycin-non-S, 10.5%), viridans group streptococci (VGS; 845 strains) and beta-haemolytic streptococci (BHS; 1,997 strains). A total of 5,750 to 6,370 clinical isolates were sampled each year from 13 nations (30 medical centers), the greatest numbers from France (19.4%) and Germany (16.1%). Many strains were from bacteremias (43.2%).

Results: DALB MIC results performed by validated reference methods (0.002% polysorbate-80 supplement) demonstrated high potency versus *S. aureus* (MIC_{90}, 0.06 mg/L; all strains inhibited at ≤0.25 mg/L), as well as CoNS (MIC_{90}, 0.12 mg/L), and all streptococci (MIC_{90}, ≤0.03-0.06 mg/L). Only for VanA phenotype VRE was the DALB MIC at >0.25 mg/L for the majority of strains. In the EU, *S. aureus* and CoNS were also highly S to daptomycin (DAP; 100.0%), vancomycin (VAN; 100.0%), linezolid (99.8-99.9%), and quinupristin/dalfopristin (98.2-99.7%); but less so to teicoplanin (72.0-99.3%).

European pathogen (no. tested)	DALB MIC (mg/L): MIC_{50}	MIC_{90}	Range	% inhibited at DALB MIC[a]: ≤0.25 mg/L	≤1 mg/L
All *S. aureus* (11,658)	0.06	0.06	≤0.03-0.25	100.0	-
MRSA (3,183)	0.06	0.06	≤0.03-0.25	100.0	-
CoNS (4,343)	0.06	0.12	≤0.03-2	99.6	>99.9
S. pyogenes (793)	≤0.03	≤0.03	≤0.03-0.25	100.0	-
S. agalactiae (817)	≤0.03	≤0.03	≤0.03-0.25	100.0	-
Viridans group streptococci (845)	≤0.03	0.06	≤0.03-0.12	100.0	-
All enterococci (4,982)	0.06	0.12	≤0.03->4	91.8	92.6
VRE (525)	4	>4	≤0.03->4	23.6	29.9

a. DALB MIC.

Conclusions: DALB exhibited stable, potent in vitro activity against an updated surveillance collection (2006-2009) of Gram-positive pathogens isolated in EU. The MIC_{90} results (≤0.03-0.12 mg/L; Table) remain low and DALB was generally eight- to 16-fold more potent than DAP and VAN. This long-acting lipoglycopeptide continues to demonstrate high potencies against EU pathogens through 2009.

INTRODUCTION

Dalbavancin (formerly BI397, MDL 63,399, A-A1, VER001) is an investigational lipoglycopeptide with an elimination half-life allowing weekly dosing with initial reports of high clinical successes in Phase 2 and 3 trials. The potency and spectrum of dalbavancin most closely resembles teicoplanin, however, advantages for dalbavancin include inhibition of some enterococci resistant to vancomycin (Van B phenotypes) and many coagulase-negative staphylococci (CoNS) observed to be resistant to teicoplanin. The compound is a semisynthetic derivative of a natural glycopeptide (A-40,926) produced by a 3,3-dimethylaminopropyl amide substitution on the peptide carboxyl group. Such modifications of existing structures of Gram-positive-active antimicrobial agents have been necessary to address emerging resistances, as well as the development of novel structures such as the oxazolidinones, streptogramin combinations and other classes.

In vitro international resistance surveillance programs for dalbavancin were initiated in 2002-2004 and the 2006-2009 results for the European area are presented here. A total of 23,825 Gram-positive cocci were tested, using reference methods of the Clinical and Laboratory Standards Institute (CLSI; formerly the NCCLS). Results for 2002-2004 will be compared to the dalbavancin activity documented for 2006-2009 (Jones et al. 2004; Streit et al., 2004).

MATERIALS AND METHODS

Bacterial isolates: All of the 23,825 Gram-positive strains were isolated in European medical centres over the years of 2006 (5,826 strains), 2007 (6,370 strains), 2008 (5,879 strains) and 2009 (5,750 strains). A total of 14 countries (Belgium, France, Germany, Greece, Ireland, Israel, Italy, Poland, Portugal, Spain, Sweden, Switzerland, Turkey and United Kingdom) participated using isolates from 30 hospital laboratories (99-1,295 strains/site). At least 43.2% of the Gram-positive pathogens came from bloodstream infections.

The distribution of organisms was: *S. aureus* (11,658 strains; 27.3% MRSA), CoNS (4,343 strains; 77.5% methicillin-resistant), enterococci (4,982 strains; vancomycin-non-susceptible at 10.5%), viridans group streptococci (845 strains) and β-haemolytic streptococci (1,997 strains; 39.7% *S. pyogenes* and 41.0% *S. agalactiae*)

Susceptibility testing: The MIC results were generated by the reference-quality CLSI method (M07-A8, 2009) with concurrent quality control (QC) guided by CLSI document M100-S21 (2011). All QC results were within ranges for dalbavancin (Anderegg et al., 2003) and multiple comparison agents.

The method used was a dry-form product (SensiTitre panels; TREK Diagnostic, Cleveland, Ohio, USA) validated by Jones et al. (2004) as being comparable to the CLSI M07-A8 method. The accuracy was very high having the same results in 76.2% of MIC comparisons and 98.6% ± one doubling dilution step using a collection of 429 organisms. Reproducibility was also assessed (± one doubling dilution) at 100.0%. Reference dalbavancin MIC values were tested with a 0.002% polysorbate-80 surfactant supplement to minimize drug binding to panel plastics.

RESULTS

- Table 1 illustrates the potent dalbavancin activity tested against *S. aureus* ($MIC_{50/90}$, 0.06/0.06 mg/L) and CoNS ($MIC_{50/90}$, 0.06/0.12 mg/L), regardless of methicillin susceptibility. All *S. aureus* were inhibited by ≤0.25 mg/L of dalbavancin with a clear modal MIC at 0.06 mg/L.

- Dalbavancin was four- to eight-fold more active than daptomycin, 16-fold more potent than vancomycin, and 32-fold more active than linezolid when tested against European *S. aureus* isolates (11,658 strains; Table 2).

- Enterococcal susceptibility to dalbavancin varied by the vancomycin resistance phenotypes: vancomycin-susceptible (VAN-S, $MIC_{50/90}$, 0.06/0.12 mg/L) and vancomycin-non-susceptible ($MIC_{50/90}$, 4/>4 mg/L), see Tables 1-2. VanB resistant strains were most like VAN-S strains for dalbavancin potency (data not shown).

- Dalbavancin was very active against viridans group ($MIC_{50/90}$, ≤0.03/0.06 mg/L) and β-haemolytic streptococci ($MIC_{50/90}$, ≤0.03/≤0.03 mg/L); all European isolates were inhibited by ≤0.25 mg/L (Tables 1 and 2).

Table 2. Comparative potencies of selected agents (7-10) and dalbavancin tested against European clinical isolates (2006-2009).

Organism (no. tested)	Antimicrobial agent	MIC (mg/L) 50%	90%	% susceptible:[a] CLSI	EUCAST
S. aureus (11,658)	Dalbavancin	0.06	0.06 (0.25)[b]	-[c]	-
	Daptomycin	0.25	0.5	100.0	100.0
	Teicoplanin	≤2	≤2	100.0	99.3
	Vancomycin	1	1	100.0	100.0
	Oxacillin	0.5	>2	72.7	72.7
	Erythromycin	≤0.25	>2	70.3	70.9
	Clindamycin	≤0.25	>2	88.6	88.1
	Levofloxacin	≤0.5	>4	71.3	71.3
	Tetracycline	≤2	≤2	91.4	91.2
	TMP/SMX[d]	≤0.5	≤0.5	99.0	99.0
	Linezolid	2	2	>99.9[e]	>99.9[e]
CoNS (4,343)	Dalbavancin	0.06	0.12 (2)[b]	-	-
	Daptomycin	0.25	0.5	99.8	99.8
	Teicoplanin	≤2	4	98.0	91.7
	Vancomycin	1	2	99.4	99.4
	Oxacillin	>2	>2	22.5	22.5
	Erythromycin	>2	>2	35.6	35.7
	Clindamycin	≤0.25	>2	70.9	68.5
	Levofloxacin	4	>4	41.7	41.7
	Tetracycline	≤2	>8	84.6	81.1
	TMP/SMX[d]	≤0.5	>2	60.1	60.1
	Linezolid	1	1	99.8[f]	99.8[f]
Enterococci (4,982)	Dalbavancin	0.06	0.12 (>4)[b]	-	-
	Daptomycin	1	2	100.0	-
	Teicoplanin	≤2	≤2	91.7	91.6
	Vancomycin	1	16	89.5	89.5
	Ampicillin	2	>16	66.1	65.8
	Q/D[d]	>2	>2	26.9	26.9
	Levofloxacin	>4	>4	47.2	-
	Linezolid	1	2	99.8[g]	99.9[g]
Viridans gr. streptococci (845)	Dalbavancin	≤0.03	0.06 (0.12)[b]	-	-
	Daptomycin	0.25	0.5	99.9	-
	Teicoplanin	≤2	≤2	-	100.0
	Vancomycin	0.5	1	100.0	100.0
	Penicillin	0.06	1	77.2	83.7
	Erythromycin	≤0.25	>2	63.0	63.0
	Clindamycin	≤0.25	>2	88.1	88.5
	Levofloxacin	1	2	96.8	-
	Tetracycline	≤2	>8	61.3	-
	TMP/SMX[d]	≤0.5	2	-	-
	Linezolid	1	1	100.0	-
β-haemolytic streptococci (1,997)	Dalbavancin	≤0.03	≤0.03 (0.25)	-	-
	Daptomycin	≤0.06	0.25	100.0	100.0
	Teicoplanin	≤2	≤2	-	>99.9
	Vancomycin	0.5	0.5	100.0	100.0
	Penicillin	≤0.015	0.06	100.0	100.0
	Erythromycin	≤0.25	>2	83.2	83.2
	Clindamycin	≤0.25	≤0.25	91.8	92.4
	Levofloxacin	≤0.5	1	99.6	95.2
	Tetracycline	≤2	>8	50.8	50.8
	TMP/SMX[d]	≤0.5	≤0.5	-	-
	Linezolid	1	1	100.0	100.0

a. Susceptibility criteria published in 2011.
b. Highest dalbavancin MIC in parentheses.
c. - = no published criteria.
d. TMP/SMX = trimethoprim/sulfamethoxazole (TMP concentration of a 1:19 ratio test) and Q/D = quinupristin/dalfopristin.
e. Two resistant strains.
f. 10 resistant strains.
g. 10 non-susceptible strains.

Table 1. Dalbavancin MIC distributions for the Gram-positive pathogens isolated in European hospitals in 2006-2009 (23,825 strains).

Pathogen/subset (no. tested)[a]	No. (cum.%) occurrences at MIC in mg/L: ≤0.03	0.06	0.12	0.25	0.5	1	2	4	>4
S. aureus									
All (11,658)	2,773 (23.8)	7,987 (92.3)	863 (99.7)	35 (100.0)	-	-	-	-	-
MRSA (3,183)	914 (28.7)	2,018 (92.1)	238 (99.6)	13 (100.0)	-	-	-	-	-
MSSA (8,475)	1,859 (21.9)	5,969 (92.4)	625 (99.7)	22 (100.0)	-	-	-	-	-
CoNS									
All (4,343)	1,690 (38.9)	1,906 (82.8)	575 (96.0)	153 (99.6)	14 (99.9)	4 (>99.9)	1 (100.0)	-	-
Enterococcus spp.									
All (4,982)	1,430 (28.7)	2,359 (76.1)	693 (90.0)	90 (91.8)	15 (92.1)	26 (92.6)	39 (93.4)	73 (94.8)	257 (100.0)
VAN-S (4,457)	1,412 (31.7)	2,301 (83.3)	655 (98.0)	80 (99.8)	7 (>99.9)	1 (>99.9)	1 (100.0)	-	-
VAN-NS (525)	18 (3.4)	58 (14.5)	38 (21.7)	10 (23.6)	8 (25.1)	25 (29.9)	38 (37.1)	73 (51.1)[b]	257 (100.0)[b]
Viridans gr. streptococci									
All (845)	744 (88.1)	95 (99.3)	6 (100.0)	-	-	-	-	-	-
β-haemolytic streptococci									
All (1,997)	1,893 (94.8)	85 (99.1)	15 (99.8)	4 (100.0)	-	-	-	-	-
S. pyogenes (793)	781 (98.5)	10 (99.8)	1 (99.9)	1 (100.0)	-	-	-	-	-
S. agalactiae (817)	740 (90.6)	61 (98.2)	12 (99.6)	3 (100.0)	-	-	-	-	-

a. MRSA = methicillin-resistant *S. aureus*, MSSA = methicillin-susceptible *S. aureus*, CoNS = coagulase-negative staphylococci, VAN-S = vancomycin-susceptible, and VAN-NS = vancomycin-non-susceptible.
b. VanA phenotypes.

CONCLUSIONS

- A European Gram-positive pathogen collection (2006-2009) of 23,825 organisms showed remarkable susceptibility to dalbavancin with MIC_{90} results ranging from ≤0.03 mg/L (β-haemolytic streptococci) to 0.12 mg/L (staphylococci and all enterococci)

- Highest dalbavancin MIC values of 0.5->4 mg/L occurred among CoNS (0.4%), and vancomycin-non-susceptible *Enterococcus* spp. (76.4%), usually Van-A resistant phenotypes of *E. faecium*.

- Using well standardized CLSI methods, validated to results supplemented with a polysorbate-80 surfactant (0.002%), dalbavancin MIC results for European Gram-positive pathogens have remained stable in surveillance programs over seven years (2003-2009) of monitoring. As dalbavancin resumes Phase 3 clinical trials, resistance surveillance should be extended to assure sustained activity.

REFERENCES

1. Anderegg TR, Biedenbach DJ, Jones RN (2003). Initial quality control evaluations for susceptibility testing of Dalbavancin (BI397), an investigational glycopeptide with potent gram-positive activity. *J Clin Microbiol* 41: 2795-2796.
2. Biedenbach DJ, Ross JE, Fritsche TR, Sader HS, Jones RN (2007). Activity of dalbavancin tested against *Staphylococcus* spp. and beta-hemolytic *Streptococcus* spp. isolated from 52 geographically diverse medical centers in the United States. *J Clin Microbiol* 45: 998-1004.
3. Candiani G, Abbondi M, Borgonovi M, Romano G, Parenti F (1999). In-vitro and in-vivo antibacterial activity of BI 397, a new semi-synthetic glycopeptide antibiotic. *J Antimicrob Chemother* 44: 179-192.
4. Clinical and Laboratory Standards Institute (2009). *M07-A8. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: eighth edition.* Wayne, PA: CLSI.
5. Clinical and Laboratory Standards Institute (2011). *M100-S21. Performance standards for antimicrobial susceptibility testing: 21st informational supplement.* Wayne, PA: CLSI.
6. EUCAST (2011). Breakpoint tables for interpretation of MICs and zone diameters. Version 1.3, January 2011. Available at: http://www.eucast.org/clinical_breakpoints/. March 18, 2011.
7. Jauregui LE, Babazadeh S, Seltzer E, Goldberg L, Krievins D, Frederick M, Krause D, Satilovs I, Endzinas Z, Breaux J, O'Riordan W (2005). Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. *Clin Infect Dis* 41: 1407-1415.
8. Jones RN, Fritsche TR, Sader HS, Goldstein BP (2005). Antimicrobial spectrum and potency of dalbavancin tested against clinical isolates from Europe and North America (2003): initial results from an international surveillance protocol. *J Chemother* 17: 593-600.
9. Jones RN, Streit JM, Fritsche TR (2004). Validation of commercial dry-form broth microdilution panels and test reproducibility for susceptibility testing of dalbavancin, a new very long-acting glycopeptide. *Int J Antimicrob Agents* 23: 197-199.
10. Raad I, Darouiche R, Vazquez J, Lentnek A, Hachem R, Hanna H, Goldstein B, Henkel T, Seltzer E (2005). Efficacy and safety of weekly dalbavancin therapy for catheter-related bloodstream infection caused by gram-positive pathogens. *Clin Infect Dis* 40: 374-380.
11. Seltzer E, Dorr MB, Goldstein BP, Perry M, Dowell JA, Henkel T (2003). Once-weekly dalbavancin versus standard-of-care antimicrobial regimens for treatment of skin and soft-tissue infections. *Clin Infect Dis* 37: 1298-1303.
12. Streit JM, Fritsche TR, Sader HS, Jones RN (2004). Worldwide assessment of dalbavancin activity and spectrum against over 6,000 clinical isolates. *Diagn Microbiol Infect Dis* 48: 137-143.