Comparative Activity of Dalbavancin Tested Against Indicated Gram-positive Species in Europe: Results from Two Spanish Medical Centers (DECIDE Program)

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ABSTRACT

Objective: To assess the activity of dalbavancin (DAL) tested against recent clinical Gram-positive isolates from two medical centers in Spain over the time interval of October - December, 2007. DAL has documented activity comparable to glycopeptides (vancomycin [VAN] and teicoplanin), a prolonged elimination half-life and clinical success in trials for complicated skin and skin structure infections. Potency of DAL was determined separately in five European nations to monitor potential geographic variations against indicated species.

Methods: Standardized and reference quality susceptibility (S) methods of agar diffusion were applied by each investigator. Etest (ET; AB BIODISK, Solna, Sweden) and CLSI (M2-A9) disk diffusion (DD) tests were performed with concurrent quality control (CLSI M100-S17, 2007) and repeated testing of strains showing unusual resistance (R) patterns of linezolid (LZD)-R, and VAN or DAL-non-S. A total of 150 strains were tested against DAL and VAN by ET, and LZD, cefoxitin (for methicillin testing), levofloxacin (LEV), gentamicin (GEN), tetracycline (TC), erythromycin (ERY), clindamycin (CC; plus D-test), penicillin (PEN) and ceftriaxone (CRO) by DD. All sites had acceptable control results using three QC strains. DAL-S was defined as ≤0.25 mg/L.

Results: DAL exhibited high potency against the 100 *S. aureus* ($MIC_{50/90}$, 0.047/0.094 mg/L), coagulase-negative staphylococci (CoNS; $MIC_{50/90}$, 0.047/0.125 mg/L) and beta-haemolytic streptococci (BHS; $MIC_{50/90}$, ≤0.016/≤0.016 mg/L). This activity (MIC_{50} comparison) was 16-, 32- and 64-fold greater than VAN, respectively. MRSA rates varied from 6 to 24 (15% overall) between sites and *S. aureus* S rates were LZD (100%), LEV (82%), ERY (75%), CC (96% with additional 9% inducible R). D-test positive rates in CoNS were 5%; overall CC-R was at 35%. Methicillin R did not adversely influence DAL activity. All BHS (63% *S. pyogenes*) were PEN- and CRO-S. GEN (75-95% S) and TC (85-96% S) were modestly active versus the *S. aureus* and CoNS strains.

Table. Comparative activity of DAL in Spain.

Antimicrobial	% S activity by pathogen (no.)		
	S. aureus (100)[a]	CoNS (20)	BHS (30)[b]
Dalbavancin	100	100	100
Vancomycin	100	100	100
Linezolid	100	100	100
Erythromycin	75	50	87
Clindamycin[c]	87	65	90
Levofloxacin	82	50	90
Ceftriaxone	NT	NT	100

a. MRSA rate was 15%.
b. Includes gr. A (19), gr. B (3), gr. C (2), gr. F (2) and gr. G (4); and all BHS were PEN-S (zone, ≥29 mm).
c. Includes results from D-test (inducible CC-R).

Conclusions: DAL, a novel long-acting glycolipopeptide (once weekly dosing) demonstrated high activity (MIC_{90} ranges, ≤0.016-0.125 mg/L) against tested staphylococci and BHS from Spanish hospitals. The highest recorded MIC was 0.25 mg/L, confirmed in a CoNS from Madrid. The exhibited DAL potency (≥16-fold greater than VAN) appears to cover contemporary Gram-positive pathogens endemic in this area of Europe.

INTRODUCTION

Currently, infections caused by Gram-positive pathogens are presenting medical professionals with difficulty in available treatment options. These are the most prevalent species responsible for skin and skin-structure infections (SSSIs) and antimicrobial agents that can be utilized to eradicate these pathogens should be monitored for efficacy, safety and continued activity. Among the most common causes of SSSIs are *Staphylococcus aureus* and ß-haemolytic streptococci. *S. aureus* is the more prevalent and causes most concern to physicians due to the various resistance mechanisms associated with this species. Oxacillin-resistant *S. aureus* (MRSA) are also often resistant to several other antimicrobial classes such as macrolide-lincosamide-streptogramin B (MLS_B) agents, fluoroquinolones and aminoglycosides for example. These multidrug-resistant (MDR) strains are difficult to treat and often require the use of glycopeptides such as vancomycin. Although ß-haemolytic streptococci remain susceptible to agents such as penicillin and cephalosporins, tolerance has been documented and resistance to MLS_B compounds can be found at high rates in some countries and medical centers.

Dalbavancin is a new promising lipoglycopeptide that has been approved in the United States for the treatment of SSSIs. This novel agent has unique pharmacokinetic properties that allows for once weekly dosing and has proven activity against many commonly isolated Gram-positive bacterial species including oxacillin-susceptible staphylococci, MRSA and ß-haemolytic streptococci.

This study was conducted to determine the potency of dalbavancin compared to vancomycin against staphylococci and ß-haemolytic streptococci isolated from patients in Spain. The antimicrobial susceptibility to other drug classes was also assessed and is presented here.

MATERIALS AND METHODS

A total of 150 Gram-positive bacterial pathogens were collected in two medical centers in Spain that were recruited to test these isolates locally. Sites were asked to test *S. aureus*, including oxacillin-susceptible (MSSA) and MRSA strains, coagulase-negative staphylococci (CoNS) and ß-haemolytic streptococci during 2007. Common lots of Etest (AB BIODISK, Solna, Sweden) and disk diffusion reagents were sent to each site to test a total of 75 isolates combined from the species groups listed above. Collectively, these sites tested 85 MSSA, 15 MRSA, 20 CoNS and 30 ßHS using methods described by the CLSI (M2-A9) and the Etest manufacturer's recommendations.

The following antimicrobial agents were tested for susceptibility against staphylococci: dalbavancin (Etest) and vancomycin (Etest) as well as cefoxitin (for determining MSSA and MRSA), erythromycin, clindamycin, gentamicin, levofloxacin, linezolid and tetracycline using the disk diffusion method. Streptococcal isolates were tested against dalbavancin, vancomycin using Etest and penicillin, ceftriaxone, erythromycin, clindamycin, levofloxacin and linezolid using disks. The D-test was performed on all isolates to determine inducible-clindamycin resistance using the CLSI method (M100-S18). Quality control (QC) was performed during each testing event using *S. aureus* ATCC 29213 (Etest validation only), *S. aureus* ATCC 25923 (disk validation only) and *S. pneumoniae* ATCC 49619. All QC values were within control ranges recommended by the CLSI (M100-S18).

RESULTS

- Comparing the dalbavancin MIC_{50} (0.047 mg/L) and MIC_{90} (0.094 mg/L) values against MSSA and MRSA showed that the overall potency was similar (Table 1). However, the cumulative inhibition percentages presented in this table show that more MSSA isolates (approximately 10%) were inhibited at lower concentrations of dalbavancin compared to MRSA.
- Dalbavancin (MIC_{90}, 0.094 mg/L) was 16-fold more potent than vancomycin (MIC_{90}, 1.5 mg/L) tested against *S. aureus*, as well as CoNS which had slightly higher MIC_{90} values of 0.125 mg/L and 2 mg/L for these two agents, respectively (see Table 1).
- All ß-haemolytic *Streptococcus* spp. were inhibited at a dalbavancin concentration of ≤0.06 mg/L and 90% of strains had a MIC value of ≤0.016 mg/L (Table 1). Only *S. agalactiae* isolates had dalbavancin MIC values elevated above ≤0.016 mg/L.
- Among the Gram-positive isolates tested in this study, all were susceptible to dalbavancin, vancomycin and linezolid (Table 2).
- Decreased activity among comparison agents was noted among the MRSA and CoNS isolates which were 75% oxacillin-resistant. For example, erythromycin resistance was 73.3% for the MRSA (0% inducible-clindamycin resistance) and 50.0% (50.0% inducible-clindamycin resistance) for the CoNS (Table 2).

Table 1. Dalbavancin activity compared to vancomycin when tested against 150 recent Gram-positive isolates in Spain during 2007.

Organism group (no. tested)/Antimicrobial	Cumulative % inhibited at MIC (mg/L):[a]									MIC (mg/L)[b]	
	≤0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	50%	90%
S. aureus											
Oxacillin-susceptible (85)											
Dalbavancin	0.0	8.2	89.4	100.0	-	-	-	-	-	0.047	0.094
Vancomycin	0.0	0.0	0.0	0.0	0.0	2.4	83.5	100.0	-	1	1.5
Oxacillin-resistant (15)											
Dalbavancin	6.7	6.7	80.0	100.0	-	-	-	-	-	0.047	0.094
Vancomycin	0.0	0.0	0.0	0.0	0.0	0.0	46.7	100.0	-	1.5	1.5
Coagulase-negative staphylococci (20)											
Dalbavancin	5.0	15.0	75.0	95.0	100.0	-	-	-	-	0.047	0.125
Vancomycin	0.0	0.0	0.0	0.0	0.0	0.0	10.0	100.0	-	1.5	2.0
ß-haemolytic streptococci (30)[c]											
Dalbavancin	90.0	93.3	100.0	-	-	-	-	-	-	≤0.016	≤0.016
Vancomycin	0.0	0.0	0.0	0.0	33.3	86.7	100.0	-	-	0.38	0.75

a. Etest results (AB BIODISK, Solna, Sweden), results rounded to $\log_2$ scale.
b. Etest results unrounded to the $\log_2$ scale allowing MIC precision at the one-half $\log_2$ scale (15 total dilution steps).
c. The majority of ß-haemolytic of streptococci were serotype group A (19 strains). Other serotypes (B, C, G and F) included ≤four strains.

Table 2. Dalbavancin activity compared to seven other agents when tested against 150 Gram-positive cocci in two laboratories in Spain.

Organism group (no. tested)	Antimicrobial agent	% susceptible[a]	% resistant
S. aureus			
Oxacillin-resistant (15)	Dalbavancin	100.0	-[b]
	Vancomycin	100.0	0.0
	Erythromycin	26.7	73.3
	Clindamycin	73.3	26.7
	Levofloxacin	6.7	93.3
	Gentamicin	73.3	26.7
	Tetracycline	93.3	0.0
	Linezolid	100.0	-
Oxacillin-susceptible (85)	Dalbavancin	100.0	-
	Vancomycin	100.0	0.0
	Erythromycin	83.5	12.9
	Clindamycin	100.0	0.0
	Levofloxacin	95.3	4.7
	Gentamicin	98.8	1.2
	Tetracycline	96.5	1.2
	Linezolid	100.0	-
Coagulase-negative staphylococci (20)	Dalbavancin	100.0	-
	Vancomycin	100.0	0.0
	Erythromycin	50.0	50.0
	Clindamycin	70.0	20.0
	Levofloxacin	50.0	45.0
	Gentamicin	70.0	20.0
	Tetracycline	85.0	15.0
	Linezolid	100.0	-
ß-haemolytic streptococci (30)	Dalbavancin	100.0	-
	Vancomycin	100.0	-
	Penicillin	100.0	-
	Ceftriaxone	100.0	-
	Erythromycin	86.7	13.3
	Clindamycin	90.0	3.3
	Levofloxacin	90.0	6.7
	Linezolid	100.0	-

a. Susceptibility criteria of the CLSI (M100-S18, 2008) were used where available. For dalbavancin, proposed susceptible only breakpoints of ≤0.25 mg/L for all species were used for comparisons with vancomycin, both drugs tested by Etest (AB BIODISK).
b. - = no resistant breakpoint criteria have been recommended.

- The ß-haemolytic streptococci were all categorized as susceptible to penicillin and ceftriaxone and were 90% susceptible to levofloxacin (two resistant strains detected, 6.7%) and clindamycin. Only one isolate among the three erythromycin-resistant, clindamycin-susceptible isolates had a positive D-test result.

CONCLUSIONS

- Dalbavancin was shown to have a significant potency advantage (16-fold) over vancomycin among the Gram-positive pathogens tested against this collection of Spanish isolates.
- The potency advantage of dalbavancin compared to class comparators, coupled with the advantages in patient dosing provides a promising therapeutic alternative for treating serious Gram-positive infections, including MRSA and other species which are common causes of SSSI.
- The results obtained from this limited number of isolates and two medical centers presented here will be expanded upon by increasing the number of investigator sites over the next two years. The data provided by this expansion will provide a more comprehensive analysis of the potency of dalbavancin and the rates of resistance to other antimicrobial classes in Spain.

SELECTED REFERENCES

1. Clinical and Laboratory Standards Institute. (2008). *M100-S18, Performance standards for antimicrobial susceptibility testing, 18th informational supplement*. Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute. (2006). *M2-A9. Performance standards for antimicrobial disk susceptibility tests; approved standard - ninth edition*. Wayne, PA: CLSI.
3. Fritsche TR, Rennie RP, Goldstein BP, Jones RN (2006). Comparison of dalbavancin MIC values determined by Etest (AB BIODISK) and reference dilution methods using Gram-positive organisms. *J Clin Microbiol* 44: 2988-2990.
4. 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.
5. 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.
6. Lin SW, Carver PL, DePestel DD (2006). Dalbavancin: A new option for the treatment of Gram-positive infections. *Ann Pharmacother* 40: 449-460.