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Dalbavancin (DECIDE) Tested Against Indicated Gram-positive Species in European Medical Centers: Results from France

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AMENDED ABSTRACT

Objective: To assess the dalbavancin (DAL) spectrum and potency when tested against recent clinical isolates from five medical centers in France from October - December, 2007 (373 strains).

Methods: Standardized and reference-quality susceptibility (S) methods of agar diffusion were applied by each investigator. Etest (ET; AB BIODISK, Solna, Sweden) and the 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 in linezolid (LZD)-R, vancomycin (VAN) or DAL-non-S. A total of 373 strains were tested against DAL and VAN by ET; and LZD, cefoxitin (methicillin susceptibility surrogate), levofloxacin (LEV), gentamicin (GEN), tetracycline (TC), erythromycin (ERY), clindamycin (CC; plus D-test), penicillin (PEN) and ceftriaxone (CRO) by DD. All five French sites had acceptable quality control results. DAL-S was defined at ≤0.25 mg/L for staphylococci and streptococci.

Results: DAL exhibited ≥16-fold greater activity than VAN against the 249 *S. aureus* ($MIC_{50/90}$, 0.094/0.125 mg/L), 51 coagulase-negative staphylococci (CoNS; $MIC_{50/90}$, 0.064/0.125 mg/L) and 73 beta-haemolytic streptococci (BHS; $MIC_{50/90}$, ≤0.016/0.032 mg/L). The most common beta-streptococci group was *S. pyogenes* (approx. 60% of strains). MRSA rates were uniform from 20 to 29% (average at 25%) among sites and S rates across all staphylococci were LZD (100%), LEV (55-74%), ERY (59-73%), CC (80-86% with additional 9-18% inducible R), TC (93-94%) and GEN (63-98%). D-test positive rates in BHS and CoNS were 0 and 47% of ERY-R/CC-S isolates, respectively. LEV-R BHS (one each of gr. A and G) were detected in Paris. The most elevated DAL MIC results were 0.25 mg/L (two strains, SA and CoNS) from Paris and Lyon.

Table. Comparative activity of DAL in France (5 sites).

Method/Antimicrobial	% S activity by pathogen (no.)		
	S. aureus (249)	CoNS (51)	BHS (73)
Etest			
Dalbavancin	100	100	100
Vancomycin	100	100	100
Disk diffusion			
Linezolid	100	100	99
Erythromycin	73	49	74
Clindamycin[a]	86 (9)	80 (18)	73 (0)
Levofloxacin	74	55	95
Oxacillin[b]	75	49	NT

a. Includes % R results with D-test inducible CC-R in parenthesis.
b. MRSA rate was 25% tested by cefoxitin disks (≤21 mm); and all BHS were CRO- and PEN-S.

Conclusions: DAL, a novel glycolipopeptide ($t_{1/2}$ at 6-8 days; once weekly dosing) showed high activity (MIC_{90} range, ≤0.032-0.125 mg/L) against tested staphylococci and BST from France. The documented DAL activity (≥16-fold greater than VAN) exhibited wide spectrum of coverage of contemporary Gram-positive pathogens endemic to the five centers including strains R to other antimicrobial classes.

INTRODUCTION

The vast majority of skin and skin structure infections (SSTI) are caused by Gram-positive pathogens. The most significant of these pathogens is *Staphylococcus aureus* which has become increasingly important due to the increasing resistance patterns that have evolved over the last several decades. Oxacillin (ß-lactam) resistance has become serious in *S. aureus* isolates obtained from patients with both community-acquired (CA) and nosocomial SSTI. Resistance to macrolide-lincosamide-streptogramin B (MLS_B) agents has also become problematic with many isolates having inducible clindamycin resistance. More recently, glycopeptide resistance has been documented at both high/detectible levels as well as intermediate levels of resistance. Vancomycin-intermediate (VISA) and hetero-resistant (hVISA) *S. aureus* have been detected in many countries.

ß-haemolytic streptococci are also commonly isolated from wound cultures. This group of pathogens have remained susceptible to penicillins and advanced generation cephalosporins, such as ceftriaxone. However, resistance to other antimicrobial classes is more prevalent, including MLS_B agents and tetracyclines.

Dalbavancin is a novel lipoglycopeptide antimicrobial agent that has been approved in the United States for the treatment of SSTI caused by selected Gram-positive pathogens. This long acting agent is administered once weekly and is highly potent against the common species that cause SSTI, including many resistant strains. The DECIDE Program has been designed to determine the activity of dalbavancin, compared to vancomycin, in European countries. This investigation established the potency of dalbavancin against SSTI pathogens isolated in several medical centers located in France.

MATERIALS AND METHODS

Five medical centers located throughout France (Caen, Creteil, Metz, Lille and Lyon) were recruited to test 75 consecutively collected isolates of staphylococci and ß-haemolytic *Streptococcus* spp. Laboratories were instructed to locally process 60 isolates of *S. aureus* (50 strains) and coagulase-negative staphylococci (10 strains) and 15 strains of ß-haemolytic streptococci. Each center was provided with the same lots of dalbavancin and vancomycin Etest strips (AB BIODISK, Solna, Sweden) as well as disk diffusion reagents. For staphylococci, disk diffusion results were obtained for cefoxitin, as the preferred surrogate test for oxacillin susceptibility, erythromycin, clindamycin, gentamicin, levofloxacin, tetracycline and linezolid. Penicillin, ceftriaxone, erythromycin, clindamycin, levofloxacin and linezolid were tested against the ß-haemolytic streptococci.

Tests were performed according to manufacturer's instructions (Etest) and the standardized disk diffusion method (Clinical and Laboratory Standards Institute [CLSI], M7-A9). D-test was performed and recorded for all isolates to determine inducible-clindamycin resistance using the methods described in the CLSI M100-S18 document. Quality control (QC) was performed each day the clinical isolates were tested using the same reagents and under the same test conditions with a minimum of five replicates of American Type Culture Collection (ATCC) strains. QC strains included *S. pneumoniae* ATCC 49619, *S. aureus* ATCC 25923 (disk diffusion) and *S. aureus* ATCC 29213 (Etest). All sites produced acceptable QC results.

RESULTS

- The cumulative percentages of dalbavancin MIC values are shown in Table 1. Oxacillin-susceptible *S. aureus* isolates (54% at 0.064 mg/L) were slightly more susceptible compared to oxacillin-resistant (MRSA) strains (37 versus 53.5% at ≤0.064 mg/L).
- Tested against *Staphylococcus* spp., dalbavancin was eight-fold more potent than vancomycin (Table 1). Each of the staphylococcal pathogens had MIC_{90} values of 0.125 mg/L for dalbavancin and 2 mg/L for vancomycin.
- Dalbavancin (MIC_{90}, 0.032 mg/L) was >16-fold more potent compared to vancomycin (MIC_{90}, 0.75 mg/L) tested against ß-haemolytic streptococci (Table 1). All *S. pyogenes* isolates were inhibited by dalbavancin concentrations of ≤0.016 mg/L and higher MIC values were noted for *S. agalactiae* (MIC_{90}, 0.064 mg/L).

Table 1. Dalbavancin activity compared to vancomycin when tested against 373 recent Gram-positive isolates in France 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 (187)											
Dalbavancin	1.6	6.4	53.5	98.4	100.0	-	-	-	-	0.064	0.125
Vancomycin	0.0	0.0	0.0	0.5	1.1	1.1	8.6	100.0	-	1.5	2
Oxacillin-resistant (62)											
Dalbavancin	0.0	1.6	37.1	90.3	100.0	-	-	-	-	0.094	0.125
Vancomycin	0.0	0.0	0.0	0.0	0.0	0.0	4.8	100.0	-	1.5	2
Coagulase-negative staphylococci (51)											
Dalbavancin	3.9	13.7	58.8	90.2	100.0	-	-	-	-	0.064	0.125
Vancomycin	0.0	0.0	0.0	0.0	0.0	0.0	3.9	94.1	100.0	2	2
ß-haemolytic streptococci (73)[c]											
Dalbavancin	84.9	90.4	100.0	-	-	-	-	-	-	≤0.016	0.032
Vancomycin	0.0	0.0	0.0	0.0	12.3	80.8	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 (49 strains) followed by group B (15 strains). Other serotypes (C, G and F) included ≤ four strains.

Table 2. Dalbavancin activity compared to seven other agents when tested against 373 Gram-positive cocci in five laboratories in France.

Organism group (no. tested)	Antimicrobial agent	% susceptible[a]	% resistant
S. aureus			
Oxacillin-resistant (62)	Dalbavancin	100.0	-[b]
	Vancomycin	100.0	0.0
	Erythromycin	46.8	51.6
	Clindamycin	59.7	35.5
	Levofloxacin	17.7	79.0
	Gentamicin	93.5	6.5
	Tetracycline	83.9	14.5
	Linezolid	100.0	-
Oxacillin-susceptible (187)	Dalbavancin	100.0	-
	Vancomycin	100.0	0.0
	Erythromycin	81.8	16.6
	Clindamycin	94.7	5.3
	Levofloxacin	92.5	7.5
	Gentamicin	99.5	0.5
	Tetracycline	95.7	4.3
	Linezolid	100.0	-
Coagulase-negative staphylococci (51)	Dalbavancin	100.0	-
	Vancomycin	100.0	0.0
	Erythromycin	49.0	49.0
	Clindamycin	80.4	11.8
	Levofloxacin	54.9	35.3
	Gentamicin	62.7	37.3
	Tetracycline	94.1	5.9
	Linezolid	100.0	-
ß-haemolytic streptococci (73)	Dalbavancin	100.0	-
	Vancomycin	100.0	-
	Penicillin	100.0	-
	Ceftriaxone	100.0	-
	Erythromycin	74.0	20.5
	Clindamycin	72.6	16.4
	Levofloxacin	94.5	0.0
	Linezolid	98.6	-

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.

- As presented in Table 2, all staphylococci and streptococci tested in this study were categorized as susceptible to dalbavancin and vancomycin at the defined breakpoints.

Table 3. Variation in oxacillin and macrolide resistance rates between sampled medical centers in France including inducible clindamycin resistance (D-test).

Site no.	Organism (no. tested)	% resistance[a]			
		Oxacillin	Erythromycin	Clindamycin	Clindamycin-inducible[b]
061	*S. aureus* (50)	26.0	24.0	24.0	66.7
	CoNS (10)	60.0	50.0	10.0	50.0
078	*S. aureus* (48)	29.2	14.6	6.3	66.7
	CoNS (11)	27.3	36.7	9.1	100.0
090	*S. aureus* (50)	24.0	14.0	6.0	50.0
	CoNS (10)	60.0	30.0	20.0	0.0
091	*S. aureus* (51)	25.5	41.2	29.4	83.3
	CoNS (10)	40.0	90.0	20.0	42.9
300	*S. aureus* (50)	20.0	32.0	10.0	54.6
	CoNS (10)	70.0	40.0	0.0	40.0

a. Resistance rates based upon the CLSI recommended breakpoints (CLSI, M100-S18)
b. Inducible clindamycin resistance rates were determined by D-test among erythromycin-resistant/clindamycin-susceptible strains.

- MRSA isolates were more resistant to the other antimicrobial classes that were tested: erythromycin (51.6%), clindamycin (35.5%), levofloxacin (79.0%), gentamicin (6.5%), tetracycline (14.5%) compared to oxacillin-susceptible strains: (16.6%), (5.3%), (8%), (0.5%) and (4.3%), respectively (Table 2).
- All ß-haemolytic streptococci were susceptible to penicillin and ceftriaxone with rare non-susceptible results for levofloxacin (four strains) and linezolid (one isolate; not confirmed). Erythromycin and clindamycin resistance rates were 20.5% and 16.4% with no inducible resistance detected (Table 2).
- The oxacillin resistance rates were similar across all testing centers with rates varying 20 to 29% (Table 3). Greater variation was noted for the MLS_B agents with erythromycin resistance ranging 14 to 41% and clindamycin resistance 6 to 29%. Inducible resistance among the erythromycin-resistant, clindamycin-susceptible *S. aureus* isolates was elevated in all centers (≥50%).

CONCLUSIONS

- Dalbavancin has superior potency compared to vancomycin tested against staphylococci (eight-fold) and streptococci (>16-fold).
- Similar oxacillin resistance rates (approximately 25%) were shown between medical centers in France. However, MLS_B resistance was more variable with high rates of inducible-clindamycin resistance.
- Dalbavancin had excellent activity against this limited sample of isolates tested from five French hospitals. The DECIDE Program will continue to expand upon the number of medical centers contributing data from France and other European countries during 2008 and 2009.

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