Dalbavancin and Selected Comparison Agents Tested Against Indicated Gram-positive Isolates in Italy: Results from the DECIDE Program

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ABSTRACT

Background: Dalbavancin activity was tested against isolates from three medical centers in Italy between October - December, 2007. Only reference quality and standardized CLSI methods were used.

Methods: Susceptibility methods for agar diffusion were applied by each investigator: Etest (ET; AB BIODISK) and CLSI disk diffusion (DD) tests performed with concurrent QC with repeated testing of strains showing unusual resistance patterns such as linezolid, teicoplanin or dalbavancin-non-susceptibility (MIC, >0.25 mg/L). 226 strains were tested against dalbavancin and teicoplanin by ET and linezolid, cefoxitin, levofloxacin, gentamicin, tetracycline, erythromycin, clindamycin (plus D-test), penicillin and ceftriaxone by DD. Dalbavancin susceptibility was defined at ≤0.25 mg/L.

Results: Dalbavancin showed high activity against the 152 *S. aureus* (SA; MIC range, ≤0.016-0.25 mg/L), CoNS (≤0.016-0.25 mg/L) and ß-haemolytic streptococci (BHS; ≤0.016-0.094 mg/L). This activity was 4-, 16- and ≥4-fold greater than teicoplanin when comparing MIC_{90} values, respectively. Susceptibility rates among SA were: linezolid (97%), levofloxacin (61%), erythromycin (43%), clindamycin (51%), tetracycline (86%) and gentamicin (70%). Six linezolid-non-susceptible strains were noted among SA and BHS but all had zone diameters (19-20 mm) near the breakpoint (≥21 mm). Teicoplanin-resistant CoNS and levofloxacin-resistant BHS were detected. A distinct trend toward higher dalbavancin ET MIC results was observed, a probable technical reading error also noted for false-resistant DD linezolid results for SA and BHS (six occurrences). D-test inducible-resistant rates for clindamycin varied from 38% (BHS) to 78% (SA).

	% susceptible (MIC_{50} in mg/L or median zone [mm]) by pathogen (no.):		
Antimicrobial	*S. aureus* (152)	CoNS (28)	BHS (46)
Dalbavancin	100 (0.125)	100 (0.19)	100 (≤0.016)
Teicoplanin	100 (0.5)	96 (3.0)	- (0.064)
Linezolid	97 (30)[a]	100 (30)	98 (25)[a]
Erythromycin	43 (20)	54 (25)	65 (25)
Clindamycin	51 (23)	86 (25)	80 (20)
Levofloxacin	61 (25)	68 (29)	98 (20)
Gentamicin	70 (18)	82 (25)	NT
Ceftriaxone	NT	NT	100 (31)
Oxacillin[b]	63 (25)	39 (20)	NT
Tetracycline	86 (28)	86 (27)	NT

a. Six strains with zones at 20 mm were observed, all false-resistant by disk results.
b. MRSA rate was 37%; and all BHS were penicillin-susceptible.

Conclusions: Dalbavancin, a new long-acting glycolipopeptide (once weekly dosing), demonstrated high activity (MIC_{50} ranges, ≤0.016-0.19 mg/L) against staphylococci and BHS from Italy. The recorded MIC_{90} was 0.125 mg/L, a confirmed finding suggesting a high MIC reading bias for ET. The most elevated MIC results were at 0.25 mg/L (breakpoint; 33 occurrences among SA). The exhibited dalbavancin potency (4-fold greater than teicoplanin; only tested in Italy DECIDE sample) covered all contemporary Gram-positive pathogens.

INTRODUCTION

Treating infections caused by Gram-positive pathogens can be difficult because of the limited treatment options. The prevalent species responsible for skin and skin-structure infections (SSSIs) include staphylococcal and streptococcal species. *Staphylococcus aureus* and ß-haemolytic streptococci are the most common causes of SSSIs. *S. aureus* isolates have numerous antimicrobial resistance mechanisms with oxacillin-resistant *S. aureus* (MRSA) commonly resistant to other antimicrobial classes, including macrolide-lincosamide-streptogramin B (MLS_B) agents, fluoroquinolones and aminoglycosides. Multidrug-resistant (MDR) strains often require the use of glycopeptides as a treatment regimen. ß-haemolytic streptococci remain susceptible to penicillin and cephalosporins. However, tolerance to ß-lactams and a high resistance rate to MLS_B have been documented in some countries worldwide.

Dalbavancin has been approved by regulators in the United States (USA) for the treatment of SSSIs. This agent provides once weekly dosing and proven activity against Gram-positive bacterial species including antimicrobial-resistant strains such as MRSA. This in vitro study was conducted to determine the potency of dalbavancin compared to teicoplanin and the current susceptibility rates to other drug classes when tested against staphylococci and ß-haemolytic streptococci in Italy.

MATERIALS AND METHODS

Three Italian medical centers were instructed to test 75 consecutively collected isolates of staphylococci and ß-haemolytic *Streptococcus* spp. Each laboratory processed *S. aureus*, coagulase-negative staphylococci (CoNS) and ß-haemolytic streptococci. Centers were provided with dalbavancin and teicoplanin Etest strips (AB BIODISK, Solna, Sweden) and disk diffusion reagents. Disk diffusion results were obtained for cefoxitin (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.

Manufacturer's instructions (Etest) and the standardized disk diffusion method were utilized (Clinical and Laboratory Standards Institute [CLSI], M7-A9). D-test was performed to determine inducible-clindamycin resistance (CLSI M100-S18). Quality control (QC) was performed each day of testing using the same reagents and test conditions. QC strains included American Type Culture Collection (ATCC) strains, *S. pneumoniae* ATCC 49619, *S. aureus* ATCC 25923 (disk diffusion) and *S. aureus* ATCC 29213 (Etest). All sites produced acceptable QC results.

RESULTS

- Nearly 40% of the *S. aureus* isolates tested in this study were resistant to ß-lactams based upon the cefoxitin disk diffusion results (see Table 1). All of these strains had dalbavancin MIC values that were ≤0.25 mg/L except for one isolate, which had a MIC value of only 0.5 mg/L.
- Dalbavancin (MIC_{90}, 0.25 mg/L) was eight- to 16-fold more active compared to teicoplanin (MIC_{90}, 2- 4 mg/L) against the *S. aureus* and CoNS isolates (Table 1).
- Resistance to erythromycin, gentamicin and levofloxacin was high among the *S. aureus* and CoNS isolates with rates of 17.9 to 46.4%. Tetracycline resistance was higher among CoNS (14.3%) when compared to *S. aureus* isolates (7.2%).
- Dalbavancin was more potent than teicoplanin against ß-haemolytic streptococci with MIC_{90} values of 0.06 and 0.12 mg/L, respectively. Macrolide-resistant streptococci were common (28.3%) in the sample from Italian medical centers.
- Inducible clindamycin resistance was detected at a rate of 78% for erythromycin-resistant, clindamycin-susceptible *S. aureus* isolates. Approximately 40% of the CoNS and ß-haemolytic streptococcus isolates showed inducible clindamycin resistance.
- A very small number (six) of Gram-positive isolates tested in this study were non-susceptible to linezolid (unconfirmed by a reference laboratory). ß-haemolytic streptococci with levofloxacin MIC values above the susceptible breakpoint were rare, but fluoroquinolone resistance among staphylococci was common (28.9 – 38.8%).

CONCLUSIONS

- Dalbavancin was shown to have a significant potency advantage (eight- to 16-fold) over teicoplanin when tested against Gram-positive isolates in this study from Italian medical centers.
- The potency advantage of dalbavancin compared to class comparators, coupled with the advantage of infrequent dosing provides a promising and simple therapeutic option for treating serious Gram-positive infections.
- The data provided by this study and an expansion of Italian medical center data over the next two years will provide a more comprehensive analysis of the dalbavancin activity and the rates of resistance to other antimicrobial classes.

SELECTED REFERENCES

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Table 1. Dalbavancin activity compared to other agents when tested against 226 Gram-positive cocci in three Italian laboratories.

Organism (no. tested)/antimicrobial agent	MIC_{50} (mg/L)[a]	MIC_{90} (mg/L)[a]	% Susceptible[b]	% Resistant[b]
S. aureus (152)				
Dalbavancin	0.12	0.25	99.3	-[c]
Teicoplanin	0.5	2	100.0	0.0
Cefoxitin	-	-	62.5	37.5
Erythromycin	-	-	42.8	44.1
Clindamycin	-	-	50.7	32.9
Levofloxacin	-	-	61.2	38.8
Gentamicin	-	-	70.4	29.6
Tetracycline	-	-	82.9	7.2
Linezolid	-	-	96.7	-
Coagulase-negative staphylococci (28)				
Dalbavancin	0.06	0.25	100.0	-
Teicoplanin	2	4	96.4	0.0
Cefoxitin	-	-	39.3	60.7
Erythromycin	-	-	53.6	46.4
Clindamycin	-	-	85.7	10.7
Levofloxacin	-	-	67.9	28.6
Gentamicin	-	-	82.1	17.9
Tetracycline	-	-	85.7	14.3
Linezolid	-	-	100.0	-
ß-haemolytic streptococci (46)				
Dalbavancin	≤0.016	0.06	100.0	-
Teicoplanin	0.06	0.12	-	-
Penicillin	-	-	100.0	-
Ceftriaxone	-	-	100.0	-
Erythromycin	-	-	65.2	28.3
Clindamycin	-	-	80.4	19.6
Levofloxacin	-	-	97.8	0.0
Linezolid	-	-	97.8	-

a. Dalbavancin and teicoplanin were tested by Etest (AB BIODISK). Etest results were rounded up to the next highest log_2 dilution value. Other agents were tested by disk diffusion (not applicable [NA] for MIC_{50} and MIC_{90} determinations)
b. Susceptibility criteria of the CLSI (M100-S18, 2008) were used where available. For dalbavancin, a proposed susceptible only breakpoint of ≤0.25 mg/L for all species was used for comparison with teicoplanin.
c. - = Not applicable.