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Multi-Center Surveillance Results (3,617 strains) Comparing the Gram-Positive Activity of Dalbavancin in the United States and Europe During 2005-2007

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AMENDED ABSTRACT

Background: Dalbavancin (DAL) is a novel lipoglycopeptide pending FDA approval for the treatment of complicated skin and skin structure infections (SSSI) caused by Gram-positive pathogens. DAL has an extremely long distributional half-life (5-7d) and is very potent against organisms commonly associated with SSSI including multi-drug resistant (R) isolates such as MRSA. DAL received an approvable letter from the United States Food and Drug Administration (USA-FDA) in 2007 and is currently under review by the EMEA. This study was conducted to determine the potency of DAL compared to vancomycin (VAN) or teicoplanin (TEI; Italy only) against SA, coagulase-negative staphylococci (CoNS) and ß-haemolytic streptococci (BHS) collected in multiple medical centers in the USA and Europe (EU).

Methods: 52 USA sites (2005-2006) and 15 EU (2007) sites collected MRSA, MSSA, CoNS and BHS isolates. The USA and EU samples included 2,490 and 1,127 isolates, respectively. Each site tested isolates against DAL and VAN by the Etest method (AB Biodisk, Solna, Sweden). Other antimicrobial class agents were tested by disk diffusion and inducible clindamycin (indCL)-R was detected by the D-test using the recommended CLSI method.

Results: DAL potency in the USA (MIC_{90}; 0.125-0.25 µg/ml) and EU (0.094-0.25 µg/ml) was 8- to 16-fold greater than VAN or TEI against the staphylococcal strains with slightly higher values noted for MRSA and MR-CoNS. The highest DAL MIC values were noted in Italy and USA, countries that also had highest rates of MRSA (44% and 57%) compared to other nations (8-36%). In the USA, DAL MIC_{90} values were higher for group B (BSB; 0.064 µg/ml) than to group A (BSA; 0.016 µg/ml) streptococci which was also noted in EU (BSA; 0.032 µg/ml vs. BSB; 0.047 µg/ml). In EU, indCL-R was higher among SA (72%) compared to the USA (33%). Rare strains had non-susceptible MIC values for linezolid (0.3%) and VAN (0.1%).

Conclusions: DAL susceptibility data was comparable when tested against contemporary isolates associated with SSSI that were collected from hospitals in the USA or EU. In an era of increasing bacterial resistance, DAL may offer a more potent treatment alternative than VAN, regardless of geographic location of the indicated species.

INTRODUCTION

Dalbavancin is a novel second-generation lipoglycopeptide, which is in the same class as vancomycin and teicoplanin. Currently, this class of compounds is one of the few options available for treating patients with methicillin-resistant *Staphylococcus* spp. infections. Dalbavancin has been shown to have a significant in vitro potency advantage compared to vancomycin when tested against Gram-positive pathogens, including the prevalent species that cause skin and skin-structure infections (SSSIs). In vitro studies have also shown that dalbavancin has bactericidal activity by blocking the final stages of cell wall formation. In addition to high potency and bactericidal activity, the tissue penetration and elimination half-life of dalbavancin (five to seven days) provides convenient dosing regimens compared to that of vancomycin. Clinical studies have demonstrated that dalbavancin appears to be one of the most active compounds in its class for the indicated Gram-positive species. Dalbavancin received an approvable letter from the United States Food and Drug Administration (US-FDA) in December 2007 and is under review for approval by the European Medicines Agency (EMEA).

In the USA, medical centers were recruited to test dalbavancin against *Staphylococcus* spp. and *Streptococcus* spp. isolates that were collected between 2005 and 2006. European medical centers in five countries were also recruited to test and determine the potency of dalbavancin against Gram-positive species during 2007. Vancomycin or teicoplanin (Italy only) were tested as direct comparator agents to dalbavancin. Additional antimicrobial classes were tested against these isolates to determine rates of resistance to commonly prescribed agents used for treating infections caused by staphylococci and streptococci which are commonly associated with SSSIs.

MATERIALS AND METHODS

Laboratories in the USA were recruited to test recently collected and clinically relevant isolates of *S. aureus*, coagulase-negative staphylococci (CoNS) and ß-haemolytic streptococci isolated from SSSI, lower respiratory tract and blood sources. Each laboratory was to locally process 40 isolates of staphylococci, including oxacillin-resistant isolates, and 10 strains of ß-haemolytic streptococci. A total of 52 medical centers in the USA contributed isolates to this investigation and a total of 2,490 strains were available for analysis.

A similar protocol was used for the fifteen contributing laboratories in Europe which included France (five sites), Germany (two sites), Italy (three sites), Spain (two sites) and the United Kingdom (three sites). However, these sites were instructed to test a larger number of isolates (75 total) which also included staphylococci and ß-haemolytic streptococci. In this region, each laboratory was to locally process 60 consecutively collected isolates of staphylococci (including oxacillin-resistant strains) and 15 strains of ß-haemolytic streptococci. A total of 1,127 isolates were available for analysis in the EU.

The staphylococcal and streptococcal isolates were tested against several different antimicrobial agents using the CLSI approved methods for the disk diffusion test and manufacturers recommendations for Etest (AB BIODISK, Solna, Sweden). Dalbavancin, vancomycin or teicoplanin (Italy only) were tested by Etest and other agents were tested by the disk diffusion method. D-test was performed and recorded for all isolates to determine inducible-clindamycin resistance using the methods described in the CLSI M100-S18 (2008) document. Quality control (QC) strains included *Streptococcus pneumoniae* ATCC 49619 (disk diffusion and Etest), *S. aureus* ATCC 25923 (disk diffusion) and *S. aureus* ATCC 29213 (Etest). QC was performed each day that the clinical isolates were tested using the same reagents and under the same test conditions. Failure of QC determinations resulted in the rejection of clinical isolate values and those results were not included in the analysis.

RESULTS

Table 1. Dalbavancin activity directly compared to vancomycin when tested against 3,617 recent Gram-positive isolates in the United States and Europe (2005-2007).

Organism group (no. tested) / Antimicrobial	Cumulative % inhibited at MIC (µg/ml)[a]									
	≤0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8
S. aureus (2,512)										
Dalbavancin	0.6	4.4	57.1	**90.0**[b]	99.1	100.0	-	-	-	-
Vancomycin	0.0	0.0	0.0	<0.1	<0.1	2.0	54.4	**100.0**		
Teicoplanin[c]	0.0	0.0	0.7	3.3	17.1	53.9	80.9	**97.4**	99.3	100.0
Coagulase-negative staphylococci (397)										
Dalbavancin	3.8	17.4	66.5	**93.5**	99.2	100.0	-	-	-	-
Vancomycin	0.0	0.0	0.0	0.0	0.3	2.3	14.9	86.9	**100.0**	-
Teicoplanin	0.0	0.0	0.0	0.0	17.9	25.0	46.4	75.0	**92.9**	96.4[d]
ß-haemolytic streptococci (708)										
Dalbavancin	73.6	87.1	**98.7**	99.7	100.0	-	-	-	-	-
Vancomycin	0.0	0.0	0.0	0.0	23.6	81.2	**100.0**	-	-	-
Teicoplanin	2.2	26.1	60.9	**97.8**	100.0	-	-	-	-	-

a. Etest results (AB BIODISK, Solna, Sweden), results rounded to $\log_2$ scale.
b. Bolded results indicate the MIC_{90} values.
c. Teicoplanin was only tested against isolates from three Italian medical centers.
d. One value was recorded at 12 µg/ml using the Etest.

- Dalbavancin was very potent against all *S. aureus* isolates tested in this study, regardless of geographic origin (USA or EU) or oxacillin susceptibility (Table 1). Dalbavancin (MIC_{90}, 0.125 µg/ml) was 16-fold more active compared to either vancomycin or teicoplanin (MIC_{90} values, 2 µg/ml).
- Dalbavancin had a similar potency against the CoNS isolates with an identical MIC_{90} value of 0.125 µg/ml that was observed for *S. aureus* (Table 1). This potency was 32-fold greater than either vancomycin or teicoplanin (MIC_{90}, 4 µg/ml).

Table 2. Dalbavancin activity compared to seven other agents when tested against 2,490 Gram-positive cocci in 52 laboratories by Etest and disk diffusion methods (USA, 2005-2006).

Organism group (no. tested)	Antimicrobial agent	% Susceptible[a]	% Resistant
S. aureus			
Oxacillin-resistant (1,009)	Dalbavancin	98.8	-[b]
	Vancomycin	99.8	0.0
	Erythromycin	5.4	94.1
	Clindamycin	55.2	41.7
	Levofloxacin	27.7	70.3
	Gentamicin	92.0	7.9
	Tetracycline	91.8	8.0
	Linezolid	99.7	-
Oxacillin-susceptible (762)	Dalbavancin	99.0	-
	Vancomycin	100.0	0.0
	Erythromycin	65.8	30.6
	Clindamycin	92.8	5.8
	Levofloxacin	91.1	7.6
	Gentamicin	98.7	1.3
	Tetracycline	95.1	4.4
	Linezolid	99.9	-
Coagulase-negative staphylococci[c]			
Oxacillin-resistant (182)	Dalbavancin	100.0	-
	Vancomycin	100.0	0.0
	Erythromycin	18.6	81.4
	Clindamycin	41.5	53.6
	Levofloxacin	31.9	64.3
	Gentamicin	58.2	35.6
	Tetracycline	82.4	16.4
	Linezolid	100.0	-
Oxacillin-susceptible (58)	Dalbavancin	100.0	-
	Vancomycin	100.0	0.0
	Erythromycin	45.2	51.6
	Clindamycin	79.0	21.0
	Levofloxacin	82.3	9.7
	Gentamicin	95.0	5.0
	Tetracycline	95.0	5.0
	Linezolid	98.4	-
ß-haemolytic streptococci (479)[d]	Dalbavancin	100.0	-
	Vancomycin	100.0	0.0
	Penicillin	98.3	-
	Ceftriaxone	98.9	-
	Erythromycin	76.9	20.2
	Clindamycin	87.7	6.0
	Levofloxacin	98.7	0.2
	Linezolid	99.8	-

a. Susceptibility criteria of the CLSI (M100-S18, 2008) were used where available. For dalbavancin, proposed susceptible only breakpoints of ≤0.25 µg/ml for all species were used for comparisons with vancomycin, both drugs tested by Etest (AB BIODISK).
b. - = no resistant breakpoint criteria have been recommended.
c. CoNS included *S. capitis* (three strains), *S. epidermidis* (59 strains), *S. haemolyticus* (four strains), *S. hominis* (four strains), *S. lugdunensis* (four strains), *S. saprophyticus* (one strain), *S. simulans* (two strains), *S. warneri* (four strains) and unspeciated CoNS (159 strains).
d. ß-haemolytic serotype of streptococci were group A (302 strains), group B (101 strains), group C (26 strains), group F (eight strains), and group G (42 strains).

- When tested against ß-haemolytic *Streptococcus* spp., dalbavancin had the highest activity (MIC_{90}, 0.064 µg/ml) followed by teicoplanin (MIC_{90}, 0.125 µg/ml) as illustrated in Table 1. These compounds were significantly more potent than vancomycin, which had a MIC_{90} value of 1 µg/ml.
- Utilizing the applied susceptibility breakpoint criteria, dalbavancin was very active 98.1 - 100% against all isolates tested in the USA (Table 2) and EU (Table 3). Vancomycin and linezolid were also very active against the isolate population tested (≥99% susceptibility).
- Higher resistance rates to other antimicrobial classes were found among the oxacillin-resistant staphylococci in both geographic regions (Tables 1 and 2). Rare strains with non-susceptible results to penicillin, ceftriaxone and levofloxacin were noted among the ß-haemolytic streptococci in the USA or EU.
- Slightly higher MIC values for dalbavancin were noted for oxacillin-resistant staphylococci compared to oxacillin-susceptible strains as well as group B streptococci compared to other ß-haemolytic streptococci (data not shown).

Table 3. Dalbavancin activity compared to seven other agents when tested against 1,127 Gram-positive cocci in 15 laboratories by Etest and disk diffusion methods (Europe, 2007).

Organism group (no. tested)	Antimicrobial agent	% Susceptible[a]	% Resistant
S. aureus			
Oxacillin-resistant (202)[b]	Dalbavancin	99.0	-[c]
	Vancomycin	100.0	0.0
	Teicoplanin[d]	100.0	0.0
	Erythromycin	28.2	71.3
	Clindamycin	55.4	39.1
	Levofloxacin	9.4	89.6
	Gentamicin	70.3	29.7
	Tetracycline	90.1	8.4
	Linezolid	99.0	-
Oxacillin-susceptible (539)[b]	Dalbavancin	100.0	-
	Vancomycin	100.0	0.0
	Teicoplanin[d]	100.0	0.0
	Erythromycin	79.6	13.4
	Clindamycin	92.0	2.6
	Levofloxacin	93.1	6.3
	Gentamicin	97.8	2.2
	Tetracycline	94.2	4.5
	Linezolid	99.4	-
Coagulase-negative staphylococci (157)[e]	Dalbavancin	98.1	-
	Vancomycin	100.0	0.0
	Teicoplanin[d]	96.4	0.0
	Erythromycin	47.8	49.7
	Clindamycin	80.3	12.7
	Levofloxacin	54.8	38.9
	Gentamicin	66.9	31.2
	Tetracycline	87.9	9.6
	Linezolid	100.0	-
ß-haemolytic streptococci (229)[f]	Dalbavancin	100.0	-
	Vancomycin	100.0	0.0
	Teicoplanin[d]	-	-
	Penicillin	99.6	-
	Ceftriaxone	99.6	-
	Erythromycin	76.3	18.0
	Clindamycin	79.8	11.4
	Levofloxacin	96.1	1.3
	Linezolid	99.1	-

a. Susceptibility criteria of the CLSI (M100-S18, 2008) were used where available. For dalbavancin, proposed susceptible only breakpoints of ≤0.25 µg/ml for all species were used for comparisons with vancomycin, both drugs tested by Etest (AB BIODISK).
b. Results were based upon the cefoxitin disk diffusion criteria (CLSI, M100-S18)
c. - = no resistant breakpoint criteria have been recommended.
d. Teicoplanin was tested against isolates from Italy only.
e. CoNS included *S. epidermidis* (71 strains) and unspeciated CoNS (86 strains).
f. ß-haemolytic serotype of streptococci were group A (141 strains), group B (52 strains), group C (12 strains), group F (four strains), and group G (19 strains).

CONCLUSIONS

- Dalbavancin demonstrated a significant potency advantage (16- to 32-fold) over vancomycin or teicoplanin among USA and EU isolates tested in this study.
- The superior potency 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 oxacillin-resistant staphylococci.
- The results obtained from these large collections of isolates from multiple medical centers throughout the USA and fifteen centers in five EU countries indicate that dalbavancin has consistent activity on both continents.
- This study will be expanded upon by investigating the potency of dalbavancin in a larger number of EU countries and medical centers throughout 2008 and 2009. This will provide a more comprehensive analysis of dalbavancin activity and the rates of resistance to other antimicrobial classes in the region.

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