Dalbavancin Tested Against *Staphylococcus* spp. and *Streptococcus* spp. Isolates Collected from Five European Countries: Comprehensive DECIDE Program Results (2007)

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ABSTRACT

Background: Dalbavancin is a novel lipoglycopeptide with an extended half-life and intended for treating complicated skin and skin structure infections caused by *S. aureus* (SA) and ß-haemolytic streptococci (BHS). The DECIDE Program was initiated to assess the activity of dalbavancin compared to vancomycin or teicoplanin (Italy only) against recent (2007) clinical isolates from across Europe (EU).

Methods: Fifteen sites in France, Germany, Spain, Italy and UK utilized standardized, reference-quality agar diffusion methods including Etest and CLSI (M2-A9) disk diffusion (DD) tests with concurrent QC (CLSI M100-S18, 2008). 1,127 strains were tested against dalbavancin and comparison glycopeptides by Etest. DD was used for linezolid, cefoxitin, levofloxacin, gentamicin, tetracycline, erythromycin, clindamycin (plus D-test), penicillin and ceftriaxone. Dalbavancin susceptibility was defined at ≤0.25 mg/L.

Results: Dalbavancin exhibited potent activity against the SA and coagulase-negative staphylococci (CoNS; $MIC_{50/90}$, 0.064/0.19 mg/L), and BHS ($MIC_{50/90}$, ≤0.016/0.047 mg/L). Overall, vancomycin and teicoplanin were ≥eight-fold less potent. Italy had higher dalbavancin MIC values (two-fold) for SA and the highest MRSA rate (44%) compared to other nations (8-36%). Dalbavancin MIC_{90} values were slightly higher for group B (0.047 mg/L) compared to group A (0.032 mg/L) streptococci. Nearly 4% of BHS isolates were levofloxacin-non-susceptible. Among SA, resistance rates were: erythromycin (29%), clindamycin (13%), gentamicin (10%), and levofloxacin (29%) with higher resistance rates among MRSA. Inducible clindamycin resistance was high among SA (72%) and CoNS (48%) and less among BHS (25%). Rare strains had non-susceptible MIC values for linezolid (0.3%) and vancomycin (0.1%).

Conclusions: Dalbavancin demonstrated pronounced activity (MIC, ≤0.25 mg/L) against staphylococci and BHS from European countries. Due to dalbavancin's high molecular weight, like other peptides, care must be taken when interpreting Etest-generated MICs (false resistance). Dalbavancin provides coverage of contemporary Gram-positive pathogens, including resistant isolates recovered from patients in Europe, confirming earlier USA reports.

INTRODUCTION

Skin and soft tissue infections (SSTIs) are primarily caused by *Staphylococcus aureus*. Oxacillin-resistant *S. aureus* (MRSA) has become a serious problem among both community-acquired and nosocomial SSTI strains. These MRSA isolates are difficult to treat as they are often associated with co-resistance to other antimicrobial classes. Resistance to macrolide-lincosamide-streptogramin B (MLS_B), including inducible clindamycin resistance, has been recognized in several geographic regions including European countries. Recently, vancomycin-resistant and -intermediate *S. aureus* (VISA or hVISA) are causing a more significant concern as the glycopeptide class is often a last treatment option for MRSA.

ß-haemolytic streptococci are also significant pathogens isolated from SSTIs cultures. Although this species group has remained susceptible to penicillins and advanced generation cephalosporins, resistance to other antimicrobial classes such as MLS_B and tetracyclines has become more common.

A novel lipoglycopeptide antimicrobial agent, dalbavancin, is pending regulatory approval in Europe and in the United States for the treatment of SSTIs caused by Gram-positive pathogens. This agent is administered once weekly due to its enhanced pharmacokinetic properties and is highly potent against SSTI pathogens, including multi-drug resistant strains. The DECIDE Program has been designed to determine the activity of dalbavancin, compared to vancomycin, in European countries.

MATERIALS AND METHODS

Fifteen laboratories in Europe were recruited to test 75 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. Contributing countries included France (five sites), Germany (two sites), Italy (three sites), Spain (two sites) and the United Kingdom/Ireland (three sites). Each laboratory locally processed forty isolates of staphylococci, including oxacillin-resistant isolates, and ten strains of ß-haemolytic streptococci. These medical centers contributed a total of 1,127 isolates that were available for analysis.

Isolates were tested against several 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 CLSI disk diffusion method. D-test was performed for all isolates to determine inducible-clindamycin resistance. Quality control (QC) strains included *Streptococcus pneumoniae* ATCC 49619, *S. aureus* ATCC 25923 and *S. aureus* ATCC 29213. QC failure resulted in the rejection of clinical isolate values and these results were not included in the analysis.

RESULTS

- Table 1 shows that overall, dalbavancin (MIC_{90}, 0.25 mg/L) was 16-fold more active compared to either vancomycin or teicoplanin (MIC_{90} values, 2 mg/L). Dalbavancin was very potent against *S. aureus* isolates with slightly lower MIC values (MIC_{90}, 0.12 mg/L) noted for the oxacillin-susceptible isolates compared to MRSA (MIC_{90}, 0.25 mg/L).
- Dalbavancin was also active (MIC_{90}, 0.25 mg/L) against CoNS isolates (Table 1). This potency was eight- to 16-fold greater than vancomycin or teicoplanin (MIC_{90}, 2 - 4 mg/L).
- Dalbavancin (MIC_{90}, 0.06 mg/L) was also two- to 16-fold more active against all ß-haemolytic streptococci compared to vancomycin (MIC_{90}, 1 mg/L) and teicoplanin (MIC_{90}, 0.12 mg/L) as shown in Table 1. Compared to the other serogroups, Group B streptococcal isolates were slightly less susceptible to dalbavancin with a MIC_{90} value of 0.06 mg/L (data not shown).
- Utilizing the proposed susceptibility breakpoint criteria, dalbavancin was nearly 100% active against all isolates tested in Europe (Table 2). 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 (Table 2). Inducible clindamycin resistance was detected in 71.8% of *S. aureus* and 48.3% of CoNS.
- Among the ß-haemolytic streptococci, macrolide resistance was 18.0% and constitutive clindamycin resistance was 11.4%. The erythromycin-resistant, clindamycin-susceptible isolates showed 25.0% inducible-clindamycin resistance. Levofloxacin, linezolid, penicillin or ceftriaxone non-susceptible isolates were rarely detected amongst this species group.

Table 1. Dalbavancin activity directly compared to vancomycin and teicoplanin when tested against 1,127 recent Gram-positive isolates from Europe (2007).

Organism group (no. tested) /Antimicrobial	Cumulative % inhibited at MIC (mg/L)[a]									
	≤0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8
S. aureus (741)										
Dalbavancin	1.9	9.3	54.0	88.3	**99.7**[b]	100.0	-	-	-	-
Vancomycin	0.0	0.0	0.0	0.2	0.3	1.5	41.8	**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 (157)										
Dalbavancin	4.5	16.6	59.9	85.4	**98.1**	100.0	-	-	-	-
Vancomycin	0.0	0.0	0.0	0.0	0.0	1.6	9.3	**95.3**	100.0	-
Teicoplanin[c]	0.0	0.0	0.0	0.0	17.9	25.0	46.4	75.0	**92.9**	96.4[d]
ß-haemolytic streptococci (229)										
Dalbavancin	74.1	88.6	**99.1**	100.0	-	-	-	-	-	-
Vancomycin	0.0	0.0	0.0	0.0	18.1	87.4	**100.0**	-	-	-
Teicoplanin[c]	2.2	26.1	60.9	**97.8**	100.0	-	-	-	-	-

a. Etest results rounded to log_2 scale (AB BIODISK, Solna, Sweden).
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 mg/L using the Etest.

Table 2. 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	% Susceptible[a]	% Resistant
S. aureus			
Oxacillin-resistant (202)[b]	Dalbavancin	100.0	-[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	99.0	-
	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 mg/L 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 breakpoint criteria have been recommended for this category or organism.
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 compared to vancomycin or teicoplanin among staphylococci and streptococci isolated in Europe.
- Dalbavancin possesses potency advantage and patient dosing convenience, therefore, is a promising therapeutic alternative for treating serious Gram-positive infections, including oxacillin-resistant staphylococci.
- This study will be expanded upon by investigating the activity of dalbavancin in a larger number of European 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 this region.

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