Dalbavancin Activity Tested Against a Contemporary Collection of Gram-positive Bacteria from Hospitals in the UK and Ireland: Results from the DECIDE Program

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ABSTRACT

Background: Activity of dalbavancin was compared to other antimicrobials against a collection of Gram-positives cultured from patients in the UK and Ireland. Dalbavancin is a novel lipoglycopeptide with an extremely long elimination half-life. Dalbavancin is projected for treatment of skin and skin structure infections including those caused by *S. aureus* (SA) and ß-haemolytic streptococci (BHS).

Methods: Sites in UK and Ireland were recruited to test 60 strains of SA (50) and coagulase-negative staphylococci (CoNS; 10), including methicillin-resistant (MR) strains and 15 BHS. Dalbavancin and vancomycin were tested by Etest and results compared to other antimicrobial classes tested by disk diffusion. Inducible clindamycin resistance was determined by D-Test. QC strains were included during each day of testing and comparison drug susceptibility was calculated using CLSI criteria. Dalbavancin susceptibility was defined as ≤0.25 mg/L.

Results: Dalbavancin and vancomycin inhibited all SA isolates below defined breakpoints with MIC_{90} values of 0.125 and 1.5 mg/L, respectively. Except two CoNS with dalbavancin MIC values slightly above breakpoint (0.38 mg/L), all staphylococci were inhibited by dalbavancin, vancomycin and linezolid. Most SA isolates were also susceptible to tetracycline (96.4%) and gentamicin (99.3%). Staphylococci included MRSA (35.7%) and MR-CoNS (68.4%); and MRSA isolates were resistant to levofloxacin (96%) and erythromycin (74%). All clindamycin-susceptible SA had inducible resistance. Dalbavancin (MIC_{90}; 0.047 mg/L) was 10-fold more potent than vancomycin (MIC_{90}; 0.5 mg/L) against BHS. Erythromycin susceptibility was 82% with a 25% inducible clindamycin resistance.

Conclusions: The DECIDE study demonstrated in UK and Ireland that dalbavancin has excellent activity and was more potent when directly compared to vancomycin. Dalbavancin was active against all MRSA, although the current susceptibility profiles for other antimicrobial classes tested were of great concern, particularly inducible clindamycin resistance (100%). Monitoring dalbavancin activity should be continued as this newer long-acting agent is introduced into EU clinical practice.

INTRODUCTION

Infections caused by Gram-positive bacterial species have become more difficult to treat because of the limited therapeutic options available. Staphylococci and streptococci are prevalent pathogens that cause skin and soft tissue infections (SSTIs), the most common of which are *Staphylococcus aureus* and ß-haemolytic streptococci. *S. aureus* causes significant concern due to resistance to oxacillin (MRSA) which is commonly resistant to other antimicrobials. Multidrug-resistant (MDR) strains include resistance to macrolides, fluoroquinolones and aminoglycosides and these organisms are therapeutic problems that may require glycopeptides such as vancomycin. Tolerance has been documented to ß-lactams among ß-haemolytic streptococci and macrolide resistance can be high in some countries.

Dalbavancin is a new lipoglycopeptide pending regulatory approval in Europe and in the United States for treating SSTIs. This agent has unique pharmacokinetic properties allowing once weekly dosing. Dalbavancin has proven activity against common Gram-positive bacteria such as staphylococci (including MRSA) and ß-haemolytic streptococci. This study determined the potency of dalbavancin compared to vancomycin against staphylococci and ß-haemolytic streptococci isolated from patients in the United Kingdom (UK) and Ireland. The antimicrobial susceptibility to other drug classes was also assessed.

MATERIALS AND METHODS

Three medical centers that were located in Cardiff (Wales, UK), Bristol (England, UK) and Galway (Ireland) 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 vancomycin 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

- Dalbavancin (MIC_{90}, 0.12 mg/L) was 16-fold more active than vancomycin (MIC_{90}, 2 mg/L) when tested against *S. aureus*, including MRSA isolates collected in the UK and Ireland (Table 1).
- The MRSA rate in the collection of isolates was 36.4% (data not shown). Among the MRSA isolates, resistance to erythromycin (74.5%), levofloxacin (94.1%) and gentamicin (2.0%) was higher compared to the oxacillin-susceptible strains which had rates of 13.5%, 3.4% and 0.0%, respectively.
- Among CoNS, oxacillin resistance (68.4%) was nearly twice that compared to *S. aureus*. Dalbavancin (MIC_{90}, 0.25 mg/L) was also 16-fold more active than vancomycin (MIC_{90}, 4 mg/L) against these CoNS isolates (Table 1).
- All isolates of ß-haemolytic streptococci were susceptible to dalbavancin (MIC_{90}, 0.06 mg/L), which was eight-fold more potent than vancomycin (MIC_{90}, 0.5 mg/L). Rare isolates were non-susceptible to penicillin, ceftriaxone, levofloxacin and linezolid (not confirmed).
- High rates of inducible clindamycin resistance were noted among MRSA (100%), CoNS (57.9%) and ß-haemolytic streptococci (25.0%).

CONCLUSIONS

- High susceptibility rates were noted for dalbavancin, vancomycin and linezolid when tested against this collection of staphylococci and streptococci.
- Dalbavancin demonstrated superior potency advantage (eight- to 16-fold) compared to vancomycin against this collection of Gram-positive pathogens.
- With the exception of daptomycin, vancomycin and linezolid, high rates of resistance to other antimicrobial classes was observed for oxacillin-resistant *Staphylococcus* spp. tested among this collection of isolates from the UK and Ireland.

SELECTED REFERENCES

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Table 1. Dalbavancin activity compared to other agents when tested against 228 Gram-positive cocci in three laboratories in the UK and Ireland (DECIDE Program 2007).

Organism (no. tested)/ antimicrobial agent	MIC_{50} (mg/L)[a]	MIC_{90} (mg/L)[a]	% Susceptible[b]	% Resistant[b]
S. aureus (140)[c]				
Dalbavancin	0.06	0.12	100.0	-[d]
Vancomycin	1	2	100.0	0.0
Erythromycin	-	-	58.6	35.7
Clindamycin	-	-	93.6	3.6
Levofloxacin	-	-	63.6	36.4
Gentamicin	-	-	99.3	0.7
Tetracycline	-	-	96.4	3.6
Linezolid	-	-	100.0	-
Coagulase-negative staphylococci (38)[c]				
Dalbavancin	0.06	0.25	94.7[e]	-
Vancomycin	2	4	100.0	0.0
Erythromycin	-	-	52.6	39.5
Clindamycin	-	-	84.2	7.9
Levofloxacin	-	-	47.4	47.4
Gentamicin	-	-	57.9	39.5
Tetracycline	-	-	81.6	7.9
Linezolid	-	-	100.0	-
ß-haemolytic streptococci (50)				
Dalbavancin	≤0.016	0.06	100.0	-
Vancomycin	0.5	0.5	-	-
Penicillin	-	-	98.0[f]	-
Ceftriaxone	-	-	98.0[f]	-
Erythromycin	-	-	82.0	6.0
Clindamycin	-	-	84.0	2.0
Levofloxacin	-	-	98.0	2.0
Linezolid	-	-	96.0	-
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 to the next highest log_2 dilution value. Other agents were tested by disk diffusion (not applicable [-] 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 comparisons with vancomycin.
c. 36.4% of S. aureus isolates and 68.4% of CoNS were oxacillin-resistant based upon cefoxitin disk zone diameter results.
d. - = Not applicable category.
e. Two isolates had slightly elevated dalbavancin Etest MIC values (0.38 mg/L).
f. One isolate with a zone diameter of 22 mm for penicillin and 23 mm for ceftriaxone was noted.