Dalbavancin Comparative Activity Tested Against Gram-positive Species in German Medical Centers: Results from the DECIDE Program

G JUST-NUEBLING, W FALK, FJ SCHMITZ, A RODLOFF, DJ BIEDENBACH, RN JONES

University of Frankfurt, Frankfurt, Germany; Labor Dres Ballies, Kiel, Germany; Klinikum Minden, Minden, Germany; University of Leipzig School of Medicine, Leipzig, Germany; JMI Laboratories, North Liberty, IA, USA

ICID 2008
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
douglas-biedenbach@jmilabs.com

ABSTRACT

Background: Dalbavancin, a long-acting glycolipopeptide, was tested against clinical isolates from four hospitals in Germany in the last quarter of 2007.

Methods: Investigators used standardized and reference-quality agar diffusion methods including Etest (ET; AB BIODISK) and CLSI disk diffusion (DD) tests with concurrent QC and repeated testing of strains showing unusual resistance patterns such as linezolid resistance and vancomycin or dalbavancin-non-susceptibility. 150 strains were tested (100 *S. aureus* [SA], 20 coagulase-negative staphylococci [CoNS], 30 ß-haemolytic streptococci [BHS] with most being group A or *S. pyogenes*) against dalbavancin and vancomycin by ET; and linezolid, cefoxitin (determination of methicillin resistance), levofloxacin, gentamicin, tetracycline, erythromycin, clindamycin (plus D-test), penicillin and ceftriaxone by DD. All German sites having acceptable QC results were tabulated. Dalbavancin susceptibility was defined at ≤0.25 mg/L.

Results: Dalbavancin exhibited excellent activity against SA ($MIC_{50/90}$, 0.047/0.125 mg/L), CoNS ($MIC_{50/90}$, 0.047/0.19 mg/L) and BHS ($MIC_{50/90}$, ≤0.016/0.032 mg/L). This activity was 16- to 32-fold greater than vancomycin. MRSA rates were low (8%) but varied modestly from 4 to 12% among hospitals. S rates were: linezolid (100%), levofloxacin (55-83%), erythromycin (50-80%), and clindamycin (65-84%). D-test positive rates were 33-86% for the SA, CoNS and BHS; overall clindamycin-resistant at 16% for SA, but nil for BHS. SA was also very susceptible to gentamicin (95%) and tetracycline (93%). Methicillin susceptibility or resistance did not influence dalbavancin potency versus SA or CoNS. Highest recorded dalbavancin MIC was 0.38 mg/L, two confirmed staphylococci from Frankfurt. Some German centers read Etest results higher (0.5-1.0 log_2) than other laboratories in Europe.

	% susceptible (MIC_{50} in mg/L) activity by pathogen (no.)[a]		
Antimicrobial	*S. aureus* (SA)	CoNS	BHS
Dalbavancin	99 (0.047)	95 (0.047)	100 (≤0.016)
Vancomycin	100 (1)	100 (1.5)	100 (0.38)
Linezolid	100	100	100
Erythromycin	80	50	79
Clindamycin[b]	84	65	79
Levofloxacin	83	55	100
Ceftriaxone	92	50	100

a. MRSA rate was only 9.0%; and all BHS were ceftriaxone- and penicillin-susceptible.
b. Includes results from D-test inducible clindamycin-resistant (6 of 10 strains of SA).

Conclusions: Dalbavancin, with a 7-8 day $T_{1/2}$ (once weekly dosing), demonstrated high potency (MIC_{50} ranges, ≤0.016-0.047 mg/L) against staphylococci and BHS from Germany. Documented dalbavancin activity (≥16-fold) was significantly greater than vancomycin, and dalbavancin inhibited essentially all endemic Gram-positive pathogens from sampled sites.

INTRODUCTION

The majority of skin and soft tissue infections (SSTI) are caused by *Staphylococcus aureus*. This pathogen is significant due to co-resistance patterns to other agent classes that have been evolving over the past several decades. Oxacillin-resistant *S. aureus* (MRSA) has become a serious problem among both community-acquired and nosocomial SSTI strains. Resistance to macrolide-lincosamide-streptogramin B (MLS_B), including inducible clindamycin resistance has also been increasing in many countries. More recently, vancomycin-resistant and -intermediate *S. aureus* (VISA or hVISA) are causing concern. ß-haemolytic streptococci are also commonly isolated from wound cultures. These pathogens have remained susceptible to penicillins and advanced generation cephalosporins. However, resistance to other antimicrobial classes such as macrolides and tetracyclines has become more prevalent.

Dalbavancin, a novel lipoglycopeptide antimicrobial agent, is pending regulatory approval in Europe and in the United States for the treatment of SSTI caused by Gram-positive pathogens. This long acting agent is administered once weekly and is highly potent against SSTI pathogens, including 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 pathogens isolated in a few German medical centers.

MATERIALS AND METHODS

Two medical centers located in Frankfurt and Kiel (two sites have data pending) 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 had greater activity (MIC_{90}, 0.12 mg/L) compared to vancomycin (MIC_{90}, 2 mg/L) when tested against the *S. aureus* isolates collected from patients in Germany (Table 1). Dalbavancin (MIC_{90}, 0.12 mg/L) was also more active compared to vancomycin (MIC_{90}, 2 mg/L) against the tested CoNS.
- The potency of dalbavancin was shown to be 16-fold and eight-fold greater than that of vancomycin against *S. aureus* and CoNS, respectively (Table 1).
- Only 8.0% of *S. aureus* isolates were oxacillin-resistant compared to 50.0% of the CoNS isolates tested. One isolate each of *S. aureus* and CoNS had dalbavancin Etest MIC values slightly above (MIC, 0.38 mg/L) the proposed susceptible breakpoint. The highest susceptibility rates among the staphylococci were dalbavancin (95.0 – 99.0%), vancomycin (100%) and linezolid (100%). Among all tested staphylococci, the D-test positive rate (inducible clindamycin resistance) was 50.0%.
- Dalbavancin (MIC_{90}, 0.03 mg/L) was 32-fold more active than vancomycin (MIC_{90}, 1 mg/L) when tested against the ß-haemolytic streptococci (Table 1). With the exception of erythromycin and clindamycin, which had susceptibility rates <80%, other comparator agents showed 100% susceptibility rates. Inducible clindamycin resistance was noted for 33.3% of the tested strains.

CONCLUSIONS

- Dalbavancin had significant potency advantage (eight- to 32-fold) over vancomycin when tested against Gram-positive isolates in this study sample from German medical centers.
- The potency advantage of dalbavancin compared to vancomycin and the advantage of infrequent dosing (once weekly) provides a significant treatment option for serious Gram-positive infections.
- A more comprehensive understanding of dalbavancin activity and resistance rates to other antimicrobial classes will be determined using this study design and an expansion of German medical centers over the next two years.

SELECTED REFERENCES

1. Clinical and Laboratory Standards Institute. (2006). *M7-A7, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - seventh edition.* Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute. (2008). *M100-S18, Performance standards for antimicrobial susceptibility testing, 18th informational supplement*. Wayne, PA: CLSI.
3. Fritsche TR, Rennie RP, Goldstein BP, Jones RN (2006). Comparison of dalbavancin MIC values determined by Etest (AB BIODISK) and reference dilution methods using Gram-positive organisms. *J Clin Microbiol* 44: 2988-2990.
4. Jauregui LE, Babazadeh S, Seltzer E, Goldberg L, Krievins D, Frederick M, Krause D, Satilovs I, Endzinas Z, Breaux J, O'Riordan W (2005). Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. *Clin Infect Dis* 41: 1407-1415.
5. Jones RN, Fritsche TR, Sader HS, Goldstein BP (2005). Antimicrobial spectrum and potency of dalbavancin tested against clinical isolates from Europe and North America (2003): Initial results from an international surveillance protocol. *J Chemother* 17: 593-600.

Table 1. Dalbavancin activity compared to other agents when tested against 150 Gram-positive cocci in Germany (DECIDE Program 2007).

Organism (no. tested)/antimicrobial agent	MIC_{50} (mg/L)[a]	MIC_{90} (mg/L)[a]	% Susceptible[b]	% Resistant[b]
S. aureus (100)[c]				
Dalbavancin	0.06	0.12	99.0	-[d]
Vancomycin	1	2	100.0	0.0
Erythromycin	-	-	80.0	15.0
Clindamycin	-	-	90.0	8.0
Levofloxacin	-	-	83.0	16.0
Gentamicin	-	-	95.0	5.0
Tetracycline	-	-	93.0	7.0
Linezolid	-	-	100.0	-
Coagulase-negative staphylococci (20)[c]				
Dalbavancin	0.06	0.25	95.0	-
Vancomycin	2	2	100.0	0.0
Erythromycin	-	-	50.0	50.0
Clindamycin	-	-	75.0	20.0
Levofloxacin	-	-	55.0	40.0
Gentamicin	-	-	65.0	30.0
Tetracycline	-	-	90.0	10.0
Linezolid	-	-	100.0	-
ß-haemolytic streptococci (30)				
Dalbavancin	≤0.016	0.03	100.0	-
Vancomycin	0.5	1	-	-
Penicillin	-	-	100.0	-
Ceftriaxone	-	-	100.0	-
Erythromycin	-	-	79.3	20.7
Clindamycin	-	-	79.3	10.3
Levofloxacin	-	-	100.0	0.0
Linezolid	-	-	100.0	-

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 comparisons with teicoplanin.
c. 8.0% of *S. aureus* isolates and 50.0% of CoNS were oxacillin-resistant based upon cefoxitin disk zone diameter results.
d. - = Not applicable.