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# In Vitro Activity of Dalbavancin Tested Against a Worldwide Collection of 81,673 Gram-Positive Bacterial Isolates

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## ABSTRACT

**Background:** Dalbavancin (DAL) is a lipoglycopeptide with a novel once-weekly dosing schedule that has been developed for the treatment of skin and skin structure infections (SSSI) caused by Gram-positive pathogens. This study was designed to generate a large volume of susceptibility (S) data for DAL and comparator agents from worldwide geographic locations.

**Methods:** 210 medical centers in 33 countries (4 continents) contributed *S. aureus* (SA; 46,773 isolates), coagulase-negative staphylococci (CoNS; 12,308), including oxacillin-resistant (OXA-R; MRSA) strains. Viridans group (VGS; 2,148) and ß-haemolytic (ßHS; 5,316) streptococci, *E. faecalis* (EF; 10,374) and *E. faecium* (EFM; 4,754), including vancomycin (VANC)-S and -R isolates, were also tested. Isolates, during 2002-2007, were S tested with CLSI broth microdilution methods using validated panels (TREK Diagnostics) and appropriate supplements for processing fastidious species.

**Results:** Nearly all (99.9%) of tested *Staphylococcus* spp. were inhibited by ≤0.25 µg/ml of DAL. All (100.0%) ßHS and VGS were inhibited by ≤0.25 µg/ml. The VANC-S enterococci were readily inhibited by DAL (>99% at ≤0.12 µg/ml; $MIC_{50}$, ≤0.03-0.06 µg/ml) compared to the VANC-R strains ($MIC_{50}$, >4 µg/ml).

| | Cumulative % inhibited at MIC (µg/ml) | | | | | | |
|---|---|---|---|---|---|---|---|
| Organism group (no.) | ≤0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 |
| OXA-S SA (27,052) | 30.8 | 93.9 | 99.8 | 100.0 | - | - | - |
| OXA-R SA (19,721) | 28.4 | 91.5 | 99.6 | >99.9 | 100.0 | - | - |
| OXA-S CoNS (2,836) | 62.9 | 91.9 | 98.9 | 99.8 | 99.9 | 100.0 | - |
| OXA-R CoNS (9,472) | 51.4 | 82.6 | 95.4 | 99.2 | 99.8 | >99.9 | 100.0 |
| ßHS (5,316) | 94.9 | 99.0 | 99.8 | 100.0 | - | - | - |
| VGS (2,148) | 93.5 | 99.3 | 100.0 | - | - | - | - |
| EF (10,374) | 50.1 | 93.6 | 97.4 | 97.6 | 97.6 | 97.7 | 97.8 |
| EFM (4,754) | 14.8 | 38.9 | 55.8 | 59.2 | 61.4 | 64.1 | 67.5 |

**Conclusions:** DAL demonstrated potent activity ($MIC_{90}$, ≤0.12 µg/ml) against this large preclinical collection of SA, CoNS, VGS and ßHS. VANC-R will likely be categorized as DAL-R among the majority of EF and EFM isolates (VAN A patterns). DAL represents an important, once weekly alternative therapy for SSSI caused by common Gram-positive pathogens which are increasingly becoming more R to other antimicrobial classes, especially the emerging community-acquired MRSA.

## INTRODUCTION

Skin and skin structure infections (SSSI) are most commonly caused by Gram-positive pathogens and the most significant organism is *Staphylococcus aureus*. This species has become increasingly resistant to numerous antimicrobial classes over the last several decades. Oxacillin-(ß-lactam-) resistant *S. aureus* presents a serious treatment dilemma for both community-acquired (CA) and nosocomial SSSI since most strains are multidrug-resistant (MDR). Macrolide-lincosamide-streptogramin B ($MLS_B$) resistance including inducible clindamycin resistance has also become problematic in this species. Glycopeptide resistance has been documented at both high/detectible levels as well as intermediate levels of resistance. Vancomycin-intermediate (VISA) and hetero-resistant (hVISA) *S. aureus* have been detected in many countries.

ß-haemolytic streptococci (ßHS) are commonly isolated from wound cultures and although these species have remained susceptible to penicillins and advanced generation cephalosporins, resistance to other antimicrobial classes such as $MLS_B$ agents and tetracyclines is more prevalent. Enterococci and coagulase-negative staphylococci (CoNS) are also commonly associated with SSSI and viridians group streptococci (VGS) are common causes of oral abscesses.

Dalbavancin is a novel lipoglycopeptide antimicrobial agent seeking approval in the United States (USA) for the treatment of SSSI caused by selected Gram-positive pathogens. This long-acting agent is administered once weekly and is highly potent against the common species that cause SSSI, including many antimicrobial-resistant strains. This investigation established the potency of dalbavancin against a very large collection of SSSI pathogens collected from medical centers located throughout the world.

## MATERIALS AND METHODS

During a six year period (2002-2007), a total of 81,673 isolates of staphylococci, enterococci, ßHS and VGS were collected from 210 medical centers in 33 countries. North America contributed 37,085 isolates (45.4% of the collection) from 86 sites located in the USA (80) and Canada (6). European medical centers also provided a significant number of isolates (30.5%) with a total of 24,932 strains from 35 sites in 14 countries. Centers in the Asia-Pacific (77 sites in 12 countries) and Latin America (12 sites in five countries) provided a smaller number of isolates, representing 11.9 and 12.2% of the collection, respectively. The majority (55.9%) of the isolates were collected during 2006-2007 (45,670 strains). Isolates were confirmed for appropriate species identification by each of the reference, monitoring laboratories which included JMI Laboratories (North Liberty, IA, USA) and Women's and Children's Hospital (North Adelaide, Australia).

MIC testing was performed with validated panels (TREK Diagnostics, Cleveland, OH) using the CLSI reference methods (M7-A7, 2006). Categorization of susceptibility and resistance followed the CLSI M100-S18 criteria (2008). Differentiation of vancomycin-resistant *Enterococcus* spp. isolates into vanA and vanB phenotypes excluded isolates with intermediate MIC values for teicoplanin or vancomycin. Quality control utilized appropriate American Type Culture Collection (ATCC) strains including *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619 to assure the validity of all test results.

## RESULTS

- Dalbavancin ($MIC_{90}$, 0.06 µg/ml) was 16-fold more active compared to vancomycin ($MIC_{90}$, 1 µg/ml) against both oxacillin-susceptible and -resistant *S. aureus* isolates (Table 1). Dalbavancin displayed a similar potency advantage to vancomycin (16- to 32-fold) against the CoNS in this collection.
- Resistance to other antimicrobial classes, particularly among the oxacillin-resistant population, had no effect on the activity of dalbavancin against staphylococci. However, oxacillin-resistant CoNS had a slightly higher $MIC_{90}$ value (0.12 µg/ml), as shown in Table 1.
- Dalbavancin activity was similar to *Staphylococcus* spp. when tested against vancomycin-susceptible *Enterococcus* spp. isolates with $MIC_{90}$ values of 0.06 and 0.12 µg/ml for *E. faecalis* and *E. faecium*, respectively (Table 1). Overall, dalbavancin was less active against vancomycin-resistant strains although this agent was more active against isolates exhibiting a vanB phenotype ($MIC_{50}$ values, 0.06-0.12 µg/ml) as shown in Table 2.
- Dalbavancin was very active against VGS and ßHS with all MIC values ≤0.25 µg/ml and only $MLS_B$ agents (56.0-91.4%) and penicillin (71.7%, VGS only) had reduced susceptibility against these species (Table 1). Group B streptococci had slightly higher dalbavancin MIC values with 90.3% of strains inhibited by ≤0.03 µg/ml compared to Group A, C, G and F, which were inhibited by ≤0.03 µg/ml at rates of 95.6-99.4% (Table 2).
- Significant variation in the rates of oxacillin resistance among *S. aureus* was observed between geographic regions with higher rates in the USA (46.1%) and Asia-Pacific countries (44.2%), see Table 3. Medical centers in the USA had significantly higher rates of vancomycin-resistant *E. faecium* (73.3%) and *E. faecalis* (5.7%) isolates compared to Canada and countries on other continents (Table 3).

**Table 2.** Activity of dalbavancin when tested against vancomycin-resistant *Enterococcus* spp. and ß-haemolytic *Streptococcus* spp.

| Organism group/resistance phenotype or serogroup (no. tested) | Cumulative % inhibited at MIC (µg/ml): ≤0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | >4 |
|---|---|---|---|---|---|---|---|---|---|
| *E. faecalis* | | | | | | | | | |
| vanA (230) | 0.4 | 0.9 | 2.6 | 3.9 | 4.3 | 4.3 | 7.4 | 14.8 | 100.0 |
| vanB (84) | 9.5 | 33.3 | 70.2 | 70.2 | 75.0 | 78.6 | 85.7 | 91.7 | 100.0 |
| *E. faecium* | | | | | | | | | |
| vanA (1,744) | 0.1 | 0.3 | 1.2 | 3.1 | 6.6 | 11.5 | 18.3 | 33.1 | 100.0 |
| vanB (134) | 26.1 | 56.0 | 71.6 | 77.6 | 85.1 | 90.3 | 94.0 | 97.8 | 100.0 |
| ß-haemolytic streptococci | | | | | | | | | |
| Group A (2,182) | 98.8 | 99.9 | >99.9 | 100.0 | - | - | - | - | - |
| Group B (2,265) | 90.3 | 98.0 | 99.6 | 100.0 | - | - | - | - | - |
| Group C (174) | 99.4 | 100.0 | - | - | - | - | - | - | - |
| Group G (502) | 95.6 | 99.6 | 100.0 | - | - | - | - | - | - |
| Group F (35) | 97.1 | 97.1 | 100.0 | - | - | - | - | - | - |

**Table 1.** Activity of dalbavancin and comparator agents when tested against 81,673 Gram-positive cocci isolated from 33 countries worldwide.

| Organism group/susceptibility subset (no. tested) | Antimicrobial agent | MIC (µg/ml) 50% | 90% | Range | % susceptible[a] | % resistant |
|---|---|---|---|---|---|---|
| *S. aureus* | | | | | | |
| Oxacillin-susceptible (27,052) | Dalbavancin | 0.06 | 0.06 | ≤0.03-0.25 | 100.0 | -[b] |
| | Vancomycin | 1 | 1 | ≤0.12-4 | >99.9 | 0.0 |
| | Erythromycin | ≤0.25 | >2 | ≤0.25->2 | 78.7 | 20.7 |
| | Clindamycin | ≤0.25 | ≤0.25 | ≤0.25->2 | 95.8 | 4.0 |
| | Levofloxacin | ≤0.5 | ≤0.5 | ≤0.5->4 | 92.8 | 6.7 |
| | Gentamicin | ≤2 | ≤2 | ≤2->8 | 97.1 | 2.6 |
| | Tetracycline | ≤4 | ≤4 | ≤4->8 | 93.7 | 5.8 |
| | Linezolid | 2 | 2 | 0.12-4 | 100.0 | - |
| Oxacillin-resistant (19,721) | Dalbavancin | 0.06 | 0.06 | ≤0.03-0.5 | >99.9 | - |
| | Vancomycin | 1 | 1 | 0.25-4 | >99.9 | 0.0 |
| | Erythromycin | >2 | >2 | ≤0.25->2 | 10.9 | 88.8 |
| | Clindamycin | >2 | >2 | ≤0.25->2 | 47.8 | 52.1 |
| | Levofloxacin | >4 | >4 | ≤0.5->4 | 18.3 | 80.1 |
| | Gentamicin | ≤2 | >8 | ≤2->8 | 74.1 | 24.8 |
| | Tetracycline | ≤4 | >8 | ≤4->8 | 81.1 | 18.4 |
| | Linezolid | 1 | 2 | ≤0.25->8 | >99.9 | 0.04 |
| Coagulase-negative staphylococci | | | | | | |
| Oxacillin-susceptible (2,836) | Dalbavancin | ≤0.03 | 0.06 | ≤0.03-1 | 99.8 | - |
| | Vancomycin | 1 | 2 | ≤0.12-4 | 100.0 | 0.0 |
| | Erythromycin | ≤0.25 | >2 | ≤0.25->2 | 66.0 | 33.6 |
| | Clindamycin | ≤0.25 | ≤0.25 | ≤0.25->2 | 93.5 | 5.7 |
| | Levofloxacin | ≤0.5 | 4 | ≤0.5->4 | 87.5 | 11.1 |
| | Gentamicin | ≤2 | ≤2 | ≤2->8 | 95.0 | 3.1 |
| | Tetracycline | ≤4 | >8 | ≤4->8 | 86.7 | 12.6 |
| | Linezolid | 1 | 1 | ≤0.25->8 | 99.9 | - |
| Oxacillin-resistant (9,472) | Dalbavancin | ≤0.03 | 0.12 | ≤0.03-2 | 99.2 | - |
| | Vancomycin | 1 | 2 | ≤0.12-8 | >99.9 | 0.0 |
| | Erythromycin | >2 | >2 | ≤0.25->2 | 24.1 | 75.4 |
| | Clindamycin | ≤0.25 | >2 | ≤0.25->2 | 57.0 | 41.7 |
| | Levofloxacin | 4 | >4 | ≤0.5->4 | 31.8 | 61.4 |
| | Gentamicin | 4 | >8 | ≤2->8 | 50.7 | 35.3 |
| | Tetracycline | ≤4 | >8 | ≤4->8 | 83.4 | 15.8 |
| | Linezolid | 1 | 1 | ≤0.25->8 | 99.5 | - |
| *E. faecalis* | | | | | | |
| Vancomycin-susceptible (10,025) | Dalbavancin | ≤0.03 | 0.06 | ≤0.03-0.5 | >99.9 | - |
| | Ampicillin | ≤2 | ≤2 | ≤2->16 | 99.6 | 0.2 |
| | Ciprofloxacin | 1 | >4 | 0.06->4 | 62.2 | 33.6 |
| | Gentamicin (HL) | ≤500 | >1000 | ≤500->1000 | 68.5 | 31.5 |
| | Linezolid | 1 | 2 | ≤0.25->8 | 99.8 | 0.1 |
| Vancomycin-non-susceptible (349) | Dalbavancin | >4 | >4 | ≤0.03->4 | 27.8 | - |
| | Ampicillin | ≤2 | 4 | ≤2->16 | 96.0 | 4.0 |
| | Ciprofloxacin | >4 | >4 | 0.5->4 | 3.7 | 96.3 |
| | Gentamicin (HL) | >1000 | >1000 | ≤500->1000 | 28.4 | 71.6 |
| | Linezolid | 1 | 2 | 0.25->8 | 98.6 | 1.4 |
| *E. faecium* | | | | | | |
| Vancomycin-susceptible (2,578) | Dalbavancin | 0.06 | 0.12 | ≤0.03-2 | 99.6 | - |
| | Ampicillin | >16 | >16 | ≤2->16 | 15.6 | 84.4 |
| | Ciprofloxacin | >4 | >4 | 0.06->4 | 8.1 | 83.7 |
| | Gentamicin (HL) | ≤500 | >1000 | ≤500->1000 | 61.8 | 38.2 |
| | Linezolid | 1 | 2 | ≤0.25->8 | 99.6 | 0.3 |
| Vancomycin-non-susceptible (2,176) | Dalbavancin | >4 | >4 | ≤0.03->4 | 11.4 | - |
| | Ampicillin | >16 | >16 | ≤2->16 | 0.8 | 99.2 |
| | Ciprofloxacin | >4 | >4 | ≤0.03->4 | 0.7 | 98.3 |
| | Gentamicin (HL) | ≤500 | >1000 | ≤500->1000 | 64.3 | 35.7 |
| | Linezolid | 1 | 2 | 0.5->8 | 97.6 | 1.8 |
| ß-haemolytic streptococci (5,316) | Dalbavancin | ≤0.03 | ≤0.03 | ≤0.03-0.25 | 100.0 | - |
| | Vancomycin | 0.5 | 0.5 | ≤0.12-1 | 100.0 | - |
| | Penicillin | ≤0.015 | 0.06 | ≤0.015-1 | 99.9 | - |
| | Ceftriaxone | ≤0.25 | ≤0.25 | ≤0.25-4 | 99.9 | - |
| | Erythromycin | ≤0.25 | >2 | ≤0.25->2 | 79.6 | 19.9 |
| | Clindamycin | ≤0.25 | ≤0.25 | ≤0.25->2 | 91.4 | 8.2 |
| | Levofloxacin | ≤0.5 | 1 | ≤0.5->4 | 98.6 | 1.3 |
| | Linezolid | 1 | 1 | ≤0.25-2 | 100.0 | - |
| Viridans group streptococci (2,148) | Dalbavancin | ≤0.03 | ≤0.03 | ≤0.03-0.12 | 100.0 | - |
| | Vancomycin | 0.5 | 1 | ≤0.12-2 | >99.9 | - |
| | Penicillin | 0.06 | 1 | ≤0.03->32 | 71.7 | 6.0 |
| | Ceftriaxone | ≤0.25 | 1 | ≤0.25->32 | 92.5 | 4.3 |
| | Erythromycin | ≤0.25 | >2 | ≤0.25->2 | 56.0 | 41.7 |
| | Clindamycin | ≤0.25 | 0.5 | ≤0.25->2 | 89.8 | 9.5 |
| | Levofloxacin | 1 | 2 | ≤0.5->4 | 95.7 | 3.6 |
| | Linezolid | 1 | 1 | ≤0.25-8 | >99.9 | - |

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 only with vancomycin.
b. - = no resistant breakpoint criteria have been recommended.

**Table 3.** Variation in oxacillin and vancomycin resistance rates between geographic regions.

| | Country/continent (% resistance)[a] | | | |
|---|---|---|---|---|
| Resistance phenotype | Canada/USA | Europe | Latin America | Asia-Pacific |
| Oxacillin-resistant *S. aureus* | 26.5/46.1 | 27.9 | 38.6 | 44.2 |
| Vancomycin-resistant *E. faecalis* | 0.8/5.7 | 1.6 | 4.4 | 0.9 |
| Vancomycin-resistant *E. faecium* | 13.2/73.3 | 22.1 | 30.7 | 15.8 |

a. Resistance rates based upon the CLSI recommended breakpoints (CLSI, M100-S18).

## CONCLUSIONS

- Overall, dalbavancin was 8- to 32-fold more active than vancomycin against this large collection of commonly isolated Gram-positive pathogens (81,673 strains) collected from diverse geographic regions.
- Resistance to other antimicrobial classes had no effect on the activity of dalbavancin, with the exception of vancomycin and *Enterococcus* spp., particularly those with a vanA pattern.
- The potency advantage of dalbavancin compared to class comparators, coupled with the advantages of infrequent patient dosing provides a promising therapeutic alternative for treating serious Gram-positive infections, including oxacillin-resistant staphylococci and other species which are common causes of SSSI.

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