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Comprehensive Update of Dalbavancin Activity when Tested against Uncommonly Isolated Streptococci, *Corynebacterium* spp., *Listeria monocytogenes* and *Micrococcus* spp.

RN JONES, RK FLAMM, HS SADER, MG STILWELL
JMI Laboratories, North Liberty, Iowa, USA

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JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
ph. 319.665.3370, fax 319.665.3371
ronald-jones@jmilabs.com

ABSTRACT

Background: Continuing resistance among Gram-positive (GP) pathogens requires ongoing development of antimicrobials with unique cost-effective delivery and safety. Dalbavancin (DALBA) among candidate parenteral agents has proven spectrum resembling vancomycin. To enhance the understanding of DALBA spectrum versus GP pathogens, we report results of this investigational, long-acting lipoglycopeptide against uncommonly isolated streptococci and three other GP groups.

Methods: 1,357 organisms were selected from documented infections (one strain/episode) and identified by the sites and confirmed by international monitor achieved by Vitek 2, 16S sequencing and MALDI-TOF. The collection included: β-haemolytic streptococci, other than *S. pyogenes* and *S. agalactiae* (BHS; 598); viridans group streptococci (VGS; 675, seven groups/species); *Corynebacterium* spp. (19; five species); *L. monocytogenes* (39); and *Micrococcus* spp. (26). Strains were isolated in 2008-2011 at 133 worldwide locations, predominately in USA hospitals (79). Susceptibility (S) testing was performed using reference CLSI methods in cation-adjusted MH broth supplemented with 2.5-5% lysed horse blood.

Results: Table 1 shows the DALBA results against the streptococci (1,273 strains; >75% from bloodstream and skin and skin structure infections). DALBA was very active against BHS serogroups C, F and G ($MIC_{50/90}$, ≤0.03/≤0.03 μg/ml); highest MIC was only 0.12 μg/ml. Seven groups of VGS were tested each having DALBA MIC values at ≤0.25 μg/ml. *S. anginosus/S. milleri,* were most DALBA-S (MIC_{90}, ≤0.03 μg/ml), while *S. mitis* group and *S. salivarius/ vestibularis* group isolates had the highest recorded DALBA results (0.25 μg/ml; $MIC_{50/90}$, ≤0.03/0.06 μg/ml). The three other GP groups, like the streptococci, had low DALBA MICs e.g. *Corynebacterium* spp. ($MIC_{50/90}$, 0.06/0.12 μg/ml), *L. monocytogenes* ($MIC_{50/90}$, 0.06/0.12 μg/ml) and *Micrococcus* spp. ($MIC_{50/90}$, ≤0.03/≤0.03 μg/ml).

Conclusions: DALBA MIC values for recent but unusual GP species presented here, expands the S detail for this once-weekly agent prior to review and potential approval by regulatory agencies. Among the 1,357 strains reported, 99.8% of this collection were inhibited by ≤0.12 μg/ml of DALBA, proving the breadth and extent of activity.

INTRODUCTION

The recurring development of resistance among prevalent Gram-positive pathogens requires new antimicrobials with improvements in potency or novel mechanisms of action. Among candidate parenteral agents, dalbavancin has a proven in vitro spectrum resembling vancomycin, teicoplanin and telavancin as well as a greater potency most similar to another lipoglycopeptide, oritavancin. The safety and efficacy of dalbavancin have been reported for complicated or acute bacterial skin and skin structure infections (cSSSI or ABSSSI) in numerous reports and for catheter-related bloodstream infections. Extensive information covering the spectrum of dalbavancin was reported from international surveillance programs dating from 2002-2003, updated with tens of thousands of pathogens including samples of recent clinical isolates published by Jones and colleagues. Most recently, dalbavancin was designated by the United States (USA) Food and Drug Administration (FDA) as a "Qualified Infectious Disease Product (QIDP)" enabling the sponsor (Durata Therapeutics, Inc., Chicago, Illinois USA) to have a priority review and preliminary results from the dalbavancin ABSSSI trial (DISCOVER 1) showed that the agent "achieved its primary endpoint of non-inferiority at 48-72 hours after therapy" (Durata Therapeutics, data on file).

Beyond the pathogens associated with ABSSSI, dalbavancin has demonstrated in vitro activity against selected anaerobes, cutaneous Gram-positive flora, vancomycin-susceptible enterococci and *Bacillus anthracis*. To enhance the understanding of dalbavancin spectrum and potency versus potential Gram-positive pathogens, we report the results of testing this investigational, long-acting lipoglycopeptide with its unique and potentially cost-effective dosing regimen against uncommonly isolated species of streptococci, *Corynebacterium* spp., *Micrococcus* spp. and *Listeria monocytogenes*.

MATERIALS AND METHODS

A total of 1,357 organisms were selected from unique, documented infections (one strain per episode) and identified by the participating surveillance medical center and confirmed by the international monitor (JMI Laboratories, North Liberty, Iowa USA). Validation of the identification was achieved by Vitek 2, 16S sequencing and MALDI-TOF methods. The collection included: β-haemolytic streptococci, other than *S. pyogenes* and *S. agalactiae* (598), viridans group streptococci (675; seven groups/species), *Corynebacterium* spp. (19; five species), *L. monocytogenes* (39) and *Micrococcus* spp. (26). All strains were isolated in 2008-2011 in worldwide locations, predominately in 79 USA hospitals. Fifty-four non-USA medical centers also contributed isolates to this collection.

All susceptibility testing was performed using reference Clinical and Laboratory Standards Institute (CLSI) methods in cation-adjusted Mueller-Hinton broth supplemented with 2.5-5% lysed horse blood; all quality control results were within published ranges for dalbavancin applying *Staphylococcus aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619. Organisms at the extremes of the MIC distribution (MIC, ≥0.12 μg/ml) were re-identified and replicate tested for susceptibility to dalbavancin and similar agents (teicoplanin and vancomycin).

RESULTS

- **Table 1** shows the results from testing dalbavancin against the streptococci (1,273 of 1,357 strains; >75% from bloodstream and skin and skin structure infections).
- Dalbavancin was very active against β-haemolytic streptococcal serogroups C, F and G ($MIC_{50/90}$, ≤0.03/≤0.03 μg/ml). The highest MIC was only 0.12 μg/ml and these results for dalbavancin confirm prior reports by others using organism collections from earlier years.
- Also in **Table 1**, seven groups of "viridans *Streptococcus* spp." were tested each having dalbavancin MIC values at ≤0.25 μg/ml. *S. anginosus* and so-called *S. milleri,* were most susceptible to dalbavancin (MIC_{90}, ≤0.03 μg/ml), while *S. mitis* group and *S. salivarius/vestibularis* group isolates had the highest recorded dalbavancin results (0.25 μg/ml; $MIC_{50/90}$, ≤0.03/0.06 μg/ml). Previously published results for viridans group streptococci generally did not precisely list the species or species group data; see Billeter et al. (2008).
- Finally, **Table 2** presents the dalbavancin potency results (84 strains) when tested against three other uncommonly isolated groups of Gram-positive pathogens. Like the streptococcal values (**Table 1**), dalbavancin was very active against *Corynebacterium* spp. ($MIC_{50/90}$, 0.06/0.12 μg/ml), *L. monocytogenes* ($MIC_{50/90}$, 0.06/0.12 μg/ml) and *Micrococcus* spp. ($MIC_{50/90}$, ≤0.03/≤0.03 μg/ml).

Table 1. Dalbavancin activity tested against 1,273 strains of uncommonly isolated streptococci.

	Cumulative % inhibited by dalbavancin at MIC (μg/ml):				MIC (μg/ml)
Group/organism (no. tested)	≤0.03	0.06	0.12	0.25	50/90
Beta-haemolytic species					
Serogroup C (207)	92.8	99.0	100.0	-	≤0.03/≤0.03
Serogroup F (56)	96.4	100.0	-	-	≤0.03/≤0.03
Serogroup G (335)	94.6	98.2	100.0	-	≤0.03/≤0.03
All (598)	94.1	98.7	100.0	-	≤0.03/≤0.03
Viridans group species					
S. anginosus gr (190)[a]	98.4	100.0	-	-	≤0.03/≤0.03
S. milleri (14)[b]	92.9	100.0	-	-	≤0.03/≤0.03
S. bovis gr (47)	68.1	97.9	100.0	-	≤0.03/0.06
S. dysgalactiae gr (50)[c]	88.0	96.0	100.0	-	≤0.03/0.06
S. mitis gr (305)[d]	84.3	98.0	99.7	100.0	≤0.03/0.06
S. mutans gr (20)	55.0	95.0	100.0	-	≤0.03/0.06
S. salivarius/S. vestibularis group (49)	81.6	95.9	98.0	100.0	≤0.03/0.06
All (675)	86.5	98.2	99.7	100.0	≤0.03/0.06

a. Includes: *S. anginosus* (124), *S. constellatus* (44), and *S. intermedius* (22).
b. Vague historical taxonomy, but this species has been most related to the *S. anginosus* group.
c. Includes: *S. dysgalactiae* (32) and *S. equisimilis* (18).
d. Includes: *S. mitis* (197), *S. gordonii* (13), *S. oralis* (25), *S. parasanguinis* (35) and *S. sanguinis* (35).

Table 2. Dalbavancin activity tested against isolates of *Corynebacterium* spp., *Listeria monocytogenes* and *Micrococcus* spp.

	MIC (μg/ml)			%
Organism (no. tested)	50%	90%	Range	≤0.12 μg/ml
Corynebacterium spp. (19)[a]	0.06	0.12	≤0.03-0.25	94.7
L. monocytogenes (39)	0.06	0.12	≤0.03-0.12	100.0
Micrococcus spp. (26)	≤0.03	≤0.03	≤0.03-0.06	100.0

a. Includes: *C. amycolatum* (6), *C. aurimucosum* (1), *C. jeikeium* (3), *C. pseudodiphtheriae* (1), and *C. striatum* (8).

CONCLUSIONS

- Dalbavancin potencies against common Gram-positive pathogens such as *S. aureus* (MIC_{90}, 0.06 μg/ml), coagulase-negative staphylococci (MIC_{90}, 0.06-0.12 μg/ml) and vancomycin-susceptible enterococci (MIC_{90}, 0.06-0.12 μg/ml) have been previously documented. Other uncommonly isolated species inhibited by dalbavancin have been the Gram-positive anaerobes and *Bacillus* spp.
- Among the 1,357 strains reported here (**Tables 1** and **2**), 99.8% of this collection were inhibited by ≤0.12 μg/ml of dalbavancin. The dalbavancin MIC values for these unusual Gram-positive species expand the spectrum/potency detail for this once-weekly-dosed agent prior to review and potential approval by regulatory agencies.

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