Dalbavancin Activity in the USA: Reported from the SENTRY Programme (2012)

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ABSTRACT

Objective: To determine the activity/potency of dalbavancin (DAL), a late Phase 3 investigational lipoglycopeptide with an extended serum half-life offering once weekly parenteral administration. DAL potency was assessed in the 2012 SENTRY Antimicrobial Surveillance Programme among 1,589 isolates sampled from the nine USA Census regions (27 medical centres) to update the 38,813 organism collections reported for 2006-2011 (2011 and 2012 ICAAC).

Methods: Monitored Gram-positive cocci included *Staphylococcus aureus* (SA; 1,000/50% MRSA), coagulase-negative staphylococci (CoNS; 122); *Enterococcus faecalis* (30); *E. faecium* (30); *Streptococcus pyogenes* (151); *S. agalactiae* (134; 336 β-haemolytic streptococci overall) and viridans group streptococci (VGS; 71). All susceptibility (S) testing used CLSI reference broth microdilution methods and EUCAST interpretations for comparison agents.

Results: DAL ($MIC_{50/90}$, 0.06/0.06 mg/L) was eight to 16-fold more active than daptomycin (DAP), linezolid (LZD) and vancomycin (VAN), against SA; with MSSA and MRSA having the same MIC_{90} results. CoNS was equally DAL-S (MIC_{90}, 0.06 mg/L). The highest staphylococcal DAL MIC was only 0.25 mg/L as it was in 2011. β-haemolytic streptococci (βHS) and VGS had DAL MIC values ranging from ≤0.03 to 0.25 mg/L (MIC_{90}, ≤0.03-0.06 mg/L) and only enterococci showed elevated DAL MIC results. VanA phenotype-resistant *E. faecalis* or *E. faecium* had non-S DAL MIC values (≥4 mg/L). VanB resistance strains were DAL-S (MIC, ≤0.12 mg/L). All cited DAL quantitative values were consistent with earlier surveillance data (2006-2011), without evidence of MIC creep. LZD-R CoNS was detected (modified target mechanism).

Conclusions: Year 2012 SENTRY Programme surveillance results for DAL document sustained potent activity against SA, CoNS, βHS, VGS, VAN-S and VAN-B phenotype enterococci, that averaged four-to 32-fold greater than VAN, DAP or LZD. Based on its in vitro potency, further development of DAL with its long half-life and infrequent dosing, appears warranted.

	Cumulative % inhibited at DAL MIC (mg/L):						
Organism (no. tested)	≤0.03	0.06	0.12	0.25	0.5	1	≥2
S. aureus (1,000)							
MRSA (500)	16.8	90.0	99.8	100.0	-	-*	-
MSSA (500)	21.6	91.6	100.0	-	-	-*	-
CoNS (122)	49.2	91.8	99.2	100.0	-	-	-*
βHS (336)	91.1	97.9	99.1	100.0	-*	-	-
VGS (71)	84.5	98.6	100.0	-	-	-*	-
Enterococci (60)							
Van-susceptible (33)	0.0	66.7	93.9	100.0	-	-*	-
VanA (25)	0.0	0.0	0.0	0.0	0.0	0.0	100.0
VanB (2)	50.0	50.0	100.0	-	-	-	-
All (1,589)	39.1	90.7	98.0	98.4	98.4	98.4	100.0

*Vancomycin MIC_{90}

INTRODUCTION

Dalbavancin is an investigational lipoglycopeptide that has recently completed its Phase 3 development for the treatment of acute bacterial skin and skin structure infections (ABSSSI), directed against susceptible Gram-positive bacteria such as *Staphylococcus aureus* (including MRSA), *Streptococcus pyogenes* (Group A) and *S. agalactiae* (Group B). The pharmacokinetics and pharmacodynamics of dalbavancin support infrequent, once weekly dosing with the potential to avoid costly hospitalizations in a subset of patients with ABSSSI. Dalbavancin (Durata Therapeutics, Chicago, Illinois, USA) has received the designation of 'Qualified Infectious Disease Product' (QIDP) from the USA Food and Drug Administration (FDA) that expedites regulatory review.

The potency and spectrum of dalbavancin has been monitored in the USA and Europe for a decade and the most recent sampling of USA isolates indicates a stable activity profile. Recently our research group published an update of the dalbavancin spectrum and activity for the United States (USA) surveillance programme covering strains of Gram-positive pathogens isolated in 2011. Here we present the latest potency profiles of dalbavancin from a surveillance study run in 2012 tested by validated reference methods against 1,589 isolates of staphylococci, β-haemolytic and viridans group streptococci and *Enterococcus* spp.

MATERIALS AND METHODS

The sampling protocol for 2012 tested nearly 1,600 Gram-positive isolates distributed as follows (**Table 1**): *S. aureus* (1000; 50.0% MRSA), coagulase-negative staphylococci (CoNS; 122, 68.9% methicillin-resistant [MR]), β-haemolytic streptococci (336; 84.8% Group A and B), viridans group *Streptococcus* spp. (71), and 60 *Enterococcus faecalis* and *E. faecium* selected for vancomycin resistant (VRE) and wildtype (WT) susceptible representatives. All strains were identified by the participant medical center and by the monitoring reference laboratory (JMI Laboratories, North Liberty, Iowa USA). Reference broth microdilution methods were guided by published quality control limits by Anderegg et al, (2003) and CLSI (2013).

RESULTS

- **Table 1** presents the dalbavancin MIC distributions for organisms possibly associated with documented ABSSSI (1,589 strains from 27 medical centres in USA).
- Dalbavancin $MIC_{50/90}$ results against the staphylococci were consistent at ≤0.03-0.06/0.06-0.12 mg/L and identical to those reported for year 2011 samples; see Jones et al, (2013).
- Dalbavancin MIC_{90} values for MRSA and MSSA have been stable at 0.06/0.06 mg/L for more than 10 years.
- Only MR-CoNS strains had slightly higher dalbavancin MIC_{90} values at 0.12 mg/L, a finding noted previously among 9,472 strains from 33 countries and reported in 2009.
- A slightly greater variation in dalbavancin potency has been identified among streptococci, ranging from a MIC_{90} of ≤0.03 mg/L for *S. pyogenes* to 0.06 mg/L for viridans group species and *S. agalactiae* (**Table 1**).
- Enterococcal susceptibility results for dalbavancin were highly influenced by the VRE phenotype and genotype. Vancomycin-susceptible strains of either *E. faecalis* or *E. faecium* had dalbavancin MIC values at ≤0.25 mg/L (33 strains), but VRE isolates of the VanA phenotype exhibited dalbavancin MIC values at ≥4 mg/L (25 strains). Both VanB phenotype isolates in this collection had very low (≤0.12 mg/L) dalbavancin MIC results (**Table 1**).

Table 1. Cumulative frequency distribution of dalbavancin MIC values for targeted Gram-positive pathogens collected from 27 medical centres in the United States during 2012.

	MIC (mg/L)										
Organism (no. tested)	≤ 0.03	0.06	0.12	0.25	0.5	1	2	4	> 4	MIC_{50}	MIC_{90}
Staphylococcus aureus (1000)	192 (19.2)	716 (90.8)	91 (99.9)	1 (100.0)	--	--	--	--	--	0.06	0.06
MSSA (500)	108 (21.6)	350 (91.6)	42 (100.0)	--	--	--	--	--	--	0.06	0.06
MRSA (500)	84 (16.8)	366 (90.0)	49 (99.8)	1 (100.0)	--	--	--	--	--	0.06	0.06
Coagulase-negative staphylococci (122)	60 (49.2)	52 (91.8)	9 (99.2)	1 (100.0)	--	--	--	--	--	0.06	0.06
MS-CoNS (38)	24 (63.2)	13 (97.4)	1 (100.0)	--	--	--	--	--	--	≤0.03	0.06
MR-CoNS (84)	36 (42.9)	39 (89.3)	8 (98.8)	1 (100.0)	--	--	--	--	--	0.06	0.12
β-haemolytic streptococci (336)	308 (91.7)	21 (97.9)	4 (99.1)	3 (100.0)	--	--	--	--	--	≤0.03	≤0.03
Group A Streptococcus (151)	145 (96.0)	5 (99.3)	1 (100.0)	--	--	--	--	--	--	≤0.03	≤0.03
Group B Streptococcus (134)	118 (88.1)	11 (96.3)	3 (98.5)	2 (100.0)	--	--	--	--	--	≤0.03	0.06
Viridans group streptococci (71)	60 (84.5)	10 (98.6)	1 (100.0)	--	--	--	--	--	--	≤0.03	0.06
Enterococcus spp. (60)	1 (1.7)	22 (38.3)	10 (55.0)	2 (58.3)	0 (58.3)	0 (58.3)	0 (58.3)	1 (60.0)	24 (100.0)	0.12	>4
vancomycin-susceptible (33)	0 (0.0)	22 (66.7)	9 (93.9)	2 (100.0)	--	--	--	--	--	0.06	0.12
vancomycin-resistant (27)[a]	1 (3.7)	0 (3.7)	1 (7.4)	0 (7.4)	0 (7.4)	0 (7.4)	0 (7.4)	1 (11.1)	24 (100.0)	>4	>4
VanA (25)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)	24 (100.0)	>4	>4
VanB (2)	1 (50.0)	0 (0.0)	1 (100.0)	--	--	--	--	--	--	≤0.03	--

a. Includes: 19 *E. faecium* and six *E. faecalis* isolates with a VanA phenotype and one each of *E. faecium* and *E. faecalis* with a VanB phenotype.

CONCLUSIONS

- Dalbavancin is highly active against the Gram-positive organisms associated with ABSSSI.
- The in vitro potency of dalbavancin against Gram-positive organisms has remained unchanged since 2002.

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