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Antimicrobial Activity of Dalbavancin against *Staphylococcus aureus* with Decreased Susceptibility to Glycopeptides, Daptomycin, and/or Linezolid from U.S. Medical Centers

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ABSTRACT Dalbavancin activity was assessed against a large collection of *Staphylococcus aureus* isolates (n = 59,903), including isolates with decreased susceptibility to vancomycin (MIC, ≥2 mg/liter; n = 1,141), daptomycin (MIC, ≥2 mg/liter; n = 48), telavancin (MIC, ≥0.12 mg/liter; n = 52), teicoplanin (MIC, ≥4 mg/liter; n = 143), and/or linezolid (MIC, ≥8 mg/liter; n = 25). Dalbavancin displayed susceptibility rates ranging from 90.4% (isolates with telavancin MIC ≥0.12 mg/liter) to 100.0% (linezolid-resistant isolates) and lower MIC values than the comparators against these resistant subsets.

KEYWORDS glycopeptides, lipoglycopeptides, vancomycin-intermediate *S. aureus*

Staphylococcus aureus continues to be a major cause of community-acquired and health care-associated infections, including skin and skin structure infections, pneumonia, bacteremia, endocarditis, osteomyelitis, prosthetic joint infections, and catheter-related infections (1). The prevalence of nosocomial infections caused by methicillin-resistant *S. aureus* (MRSA) has remained markedly high in the United States in the last years (2, 3).

Vancomycin has been used to treat MRSA infections for >50 years. Although susceptibility rates remain high (>99%) in the United States and worldwide, there have been numerous reports of treatment failure, which appears to be related to increased vancomycin MICs that occur within the susceptibility range (2 mg/liter); however, the reasons related to treatment failure remain an area of clinical debate (4, 5). Linezolid and daptomycin have been used increasingly worldwide in the last decade, and resistance to these two compounds is still very uncommon among *S. aureus* strains isolated in U.S. hospitals (3).

Dalbavancin is a semisynthetic lipoglycopeptide derived structurally from antibiotic A-40926, a natural antibiotic similar to teicoplanin and produced by *Nonomuraea* spp. (6). Dalbavancin exerts its antimicrobial activity by binding to the terminal D-alanyl-D-alanine residues of peptidoglycan precursors. This binding prevents transpeptidation and subsequent transglycosylation, interfering with cross-linking and polymerization in the cell wall and ultimately causing bacterial death (7).

Dalbavancin was approved by the U.S. Food and Drug Administration (FDA) in 2014 and by the European Medicines Agency (EMA) in 2015 to treat adults with acute bacterial skin and skin structure infections (ABSSSIs) caused by susceptible isolates of *S. aureus*, including MRSA and methicillin-susceptible *S. aureus* (MSSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group, and vancomycin-susceptible *Enterococcus faecalis*. Dalbavancin allows for convenient parenteral administration to treat ABSSSI, which can be a single dose of 1,500 mg or a dose of 1,000 mg followed by 500 mg a week later (8, 9).

Although vancomycin, linezolid, daptomycin, telavancin, and teicoplanin are very active against *S. aureus*, isolates with decreased susceptibility to these antimicrobial

Received 21 November 2017 **Returned for modification** 6 December 2017 **Accepted** 15 December 2017

Accepted manuscript posted online 20 December 2017

Citation Sader HS, Mendes RE, Duncan LR, Pfaller MA, Flamm RK. 2018. Antimicrob Agents Chemother 62:e02397-17. https://doi.org/10.1128/AAC.02397-17.

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TABLE 1 Activity of dalbavancin and comparator antimicrobial agents tested against *S. aureus* isolates with decreased susceptibility to glycopeptides, daptomycin, and/or linezolid from U.S. medical centers

Organism subset and antimicrobial agent	MIC_{50} (mg/liter)	MIC_{90} (mg/liter)	MIC range (mg/liter)	CLSI[a]		EUCAST[a]	
				%S	%R	%S	%R
Vancomycin MIC ≥2 mg/liter (*n* = 1,141)							
Dalbavancin	0.06	0.12	≤0.03 to 0.5	99.3[b]		95.5	4.5
Daptomycin	0.5	1	≤0.12 to 4	96.8		96.8	3.2
Vancomycin	2	2	2 to 4	99.3	0.0	9.3	0.7
Teicoplanin	≤2	≤2	≤2 to 16	99.9	0.0	93.5	6.5
Linezolid	1	2	≤0.12 to >8	99.6	0.4	99.6	0.4
Oxacillin	>2	>2	≤0.25 to >2	26.9	73.1	26.9	73.1
Daptomycin nonsusceptible (*n* = 48)							
Dalbavancin	0.06	0.12	≤0.03 to 0.5	95.8[b]		91.7	8.3
Daptomycin	2	4	2 to 4	0.0		0.0	100.0
Vancomycin	2	2	1 to 4	95.8	0.0	95.8	4.2
Teicoplanin	≤2	4	≤2 to 16	97.9	0.0	87.5	12.5
Linezolid	1	2	0.5 to 4	100.0	0.0	100.0	0.0
Oxacillin	>2	>2	≤0.25 to >2	12.5	87.5	12.5	87.5
Telavancin MIC ≥0.12 mg/liter (*n* = 52)[c]							
Dalbavancin	0.06	0.25	≤0.03 to 0.5	90.4[b]		84.6	15.4
Daptomycin	0.5	1	0.25 to 2	96.2		96.2	3.8
Vancomycin	1	2	1 to 4	98.1	0.0	98.1	1.9
Telavancin	0.12	0.12	0.12 to 0.25	96.2		96.2	3.8
Teicoplanin	≤2	4	≤2 to 16	98.1	0.0	76.9	23.1
Linezolid	1	1	0.25 to 2	100.0	0.0	100.0	0.0
Oxacillin	>2	>2	≤0.25 to >2	34.6	65.4	34.6	65.4
Teicoplanin MIC ≥4 mg/liter (*n* = 143)							
Dalbavancin	0.06	0.25	≤0.03 to 0.5	95.1[b]		83.9	16.1
Daptomycin	0.5	1	0.12 to 4	95.8		95.8	4.2
Vancomycin	2	2	0.5 to 4	97.9	0.0	97.9	2.1
Teicoplanin	4	8	4 to 16	99.3	0.0	0.0	100.0
Linezolid	1	2	0.25 to 4	100.0	0.0	100.0	0.0
Oxacillin	>2	>2	≤0.25 to >2	26.6	73.4	26.6	73.4
Linezolid resistant (*n* = 25)							
Dalbavancin	0.06	0.06	≤0.03 to 0.12	100.0[b]		100.0	0.0
Daptomycin	0.5	0.5	0.25 to 0.5	100.0		100.0	0.0
Vancomycin	1	2	0.5 to 2	100.0	0.0	100.0	0.0
Teicoplanin	≤2	≤2	≤2 to ≤2	100.0	0.0	100.0	0.0
Linezolid	8	>8	8 to >8	0.0	100.0	0.0	100.0
Oxacillin	>2	>2	≤0.25 to >2	4.0	96.0	4.0	96.0

[a]Criteria as published by CLSI (11) and EUCAST (12). S, susceptible; R, resistant.
[b]Breakpoints from FDA package insert, i.e., susceptible at ≤0.25 mg/liter (13).
[c]Telavancin was only tested against isolates collected in 2011 to 2016.

agents are isolated sporadically. In the present study, we assessed the *in vitro* activity of dalbavancin against a large collection of *S. aureus* clinical isolates with decreased susceptibility to these key antimicrobial agents that are used to treat severe *S. aureus* infections.

The organism collection evaluated in this investigation included 1,141 isolates with decreased susceptibility to vancomycin (MIC, ≥2 mg/liter), 48 isolates nonsusceptible to daptomycin (MIC, ≥2 mg/liter), 52 isolates with decreased susceptibility to telavancin (MIC, ≥0.12 mg/liter), 143 isolates with decreased susceptibility to teicoplanin (MIC, ≥4 mg/liter), and 25 isolates resistant to linezolid (MIC, ≥8 mg/liter).

This organism collection was selected from among 59,903 isolates collected from 139 U.S. medical centers between 2002 and 2016. Telavancin was only tested against isolates collected during 2011 to 2016 (*n* = 22,120), whereas all other antimicrobial agents evaluated in this investigation were tested against the entire *S. aureus* collection. Isolates were determined to be clinically significant based on local guidelines and were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, IA).

TABLE 2 Summary of dalbavancin activity tested against *S. aureus* isolates with decreased susceptibility to glycopeptides, daptomycin, and/or linezolid from U.S. medical centers

Resistance phenotype	No. of isolates (cumulative %) inhibited at dalbavancin MIC (mg/liter) of[a]:					MIC_{50} (mg/liter)	MIC_{90} (mg/liter)
	≤0.03	0.06	0.12	0.25	0.5		
Vancomycin MIC ≥2 mg/liter (*n* = 1,141)	117 (10.3)	**697 (71.3)**	276 (95.5)	43 (99.3)	8 (100.0)	0.06	0.12
Daptomycin nonsusceptible (*n* = 48)	3 (6.3)	**25 (58.3)**	16 (91.7)	2 (95.8)	2 (100.0)	0.06	0.12
Telavancin MIC ≥0.12 mg/liter (*n* = 52)[b]	4 (7.7)	**24 (53.8)**	16 (84.6)	3 (90.4)	5 (100.0)	0.0.6	0.25
Teicoplanin MIC ≥4 mg/liter (*n* = 143)	14 (9.8)	**73 (60.8)**	33 (83.9)	16 (95.1)	7 (100.0)	0.06	0.25
Linezolid resistant (*n* = 25)	5 (20.0)	**18 (92.0)**	2 (100.0)			0.06	0.06
All isolates (*n* = 59,903)	22,066 (36.8)	**33,879 (93.4)**	3,795 (99.7)	155 (>99.9)	8 (100.0)	0.06	0.06

[a]Boldface data represent dalbavancin modal MIC results. The dalbavancin-susceptible breakpoint approved by the FDA for *S. aureus* is ≤0.25 mg/liter (13).
[b]Telavancin was only tested against isolates collected in 2011 to 2016.

Isolates were initially identified by the participating laboratory, and bacterial identifications were confirmed by the reference monitoring laboratory, when necessary.

Isolates were tested for susceptibility to dalbavancin and comparator agents by reference broth microdilution methods as described in the Clinical and Laboratory Standards Institute (CLSI) document M07-A10, and susceptibility interpretations were based on CLSI document M100-S27 and/or FDA guidelines and EUCAST breakpoint criteria (10–12). Dalbavancin breakpoints approved by the FDA for *S. aureus* were applied (i.e., ≤0.25 mg/liter) (11, 13).

MIC panels were manufactured at JMI Laboratories (2015 to 2016) or purchased from Thermo Fisher Scientific (before 2015) (Cleveland, OH). Organisms were tested in cation-adjusted Mueller-Hinton broth (Thermo Fisher Scientific). Quality assurance was performed by concurrently testing CLSI-recommended quality control reference strains (*S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212).

MRSA rates ranged from 65.4% to 96.0% among these resistant subsets (Table 1). Among the entire collection of *S. aureus* isolates tested against dalbavancin (*n* = 59,903), only 8 (0.01%) were categorized as dalbavancin nonsusceptible (MIC, >0.25 mg/liter), all with a dalbavancin MIC value of 0.5 mg/liter (Table 2 and Fig. 1) and vancomycin MIC values of 2 to 4 mg/liter (data not shown). Dalbavancin retained activity against 99.3% of isolates with vancomycin MICs of ≥2 mg/liter ($MIC_{50/90}$, 0.06/0.12 mg/liter) (Tables 1 and 2), and dalbavancin MIC_{50} and MIC_{90} values were 8-fold lower than those of daptomycin ($MIC_{50/90}$, 0.5/1 mg/liter; 96.8% susceptible) (Table 1). Teicoplanin ($MIC_{50/90}$, ≤2/≤2 mg/liter; 99.9/93.5% susceptible [CLSI/EUCAST])

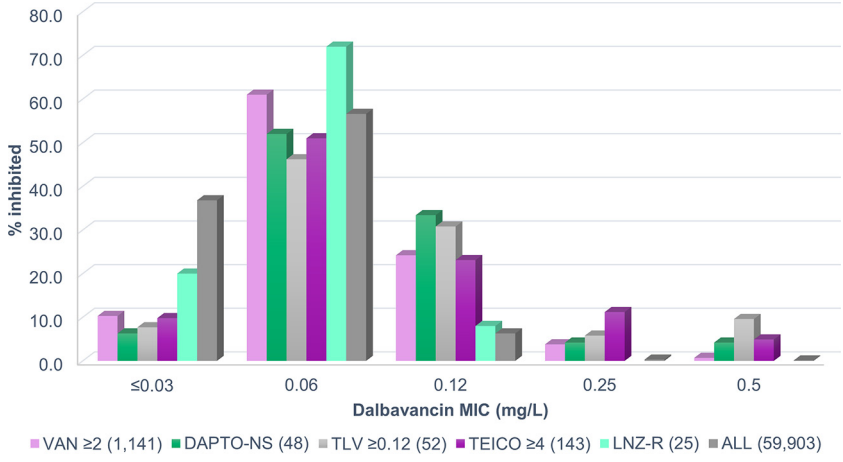

FIG 1 Summary of dalbavancin activity when tested against *S. aureus* isolates with decreased susceptibility to glycopeptides, daptomycin, and/or linezolid from U.S. medical centers. Abbreviations: VAN ≥2, isolates with vancomycin MICs of ≥2 mg/liter; DAPTO-NS, daptomycin nonsusceptible (MIC, ≥2 mg/liter); TLV ≥0.12 mg/liter, isolates with telavancin MICs of ≥0.12 mg/liter; TEICO ≥4, isolates with teicoplanin MICs of ≥4 mg/liter; LNZ-R, linezolid resistant.

and linezolid ($MIC_{50/90}$, 1/2 mg/liter; 99.6% susceptible) exhibited good activity against isolates with decreased susceptibility to vancomycin (Table 1).

Dalbavancin ($MIC_{50/90}$, 0.06/0.12 mg/liter; 95.8% susceptible [FDA]), vancomycin ($MIC_{50/90}$, 2/2 mg/liter; 95.8% susceptible), teicoplanin ($MIC_{50/90}$, ≤2/4 mg/liter; 97.9/87.5% susceptible [CLSI/EUCAST]), and linezolid ($MIC_{50/90}$, 1/2 mg/liter; 100.0% susceptible) retained good activity against daptomycin-nonsusceptible *S. aureus*, and dalbavancin MIC_{50} and MIC_{90} values were 16- to 32-fold lower than those of vancomycin and teicoplanin when tested against these organisms (Table 1). Dalbavancin was also active against isolates with decreased susceptibility (MIC, ≥0.12 mg/liter) to telavancin, with $MIC_{50/90}$ values of 0.06/0.25 mg/liter and 90.4% susceptibility (Tables 1 and 2). Furthermore, dalbavancin was more active (lower MIC values) than daptomycin ($MIC_{50/90}$, 0.5/1 mg/liter; 96.2% susceptible) and vancomycin ($MIC_{50/90}$, 1/2 mg/liter; 98.1% susceptible) against these organisms (Table 1).

When tested against *S. aureus* isolates with teicoplanin MICs of ≥4 mg/liter (nonsusceptible per EUCAST criteria), susceptibility rates for dalbavancin ($MIC_{50/90}$, 0.06/0.25 mg/liter), daptomycin ($MIC_{50/90}$, 0.5/1 mg/liter), vancomycin ($MIC_{50/90}$, 2/2 mg/liter), and linezolid ($MIC_{50/90}$, 1/2 mg/liter) were 95.1%, 95.8%, 97.9%, and 100.0%, respectively (Table 1).

All linezolid-resistant isolates were susceptible to dalbavancin ($MIC_{50/90}$, 0.06/0.06 mg/liter), daptomycin ($MIC_{50/90}$, 0.5/0.5 mg/liter), and vancomycin ($MIC_{50/90}$, 1/2 mg/liter), and dalbavancin MIC_{50} and MIC_{90} values were 8- and 16- to 32-fold lower than those of daptomycin and vancomycin, respectively (Table 1).

Dalbavancin has demonstrated potent *in vitro* and broad-spectrum activity against Gram-positive organisms commonly involved in ABSSSIs, including MRSA and other multidrug-resistant organisms (14, 15). Dalbavancin's high protein binding and prolonged half-life allow for easily and consistently attainable therapeutic levels. The free serum drug levels are adequate to provide excellent tissue penetration, and several clinical trials have demonstrated its tolerability, efficacy, and noninferiority compared with standard therapy for ABSSSI (8, 9). The results of this investigation corroborate and expand published data on the *in vitro* activity of dalbavancin against *S. aureus*. Dalbavancin displayed potent activity against a large collection of *S. aureus* isolates ($n = 59{,}903$) collected from U.S. medical centers and retained good activity against isolates with decreased susceptibility to vancomycin, daptomycin, teicoplanin, telavancin, and/or linezolid. Dalbavancin MIC_{90} values were only slightly higher among these resistant subsets (0.12 to 0.25 mg/liter) compared to those of the overall collection (0.06 mg/liter), and the vast majority of isolates with decreased susceptibility to other lipoglycopeptides remained susceptible to dalbavancin. The highest dalbavancin MIC value was only 0.5 mg/liter, which is 1 doubling dilution above the susceptible breakpoint established by the FDA.

Although dalbavancin has shown excellent coverage against Gram-positive organisms, including multidrug-resistant isolates (14, 15), and it is approved by the FDA and EMA since 2014 and 2015, respectively, very few commercial dalbavancin susceptibility tests have been validated for clinical microbiology laboratory use. Thus, until such reagents are readily available, the use of a surrogate drug in the same class, such as vancomycin, to predict or infer dalbavancin susceptibility remains a viable option with predictive accuracy of 99.98% to 100.0% (16).

In summary, the *in vitro* characteristics presented here, along with the prolonged half-life and convenient administration, make dalbavancin a valuable option for treating *S. aureus* infections, including those caused by multidrug-resistant organisms.

ACKNOWLEDGMENTS

This study was supported by Allergan. Allergan was involved in the design and decision to present these results, and JMI Laboratories received compensation for services in relation to preparing this presentation. Allergan had no involvement in the collection, analysis, or interpretation of data.

We disclose that JMI Laboratories contracted to perform services in 2016 for

Achaogen; Actelion; Allecra Therapeutics; Allergan; AmpliPhi Biosciences; API; Astellas Pharma; AstraZeneca; Basilea Pharmaceutica; Bayer AG; BD; Biomodels; Cardeas Pharma Corp.; CEM-102 Pharma; Cempra; Cidara Therapeutics, Inc.; CorMedix; CSA Biotech; Cutanea Life Sciences, Inc.; Debiopharm Group; Dipexium Pharmaceuticals, Inc.; Duke; Entasis Therapeutics, Inc.; Fortress Biotech; Fox Chase Chemical Diversity Center, Inc.; Geom Therapeutics, Inc.; GSK; Laboratory Specialists, Inc.; Medpace; Melinta Therapeutics, Inc.; Merck & Co., Inc.; Micromyx; MicuRx Pharmaceuticals, Inc.; Motif Bio; N8 Medical, Inc.; Nabriva Therapeutics, Inc.; Nexcida Therapeutics, Inc.; Novartis; Paratek Pharmaceuticals, Inc.; Pfizer; Polyphor; Rempex; Scynexis; Shionogi; Spero Therapeutics; Symbal Therapeutics; Synlogic; TenNor Therapeutics; TGV Therapeutics; The Medicines Company; Theravance Biopharma; Thermo Fisher Scientific; VenatoRx Pharmaceuticals, Inc.; Wockhardt; Zavante Therapeutics, Inc. We have no speakers' bureaus or stock options to declare.

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