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In Vitro Activity of Dalbavancin against Drug-Resistant *Staphylococcus aureus* Isolates from a Global Surveillance Program

Sandra P. McCurdy,[a] Ronald N. Jones,[b] Rodrigo E. Mendes,[b] Sailaja Puttagunta,[a] Michael W. Dunne[a]

Durata Therapeutics, Branford, Connecticut, USA[a]; JMI Laboratories, North Liberty, Iowa, USA[b]

In over a decade (2002 to 2012) of *Staphylococcus aureus* surveillance testing on 62,195 isolates, dalbavancin was demonstrated to be active against isolates that were either susceptible or nonsusceptible to daptomycin, linezolid, or tigecycline. Nearly all (99.8%) multidrug-resistant methicillin-resistant *S. aureus* isolates were inhibited by dalbavancin at ≤0.12 μg/ml ($MIC_{50/90}$, 0.06/0.06 μg/ml), the current U.S. Food and Drug Administration (U.S. FDA) breakpoint. Overall, only 0.35% of the monitored *S. aureus* isolates had a dalbavancin MIC of either 0.25 or 0.5 μg/ml (i.e., were nonsusceptible).

Staphylococcus aureus is a leading cause of bacterial infections worldwide, including skin and soft tissue infections, bacteremia, pneumonia, endocarditis, and osteomyelitis (1). Due to its propensity to evolve and adapt to its host and applied treatments, *S. aureus* has been able to acquire resistance to antimicrobial agents, ranging from penicillin in 1942 to methicillin in 1961, and in more recent years to other compounds, such as vancomycin, linezolid, and daptomycin (2, 3). Dalbavancin was recently approved by the U.S. FDA for the treatment of acute bacterial skin and skin structure infections caused by Gram-positive organisms in adults (4). Dalbavancin is a semisynthetic lipoglycopeptide structurally related to teicoplanin. Its mechanism of action involves the interruption of cell wall synthesis by binding to the terminal D-alanyl–D-alanine of the stem peptide in nascent cell wall peptidoglycans, thereby preventing cross-linking (transpeptidation and transglycosylation) of disaccharide subunits. This disruption of the cell wall results in bacterial cell death (5). To date, resistance to dalbavancin is limited to intrinsic glycopeptide-resistant species and to organisms expressing the VanA phenotype of acquired resistance. The potent *in vitro* activity of dalbavancin has been substantiated in various animal models of infection, and it possesses a pharmacokinetic (PK) profile that allows once-weekly intravenous (i.v.) dosing (4, 6). The purpose of this study was to compare the *in vitro* activity of dalbavancin against *S. aureus* isolates that are nonsusceptible (NS) to three relatively recently introduced antimicrobial agents (daptomycin, linezolid, and tigecycline) used to treat *S. aureus* infections.

More than 60,000 isolates from nonduplicate clinical specimens were collected between 2002 and 2012 during routine worldwide surveillance programs. The isolates were collected from 104 sites from the United States and 66 sites in the European (Belgium, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Romania, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom, and Ukraine), Russian, and Israeli regions. Isolates were recovered from blood (9,470 isolates [15.2%]), skin and soft tissue (18,764 isolates [30.2%]), respiratory tract (9,015 isolates [14.5%]), urinary tract (1,175 isolates [1.9%]), and other or undetermined infection sources (23,771 isolates [38.2%]) as part of the SENTRY surveillance program (JMI Laboratories, North Liberty, IA, USA).

Resistance phenotypes (nonsusceptible or resistant) for daptomycin and linezolid were based upon Clinical and Laboratory Standards Institute (CLSI) breakpoints (7), while U.S. FDA breakpoints were applied for dalbavancin (≤0.12 μg/ml for susceptible) and tigecycline. The MIC results were produced by reference broth microdilution methods (8); all quality control (QC) results were within the published QC ranges (7). Included in these analyses are 1,484 multidrug-resistant (MDR) methicillin-resistant *S. aureus* (MRSA) isolates and 94 clinical isolates of *S. aureus* characterized as daptomycin NS ($n = 37$), linezolid resistant (R) ($n = 19$), or tigecycline NS ($n = 38$). A determination of dalbavancin activity against MDR MRSA isolates was based on analysis from a more recent data set of isolates collected between 2010 and 2012. MDR was defined when an isolate displayed resistance phenotypes to ≥3 drug classes (9).

Table 1 shows the activity of dalbavancin and comparator agents tested against the daptomycin-NS, linezolid-R, and tigecycline-NS isolates. Dalbavancin was active when tested against the daptomycin-NS isolates, with $MIC_{50/90}$s of 0.06/0.12 μg/ml. By comparison, the $MIC_{50/90}$s for vancomycin against these isolates were 2/2 μg/ml, i.e., 16- to 32-fold higher. At the current U.S. FDA breakpoint, 91.9% of isolates with a daptomycin-NS phenotype would be categorized as susceptible to dalbavancin. However, against daptomycin-NS/vancomycin-susceptible isolates, the susceptibility would increase to 97.1% (data not shown). The $MIC_{50/90}$s for dalbavancin against linezolid-R *S. aureus* were 0.06/0.12 μg/ml, and for vancomycin, the $MIC_{50/90}$s were 1/2 μg/ml, again 16-fold higher. Against tigecycline-NS isolates, the $MIC_{50/90}$s for dalbavancin were 0.06/0.06 μg/ml, and for vancomycin, the $MIC_{50/90}$s were 1/2 μg/ml. Dalbavancin, daptomycin, linezolid, and vancomycin exhibited 100.0% susceptibility rates against these isolates, while 26.3% showed susceptibility to clindamycin.

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Address correspondence to Sandra P. McCurdy, mccurdysp@comcast.net.

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TABLE 1 Activity of dalbavancin and selected Gram-positive focused agents when tested against resistance phenotypes of *S. aureus* from a worldwide surveillance program, 2002 to 2012

Organism/subset (no. tested)[a]	Antimicrobial agent	MIC (μg/ml)			% susceptible[b]
		50%	90%	Range	
All *S. aureus* (62,195)	Dalbavancin	0.06	0.06	≤0.008 to 0.5	99.7
MRSA (26,975)	Dalbavancin	0.06	0.06	≤0.008 to 0.5	99.6
	Daptomycin	0.25	0.5	≤0.06 to 4	99.9
	Vancomycin	1	1	≤0.12 to 4	99.9
	Linezolid	1	2	≤0.12 to 16	99.9
	Tigecycline[c]	0.12	0.5	≤0.015 to 1	99.9
	Clindamycin	≤0.06	>2	≤0.06 to >8	60.3
Daptomycin NS (37)	Dalbavancin	0.06	0.12	≤0.03 to 0.5	91.9
	Vancomycin	2	2	1 to 4	94.6
	Linezolid	1	2	0.5 to 4	100.0
	Tigecycline	0.12	0.25	≤0.03 to 0.25	100.0
	Clindamycin	>2	>2	≤0.06 to >2	43.2
Linezolid R (19)	Dalbavancin	0.06	0.12	≤0.03 to 0.12	100.0
	Vancomycin	1	2	0.5 to 2	100.0
	Daptomycin	0.5	0.5	0.25 to 0.5	100.0
	Tigecycline	0.12	0.5	0.06 to 0.5	100.0
	Clindamycin	>2	>2	≤0.25 to >2	42.1
Tigecycline NS (38)	Dalbavancin	0.06	0.06	≤0.03 to 0.12	100.0
	Vancomycin	1	2	0.5 to 2	100.0
	Daptomycin	0.25	0.5	0.25 to 0.5	100.0
	Linezolid	2	2	1 to 2	100.0
	Clindamycin	>2	>2	≤0.06 to >2	26.3
MRSA from 2010–2012 (5,167)[d]	Dalbavancin	0.06	0.06	≤0.03 to 0.25	99.7
MDR (1,484)	Dalbavancin	0.06	0.06	≤0.03 to 0.25	99.8
	Vancomycin	1	1	≤0.12 to 2	100.0
	Daptomycin	0.25	0.5	0.12 to 2	99.8
	Linezolid	1	1	≤0.12 to 8	99.8
	Tigecycline[d]	0.12	0.25	≤0.03 to 1	99.8

[a] MRSA, methicillin-resistant *S. aureus*; NS, nonsusceptible; R, resistant; MDR, multidrug resistant.
[b] According to breakpoint criteria of the CLSI (7) and U.S. FDA (4, 10), where appropriate.
[c] Data not available for 2011 isolates; $n = 26,436$.
[d] Isolates from 2010 and 2012 were tabulated (1,332 MDR isolates).

Dalbavancin and selected comparators tested against a more recent collection of MRSA isolates with an MDR phenotype (surveillance years 2010 to 2012) (Table 1) demonstrated dalbavancin activity ($MIC_{50/90}$, 0.06/0.06 μg/ml) and a 99.8% overall susceptibility rate. This activity was comparable to that observed for daptomycin, linezolid, tigecycline, and vancomycin (99.8 to 100.0%).

In the present study, dalbavancin demonstrated potent activity against *S. aureus* isolates characterized as daptomycin NS, linezolid R, and tigecycline NS when applying current CLSI and U.S. FDA breakpoints (4, 7, 10). Dalbavancin demonstrated activity that was similar to that of the comparator agents against 1,484 MRSA isolates with an MDR phenotype. In the recently completed dalbavancin clinical trials (DISCOVER 1 and DISCOVER 2), there were no *S. aureus* isolates that had a dalbavancin MIC of >0.25 μg/ml, and there were only two isolates that had an MIC of 0.25 μg/ml out of 511 isolates tested (6). One patient with an *S. aureus* isolate with a dalbavancin MIC of 0.25 μg/ml was treated successfully with that drug. More clinical data from patients with *S. aureus* isolates at this MIC level would be informative but may be challenging to generate, given the scarcity of this phenotype in clinical practice. In >10 years of dalbavancin surveillance testing, only 0.35% of *S. aureus* isolates were encountered that exceeded the current U.S. FDA susceptibility breakpoint of ≤0.12 μg/ml for dalbavancin (4).

In summary, this study demonstrates that dalbavancin has sustained potency against the vast majority of *S. aureus* isolates that are nonsusceptible to currently used antimicrobial agents, and against MRSA isolates with MDR phenotypes in surveillance over the last 10 years. Dalbavancin appears to be a viable treatment option for patients with indicated infections caused by these challenging pathogens (4).

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