Sustained Potent Activity of Dalbavancin when Tested Against Multidrug-resistant Staphylococcal and Streptococcal Isolates Responsible for Documented Infection in European Sites (2011-2013)

P0706

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ECCMID 2015
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ABSTRACT

Objectives: To assess the *in vitro* activity of dalbavancin against Gram-positive isolates displaying a multidrug-resistant (MDR) phenotype collected from hospitalized patients in Europe and adjacent areas. Dalbavancin was approved (2014) by the Food and Drug Administration (FDA) and (2015) by the European Medicines Agency for the treatment of acute bacterial skin and skin structure infections.

Methods: Isolates were collected from 57 sites located in European, Russian, Turkish and Israeli regions as part of the SENTRY Antimicrobial Surveillance Program. Bacteria were identified by standard algorithms and MALDI-TOF. Susceptibility testing was performed by CLSI methods; interpretation of MICs used FDA (dalbavancin), and CLSI (2015) and EUCAST (2015) criteria for comparators. *S. aureus* exhibiting resistance to methicillin and at least three other drug classes were considered as MDR. Streptococci with a resistance phenotype to at least three drug classes were categorized as MDR.

Results: 42.6% of MRSA isolates met the MDR criteria. Dalbavancin had similar $MIC_{50/90}$ values (0.06/0.06 mg/L for both; ≥99.5% susceptible) when tested against MDR and non-MDR MRSA isolates (**Table 1**). Vancomycin ($MIC_{50/90}$, 1/1 mg/L), daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L) and linezolid ($MIC_{50/90}$, 1/1 mg/L) were also active (99.6 – 100.0% susceptible) against MDR MRSA, albeit with MICs at least 4-fold higher than dalbavancin ($MIC_{50/90}$, 0.06/0.06 mg/L). All viridans group streptococci (VGS) were susceptible to dalbavancin, with MIC_{50} and MIC_{90} results of ≤0.03 and 0.06 mg/L, respectively, regardless of resistance phenotype. These dalbavancin results were at least 16-fold lower than those of vancomycin ($MIC_{50/90}$, 0.5/1 mg/L; 100.0% susceptible), daptomycin ($MIC_{50/90}$, 0.5/1 mg/L; 100.0% susceptible) and linezolid ($MIC_{50/90}$, 0.5/1 mg/L; 100.0% susceptible) against MDR isolates of VGS. Other comparators had limited coverage (1.5 – 55.6% susceptible) against MDR VGS, including levofloxacin (86.7% susceptible) and ceftriaxone (62.2 – 69.6.0% susceptible). Only 7.0% of beta-haemolytic streptococci (BHS) had a MDR phenotype. The majority (95.2%) of these MDR isolates exhibited an erythromycin, clindamycin and tetracycline resistance pattern, and a great proportion (72.8%) of MDR BHS were *S. agalactiae*. Dalbavancin ($MIC_{50/90}$, ≤0.03/0.06 mg/L; 99.2 – 100.0% susceptible) and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 mg/L; 100.0% susceptible) were similarly active against both MDR and non-MDR BHS. Ceftriaxone ($MIC_{50/90}$, ≤0.06/0.12 mg/L; 99.9 – 100.0% susceptible) and levofloxacin ($MIC_{50/90}$, 0.5/1 mg/L; 92.0 – 99.3% susceptible) also had consistent MICs against MDR and non-MDR. In contrast, vancomycin (0.5 vs 0.25 mg/L) and daptomycin (0.25 vs ≤0.06 mg/L) had higher MIC_{50} values against MDR compared with non-MDR BHS isolates, respectively, albeit both agents inhibited these populations at their respective breakpoints for susceptibility.

Conclusion: Dalbavancin had potent *in vitro* activity against this contemporary collection of staphylococci and streptococci, including isolates with MDR phenotypes. In addition, dalbavancin had the most potent activity against isolates tested, relative to comparator agents, with and without MDR phenotypes.

INTRODUCTION

Dalbavancin was approved in the United States (2014) and Europe (2015) for the treatment of adults with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of *Staphylococcus aureus*, including methicillin–susceptible (MSSA) and –resistant *S. aureus* (MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus anginosus* group. The ABSSSI indication was based on two identically designed noninferiority trials (DISCOVER 1 and DISCOVER 2) comparing dalbavancin safety and efficacy to a control regimen of vancomycin/linezolid. Results showed that dalbavancin was non-inferior to comparators, and 79.7% (525/659) and 79.8% (521/653) of patients in the dalbavancin and vancomycin/linezolid arms had an early clinical response indicating treatment success in the pooled analysis, respectively. Moreover, dalbavancin is under consideration for other indications, including pediatric osteomyelitis and community acquired pneumonia.

S. aureus, including MRSA isolates remain important human pathogens. The treatment of invasive MRSA infections has relied significantly on vancomycin. However, several studies have reported increased treatment failures against isolates displaying elevated vancomycin MIC results (i.e. 2 mg/L), but still considered susceptible based on current breakpoints. Recent consensus guidelines recommend alternative therapeutic agents for the management of infections due to MRSA strains with reduced susceptibility to vancomycin. In addition, streptococcal isolates exhibiting a multidrug resistance (MDR) phenotype, mainly *Streptococcus pneumoniae*, have become commonplace. This study evaluated the *in vitro* activity of dalbavancin against Gram-positive isolates displaying a MDR phenotype collected from hospitalized patients in Europe and adjacent areas.

MATERIALS AND METHODS

Bacterial isolates. A total of 9304 *S. aureus*, 1777 β-haemolytic streptococci (BHS) and 893 viridans group streptococci (VGS) were collected from 57 sites in Europe (Belgium, Bulgaria, Croatia, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom and Ukraine), Russia, Turkey and Israel. Isolates were determined to be clinically significant based on local guidelines and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA), as part of the SENTRY Antimicrobial Surveillance Program (2011–2013). Isolates were initially identified by the participating laboratory and bacterial identifications confirmed by the reference monitoring laboratory by standard algorithms and supported by MALDI–TOF–MS (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility testing. Isolates were tested for susceptibility by broth microdilution following guidelines in the Clinical and Laboratory Standards Institute (CLSI) M07–A10 document. Testing was performed using dry–form panels manufactured by Thermo Fisher Scientific (Cleveland, Ohio, USA). Quality assurance was performed by concurrent testing of CLSI–recommended quality control reference strains (*S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619; M100-S25, 2015). All QC results were within published acceptable ranges.

The dalbavancin breakpoints approved by the Food and Drug Administration (FDA) were applied, as follows: *S. aureus*, ≤0.12 mg/L for susceptible; *S. anginosus* group, ≤0.12 mg/L for susceptible; and *S. pyogenes* and *S. agalactiae*, ≤0.12 mg/L for susceptible. Breakpoint criteria for comparator agents were those from CLSI (M100-S25, 2015) and European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2015).

Data analysis was performed against all isolates or group of isolates in aggregate and according to MDR profile. *S. aureus* exhibiting resistance to methicillin and at least three other drug classes were considered as MDR. Streptococci with a resistance phenotype to at least three drug classes were categorized as MDR.

RESULTS

- A total of 9304 *S. aureus* collected from European hospitals and adjacent regions during 2011 – 2013 were included in the study. Among these isolates, 26.6% were methicillin-resistant and approximately half (42.6%) displayed a MDR phenotype (i.e. resistance to at least additional three drug classes; **Table 1**).
- Dalbavancin had similar modal MIC, MIC_{50} and MIC_{90} values (all 0.06 mg/L) when tested against MRSA isolates, regardless of MDR phenotype (**Table 1**). Moreover, dalbavancin inhibited 99.5 – 99.9% of these isolates at the FDA breakpoint for susceptibility (i.e. ≤0.12 mg/L).
- Vancomycin ($MIC_{50/90}$, 1/1 mg/L), daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L), linezolid ($MIC_{50/90}$, 1/1 mg/L) and trimethoprim-sulfamethoxazole ($MIC_{50/90}$, ≤0.5/≤0.5 mg/L) were also *in vitro* active (96.1 – 100.0% susceptible) against MDR (**Table 2**) and non-MDR (data not shown) MRSA strains.
- Dalbavancin ($MIC_{50/90}$, 0.06/0.06 mg/L), however, showed MIC results at least four-fold lower than vancomycin, daptomycin, linezolid and trimethoprim-sulfamethoxazole against MDR (**Table 2**) and non-MDR (data not shown) MRSA strains.
- Overall, VGS were very susceptible to dalbavancin inhibiting all strains at ≤0.12 mg/L, regardless of resistance phenotype. Moreover, dalbavancin MIC_{90} results were at least 16-fold lower than tested comparator agents against VGS, and MDR and non-MDR isolate subsets (**Table 2**).
- Among antimicrobial agents tested against the MDR subset of VGS, dalbavancin, vancomycin, teicoplanin, daptomycin and linezolid (all 100.0% susceptible by CLSI and/or EUCAST criteria) demonstrated antimicrobial coverage against these isolates (**Table 2**). Other tested agents had limited activity.
- Overall, BHS were susceptible to the antimicrobial agents tested and only 7.0% exhibited a MDR phenotype. The majority (95.2%) of these MDR isolates exhibited an erythromycin, clindamycin and tetracycline resistance pattern, and a great proportion (72.8%) of these were *S. agalactiae* (data not shown).

Table 1. Activity and spectrum of dalbavancin against contemporary clinical isolates (2011 – 2013) in Europe, Russia, Turkey and Israel.

Pathogens[a] Phenotype (no. tested/%)	MIC (mg/L)		Number (cumulative %) inhibited at MIC (mg/L)[b]			
	50%	90%	≤0.03	0.06	0.12	0.25
S. aureus (9,304)	0.06	0.06	2898 (31.1)	**5624 (91.6)**	771 (99.9)	11 (100.0)
MRSA (2,472/26.6)	0.06	0.06	871 (35.2)	**1430 (93.1)**	165 (99.8)	6 (100.0)
MDR (1,054/42.6)	0.06	0.06	340 (32.3)	**615 (90.6)**	94 (99.5)	5 (100.0)
Non-MDR (1,418/57.4)	0.06	0.06	531 (37.4)	**815 (94.9)**	71 (99.9)	1 (100.0)
VGS (893)	≤0.03	0.06	**766 (85.8)**	117 (98.9)	10 (100.0)	
MDR (135/15.1)	≤0.03	0.06	**107 (79.3)**	26 (98.5)	2 (100.0)	
Non-MDR (758/84.9)	≤0.03	0.06	**659 (86.9)**	91 (98.9)	8 (100.0)	
BHS (1,777)	≤0.03	0.06	**1567 (88.2)**	159 (97.1)	38 (99.3)	13 (100.0)
MDR (125/7.0)	≤0.03	0.06	**110 (88.0)**	9 (95.2)	6 (100.0)	
Non-MDR (1,652/93.0)	≤0.03	0.06	**1457 (88.2)**	150 (97.3)	32 (99.2)	13 (100.0)

a. MRSA = methicillin-resistant *S. aureus*; MDR *S. aureus* = resistance phenotype to methicillin and at least three classes of drugs (except for daptomycin; non-susceptible phenotypes were included). VGS = viridans group streptococci; BHS = β-haemolytic streptococci. Streptococci with a resistance phenotype to at least three drug classes were categorized as MDR
b. Modal MIC results are in bold. Underlined rates represent percentages of susceptibility for dalbavancin (FDA breakpoints). *S. aureus*, ≤0.12 mg/L for susceptible. The *S. anginosus* group (≤0.12 mg/L for susceptible) and *S. pyogenes* and *S. agalactiae* (≤0.12 mg/L for susceptible) were applied for VGS and BHS, respectively.

Table 2. Antimicrobial activity of dalbavancin and comparator agents against Gram-positive clinical isolates (2011 – 2013) in Europe, Russia, Turkey and Israel.

Organism[a] (number tested) Antimicrobial agent	MIC (mg/L)			% Susceptible/Intermediate/Resistant[b]	
	Range	50%	90%	CLSI	EUCAST
MRSA (2472)					
Dalbavancin	≤0.03 – 0.25	0.06	0.06	99.8 / - / -	- / - / -
Vancomycin	0.25 – 2	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Teicoplanin	≤2 – 16	≤2	≤2	>99.9 / <0.1 / 0.0	99.2 / 0.1 / 0.9
Daptomycin	≤0.06 – 2	0.25	0.5	99.7 / - / -	99.7 / 0.0 / 0.3
Linezolid	≤0.12 – 8	1	1	99.9 / 0.0 / 0.1	99.9 / 0.0 / 0.1
Ciprofloxacin	≤0.03 – >4	>4	>4	13.5 / 0.7 / 85.8	13.5 / 0.0 / 86.5
Erythromycin	≤0.12 – >16	>16	>16	27.9 / 3.7 / 68.4	28.4 / 1.1 / 70.5
Clindamycin	≤0.25 – >2	≤0.25	>2	65.1 / 0.2 / 34.7	64.6 / 0.5 / 34.9
Gentamicin	≤1 – >8	≤1	>8	77.2 / 0.4 / 22.4	76.4 / 0.0 / 23.6
Tetracycline	≤0.25 – >8	≤0.25	>8	81.9 / 1.2 / 16.9	81.3 / 0.3 / 18.4
Trimethoprim/sulfamethoxazole	≤0.5 – >4	≤0.5	≤0.5	98.3 / 0.0 / 1.7	98.3 / 0.3 / 1.4
MDR MRSA (1054)					
Dalbavancin	≤0.03 – 0.25	0.06	0.06	99.5 / - / -	- / - / -
Vancomycin	0.25 – 2	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Teicoplanin	≤2 – 16	≤2	≤2	99.9 / 0.1 / 0.0	98.3 / 0.0 / 1.7
Daptomycin	≤0.06 – 2	0.25	0.5	99.6 / - / -	99.6 / 0.0 / 0.4
Linezolid	≤0.12 – 8	1	1	99.7 / 0.0 / 0.3	99.7 / 0.0 / 0.3
Ciprofloxacin	0.12 – >4	>4	>4	1.6 / 0.1 / 98.3	1.6 / 0.0 / 98.4
Erythromycin	≤0.12 – >16	>16	>16	4.6 / 4.7 / 90.7	4.9 / 1.3 / 93.8
Clindamycin	≤0.25 – >2	>2	>2	20.2 / 0.2 / 79.6	19.8 / 0.4 / 79.8
Gentamicin	≤1 – >8	≤1	>8	53.7 / 0.6 / 45.7	52.7 / 0.0 / 47.3
Tetracycline	≤0.25 – >8	≤0.25	>8	68.1 / 0.3 / 31.6	67.6 / 0.4 / 32.0
Trimethoprim/sulfamethoxazole	≤0.5 – >4	≤0.5	≤0.5	96.1 / 0.0 / 3.9	96.1 / 0.7 / 3.2
MDR VGS (135)					
Dalbavancin	≤0.03 – 0.12	≤0.03	0.06	100.0 / - / -	- / - / -
Vancomycin	0.25 – 1	0.5	1	100.0 / - / -	100.0 / 0.0 / 0.0
Teicoplanin	≤2	≤2	≤2	- / - / -	100.0 / 0.0 / 0.0
Daptomycin	≤0.06 – 1	0.5	1	100.0 / - / -	- / - / -
Linezolid	≤0.12 – 2	0.5	1	100.0 / - / -	- / - / -
Penicillin	≤0.06 – >8	0.25	8	45.9 / 25.2 / 28.9	55.6 / 15.5 / 28.9
Ceftriaxone	≤0.06 – >8	0.5	8	69.6 / 2.3 / 28.1	62.2 / 0.0 / 37.8
Erythromycin	≤0.12 – >16	>16	>16	1.5 / 0.0 / 98.5	- / - / -
Clindamycin	≤0.25 – >2	>2	>2	25.2 / 0.7 / 74.1	25.9 / 0.0 / 74.1
Levofloxacin	0.25 – >4	1	>4	86.7 / 0.7 / 12.6	- / - / -
Tetracycline	≤0.25 – >8	>8	>8	16.3 / 1.5 / 82.2	- / - / -
MDR BHS (125)					
Dalbavancin	≤0.03 – 0.12	≤0.03	0.06	100.0 / - / -	- / - / -
Vancomycin	≤0.12 – 0.5	0.5	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Teicoplanin	≤2	≤2	≤2	- / - / -	100.0 / 0.0 / 0.0
Daptomycin	≤0.06 – 0.5	0.25	0.25	100.0 / - / -	100.0 / 0.0 / 0.0
Linezolid	0.25 – 1	0.5	1	100.0 / - / -	100.0 / 0.0 / 0.0
Penicillin	≤0.06 – 0.12	≤0.06	≤0.06	100.0 / - / -	100.0 / 0.0 / 0.0
Ceftriaxone	≤0.06 – 0.12	≤0.06	0.12	100.0 / - / -	100.0 / 0.0 / 0.0
Erythromycin	2 – >16	>16	>16	0.0 / 0.0 / 100.0	0.0 / 0.0 / 100.0
Clindamycin	≤0.25 – >2	>2	>2	1.6 / 0.0 / 98.4	1.6 / 0.0 / 98.4
Levofloxacin	0.25 – >4	0.5	1	95.2 / 0.0 / 4.8	92.0 / 3.2 / 4.8
Tetracycline	0.25 – >8	>8	>8	0.8 / 0.0 / 99.2	0.8 / 0.0 / 99.2

a. MRSA = methicillin-resistant *S. aureus*; MDR = resistance phenotype to methicillin and at least three classes of drugs (except for daptomycin; non-susceptible phenotypes were included). VGS = viridans group streptococci; BHS = β-haemolytic streptococci.
b. Breakpoint criteria for dalbavancin according to the USA-FDA. *S. aureus*, ≤0.12 mg/L for susceptible. The *S. anginosus* group (≤0.12 mg/L for susceptible) and *S. pyogenes* and *S. agalactiae* (≤0.12 mg/L for susceptible) were applied for VGS and BHS, respectively; see CLSI results. Breakpoint criteria for comparator agents were those from CLSI (M100-S25; 2015) and EUCAST (2015). "-" = breakpoint not available.

CONCLUSIONS

- The proportion of MDR phenotype observed in the MRSA population was elevated (i.e. 42.6%), while relative rates of MDR phenotype among streptococcal isolates were lower (15.1 and 7.0% among VGS and BHS, respectively).
- Dalbavancin had potent *in vitro* activity against this contemporary (2011 – 2013) collection of staphylococcal and streptococcal clinical isolates, including isolates displaying a MDR phenotype.
- Comparator agents with similar indications, such as vancomycin, teicoplanin, daptomycin and linezolid also demonstrated *in vitro* coverage against MDR strain. However, dalbavancin had the greatest potency overall against these isolates.

ACKNOWLEDGEMENTS

This study was sponsored by an educational/research grant from Durata Therapeutics, a subsidiary of Actavis plc (Branford, Connecticut, United States) via the SENTRY Antimicrobial Surveillance Programme platform.

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