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Dalbavancin Tested against *Staphylococcus aureus* Isolates with Decreased Susceptibility to Glycopeptides and/or Lipopeptides from European Hospitals (2012–2016)

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ABSTRACT

Background: Dalbavancin was approved by the US Food and Drug Administration (2014) and European Medicines Agency (2015) for treating acute bacterial skin and skin structure infections. Dalbavancin activity was evaluated against a challenge set of *Staphylococcus aureus* clinical isolates responsible for infections in European hospitals.

Methods: A total of 12,807 *S. aureus* (3,054 methicillin-resistant *S. aureus* [MRSA]) isolates were collected from 20 European countries and surrounding regions (52 sites), including Russia (3 sites), Turkey (6 sites), and Israel (1 site). Isolates were submitted to a monitoring laboratory as part of the International Dalbavancin Evaluation of Activity (IDEA) surveillance program. Identification was confirmed and susceptibility testing was performed by CLSI methods. MIC interpretation used CLSI and EUCAST criteria. Isolates were grouped according to daptomycin, teicoplanin, and vancomycin MIC results.

Results: A total of 23.8% *S. aureus* isolates were MRSA. Among the MRSA isolates, 0.8% were resistant to teicoplanin while 1.3% and 1.8% displayed decreased susceptibility to vancomycin and daptomycin, respectively. Dalbavancin inhibited all but 1 MRSA isolate at ≤0.12 mg/L (100.0% susceptible) with similar MIC results against methicillin-susceptible *S. aureus* (MSSA) isolates. MRSA isolates with decreased susceptibility to vancomycin or teicoplanin had dalbavancin MIC_{50} results ($MIC_{50/90}$, 0.06/0.12 mg/L) 2-fold higher than the more susceptible MSSA counterparts ($MIC_{50/90}$, ≤0.03/0.06 mg/L). Linezolid ($MIC_{50/90}$, 1/1 mg/L; 95.8%–100.0% susceptible) and trimethoprim-sulfamethoxazole ($MIC_{50/90}$, ≤0.5/≤0.5-2 mg/L; 91.7%–100.0% susceptible) were active against MRSA with decreased susceptibility to glycopeptides and/or lipopeptides. Tetracycline (89.1% susceptible) was more active against MRSA isolates with decreased susceptibility to daptomycin compared to isolates less susceptible to glycopeptides (54.2%–70.7% susceptible).

Conclusions: Dalbavancin demonstrated potent *in vitro* activity against MRSA, including isolates displaying decreased susceptibility to agents commonly used for treatment of serious infections, from institutions in Europe and adjacent regions. Dalbavancin was consistently more potent than comparator agents.

INTRODUCTION

- Increased rates of infections caused by antimicrobial-resistant pathogens have challenged the empirical treatment conducted by health practitioners worldwide
- Several population-based studies documented a decrease in overall methicillin-resistant *Staphylococcus aureus* (MRSA) causing invasive or bloodstream infections in the US and European countries
  - However, incidences of community-associated invasive MRSA infections remain stable
- Concerns regarding suboptimal clinical responses to glycopeptides, the slow bactericidal activity of vancomycin, the emergence of isolates with reduced susceptibility to vancomycin and/or daptomycin complicate the management of *S. aureus* infection
- Dalbavancin belongs to the lipoglycopeptide class of antimicrobial agents that act by interrupting bacterial cell wall synthesis resulting in bacterial death
- Dalbavancin was approved in the United States (2014) and Europe (2015) to treat adults with acute bacterial skin and skin structure infections (ABSSSI) caused by indicated pathogens
- Dalbavancin allows for very convenient parenteral administrations, which can be a single dose of 1500 mg or a dose of 1000 mg followed by 500 mg a week later
- This study presents dalbavancin *in vitro* antimicrobial activity against a challenge set of *S. aureus* clinical isolates responsible for infections in European hospitals during 2012–2016

MATERIALS AND METHODS

- A total of 12,807 *S. aureus* (3,054 MRSA) isolates were collected from 20 European countries and surrounding regions (52 sites), including Russia (3 sites), Turkey (6 sites), and Israel (1 site)
- These isolates were submitted to the monitoring laboratory (JMI Laboratories; North Liberty, Iowa, USA) as part of the International Dalbavancin Evaluation of Activity (IDEA) surveillance programme
- Isolates were primarily identified by the participating laboratory and confirmed by the reference monitoring laboratory (JMI Laboratories) by standard algorithms and supported by matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) (Bruker Daltonics, Bremen, Germany)
- Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document
- Bacterial inoculum density was monitored by colony counts to assure an adequate number of cells for each testing event
- MIC value validation was performed by concurrently testing CLSI-recommended quality control (QC) reference strains (*S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212). All QC results were within published acceptable ranges (M100-S26)
- Dalbavancin MIC interpretations were based on breakpoints approved by the Food and Drug Administration (2016) and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2016). Interpretations for comparator agents used CLSI (M100-S26) and EUCAST (2016) breakpoint criteria, as available.
- *In vitro* activities of dalbavancin and comparator agents were evaluated according to the daptomycin, teicoplanin, and vancomycin MIC results (EUCAST criteria)

RESULTS

- A total of 23.8% *S. aureus* were MRSA
  - Among the MRSA isolates, 0.8% were resistant to teicoplanin while 1.3% and 1.8% displayed decreased susceptibility to vancomycin and daptomycin, respectively (Table 1)
- Dalbavancin inhibited all but 1 MRSA isolate at ≤0.12 mg/L (100.0% susceptible) with similar MIC_{50} and MIC_{90} results against MRSA ($MIC_{50/90}$, ≤0.03/0.06 mg/L) and methicillin-susceptible *S. aureus* (MSSA; $MIC_{50/90}$, ≤0.03/0.06 mg/L) populations (Table 1)
- MRSA isolates with decreased susceptibility to vancomycin (MIC ≥2 mg/L) or teicoplanin (MIC ≥4 mg/L) had dalbavancin MIC_{50} results ($MIC_{50/90}$, 0.06/0.12 mg/L) 2-fold higher than the MSSA counterparts ($MIC_{50/90}$, ≤0.03/0.06 mg/L; Table 1)
- Isolates with decreased susceptibility to daptomycin (MIC ≥1 mg/L) exhibited dalbavancin MIC_{50} results (≤0.03 mg/L) similar to those displaying daptomycin MIC at ≤0.5 mg/L (dalbavancin MIC_{50}, ≤0.03 mg/L; Table 1)
- Overall, MSSA clinical isolates showed high susceptibility rates (94.7%–100.0% susceptible) to all tested antimicrobial agents, except for erythromycin (84.8%–85.1% susceptible; Table 2)
- Most agents demonstrated *in vitro* activity against MRSA isolates with decreased susceptibility to glycopeptides and/or lipopeptides. The exceptions were clindamycin (50.0%–70.4% susceptible), erythromycin (20.8%–24.4% susceptible), levofloxacin (0.0%–9.1% susceptible), and tetracycline (54.2%–89.1% susceptible; Table 2)
- Dalbavancin showed MIC_{90} results at least 4-fold lower than comparator agents tested against MRSA isolates with decreased susceptibility to glycopeptides and/or lipopeptides (Table 2)

CONCLUSIONS

- Dalbavancin demonstrated potent *in vitro* activity against MRSA from institutions in Europe and adjacent regions, including isolates displaying decreased susceptibility to agents commonly used to treat serious infections
- These *in vitro* results suggest that dalbavancin can serve as an option for the treatment of MRSA infections in Europe when the presence of isolates with decreased susceptibility to glycopeptides and/or lipopeptides is suspected

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Table 1 Activity of dalbavancin against *S. aureus* clinical isolates causing infections in European and adjacent region hospitals

Phenotype (no. tested)	MIC (mg/L) 50%	MIC (mg/L) 90%	Number (cumulative %) inhibited at dalbavancin MIC (mg/L) of[a]: ≤0.03	0.06	0.12	0.25
Methicillin-susceptible (9,753)	≤0.03	0.06	**5,441 (55.8%)**	3,862 (95.4%)	450 (100.0%)	
Methicillin-resistant (3,054)	≤0.03	0.06	**1,791 (58.6%)**	1,163 (96.7%)	99 (>99.9%)	1 (100.0%)
Daptomycin MIC ≤0.5 mg/L (2,999)	≤0.03	0.06	**1,752 (58.4%)**	1,154 (96.9%)	92 (>99.9%)	1 (100.0%)
Daptomycin MIC ≥1 mg/L (55)	≤0.03	0.12	**39 (70.9%)**	9 (87.3%)	7 (100.0%)	
Teicoplanin MIC ≤2 mg/L (3,030)	≤0.03	0.06	**1,789 (59.0%)**	1,153 (97.1%)	88 (100.0%)	
Teicoplanin MIC ≥4 mg/L (24)	0.06	0.12	2 (8.3%)	10 (50.0%)	**11 (95.8%)**	1 (100.0%)
Vancomycin MIC ≤1 mg/L (3,013)	≤0.03	0.06	**1,788 (59.3%)**	1,143 (97.3%)	82 (100.0%)	
Vancomycin MIC ≥2 mg/L (41)	0.06	0.12	3 (7.3%)	**20 (56.1%)**	17 (97.6%)	1 (100.0%)

[a] Bold data represent dalbavancin modal MIC results

Table 2 Antimicrobial activity of dalbavancin and comparator agents against contemporary (2012–2016) clinical isolates displaying several antimicrobial susceptibility phenotypes

Organism (no. of organisms) antimicrobial agent	MIC (mg/L) 50%	MIC (mg/L) 90%	% Susceptible/%Intermediate/%Resistant[a] CLSI			EUCAST		
MSSA (9,753)								
Dalbavancin	≤0.03	0.06	100.0	—	—	100.0	—	0.0
Clindamycin	≤0.25	≤0.25	98.0	0.1	1.9	97.8	0.2	2.0
Daptomycin	0.25	0.5	>99.9	—	—	>99.9	—	<0.1
Erythromycin	0.25	>8	84.8	2.2	13.1	85.1	0.8	14.1
Levofloxacin	≤0.12	0.25	95.5	0.4	4.1	95.5	0.4	4.1
Linezolid	1	1	100.0	—	0.0	100.0	—	0.0
Teicoplanin	≤2	≤2	100.0	0.0	0.0	99.9	—	0.1
Tetracycline	≤0.5	≤0.5	94.9	0.4	4.6	94.7	0.1	5.2
TMP-SMX	≤0.5	≤0.5	99.8	—	0.2	99.8	0.1	0.1
Vancomycin	1	1	100.0	0.0	0.0	100.0	—	0.0
MRSA with daptomycin MIC of ≥1 mg/L (55)								
Dalbavancin	≤0.03	0.12	100.0	—	—	100.0	—	0.0
Clindamycin	≤0.25	>2	70.4	0.0	29.6	70.4	0.0	29.6
Daptomycin	1	1	90.9	—	—	90.9	—	9.1
Erythromycin	>8	>8	23.6	10.9	65.5	23.6	1.8	74.5

continued

Table 2 Antimicrobial activity of dalbavancin and comparator agents against contemporary (2012–2016) clinical isolates displaying several antimicrobial susceptibility phenotypes, *continued*

Organism (no. of organisms) antimicrobial agent	MIC (mg/L) 50%	MIC (mg/L) 90%	% Susceptible/%Intermediate/%Resistant[a] CLSI			EUCAST		
Levofloxacin	>4	>4	9.1	0.0	90.9	9.1	0.0	90.9
Linezolid	1	1	100.0	—	0.0	100.0	—	0.0
Teicoplanin	≤2	4	100.0	0.0	0.0	89.1	—	10.9
Tetracycline	≤0.5	8	89.1	1.8	9.1	89.1	0.0	10.9
TMP-SMX	≤0.5	≤0.5	100.0	—	0.0	100.0	0.0	0.0
Vancomycin	1	2	100.0	0.0	0.0	100.0	—	0.0
MRSA with teicoplanin MIC of ≥4 mg/L (24)								
Dalbavancin	0.06	0.12	100.0	—	—	95.8	—	4.2
Clindamycin	≤0.25	>2	65.2	0.0	34.8	60.9	4.3	34.8
Daptomycin	0.5	2	87.5	—	—	87.5	—	12.5
Erythromycin	>8	>8	20.8	16.7	62.5	20.8	4.2	75.0
Levofloxacin	>4	>4	0.0	0.0	100.0	0.0	0.0	100.0
Linezolid	1	1	95.8	—	4.2	95.8	—	4.2
Teicoplanin	4	8	95.8	4.2	0.0	0.0	—	100.0
Tetracycline	≤0.5	>8	58.3	0.0	41.7	54.2	0.0	45.8
TMP-SMX	≤0.5	2	91.7	—	8.3	91.7	0.0	8.3
Vancomycin	2	2	100.0	0.0	0.0	100.0	—	0.0
MRSA with vancomycin MIC of ≥2 mg/L (41)								
Dalbavancin	0.06	0.12	100.0	—	—	97.6	—	2.4
Clindamycin	≤0.25	>2	52.5	0.0	47.5	50.0	2.5	47.5
Daptomycin	0.5	1	90.2	—	—	90.2	—	9.8
Erythromycin	>8	>8	24.4	12.2	63.4	24.4	4.9	70.7
Levofloxacin	>4	>4	2.4	0.0	97.6	2.4	0.0	97.6
Linezolid	1	1	97.6	—	2.4	97.6	—	2.4
Teicoplanin	≤2	4	97.6	2.4	0.0	63.4	—	36.6
Tetracycline	≤0.5	>8	70.7	0.0	29.3	70.7	0.0	29.3
TMP-SMX	≤0.5	≤0.5	97.6	—	2.4	97.6	0.0	2.4
Vancomycin	2	2	100.0	0.0	0.0	100.0	—	0.0

MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; TMP-SMX, trimethoprim-sulfamethoxazole

[a] Dalbavancin breakpoint criteria according to the FDA package insert (under CLSI column) and EUCAST. Breakpoint criteria for comparator agents according to CLSI (M100-S26, 2016) and EUCAST (2016), as available; "—" = breakpoint not available

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