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Short Communication

In vitro activity of dalbavancin against multidrug-resistant *Staphylococcus aureus* and streptococci from patients with documented infections in Europe and surrounding regions (2011–2013)

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ABSTRACT

The in vitro activity of dalbavancin was evaluated against 9303 *Staphylococcus aureus* and 2670 streptococci, including multidrug-resistant (MDR) isolates, collected from hospitalised patients in Europe and surrounding regions from 2011 to 2013. Dalbavancin recently received approval for the treatment of acute bacterial skin and skin-structure infections by the US Food and Drug Administration (FDA) and the European Medicines Agency. Bacterial identification was confirmed by standard microbiological methods (including MALDI-TOF), and susceptibility testing was performed by reference broth microdilution methods. Dalbavancin susceptibility interpretations followed FDA/EUCAST criteria. Meticillin-resistant *S. aureus* (MRSA) and streptococci exhibiting resistance to at least three other drug classes were considered as MDR. Dalbavancin was highly active ($MIC_{50/90}$, 0.06/0.06 mg/L; ≥99.9% susceptible) against MDR and non-MDR MRSA isolates. Vancomycin, daptomycin and linezolid were also active (99.6–100.0% susceptible) against MDR MRSA, however MIC_{90} values for these drugs were 8- to 16-fold higher than dalbavancin (MIC_{90} values of 1, 0.5 and 1 mg/L, respectively). All viridans group streptococci (VGS) and β-haemolytic streptococci were susceptible to dalbavancin regardless of resistance phenotype ($MIC_{50/90}$ values of ≤0.03 mg/L and 0.06 mg/L, respectively). Dalbavancin $MIC_{50/90}$ results ($MIC_{50/90}$, ≤0.03/0.06 mg/L) against MDR VGS were at least eight-fold lower than those of vancomycin ($MIC_{50/90}$, 0.5/1 mg/L), daptomycin ($MIC_{50/90}$, 0.5/1 mg/L) and linezolid ($MIC_{50/90}$, 0.5/1 mg/L). Overall, dalbavancin exhibited potent in vitro antibacterial activity against *S. aureus* and streptococci, including MDR phenotypes. Dalbavancin had the lowest $MIC_{50/90}$ results against the isolates tested, relative to comparator agents, regardless of resistance phenotypes.

1. Introduction

Staphylococcus aureus, including meticillin-resistant *S. aureus* (MRSA) isolates, continue to be important community-acquired and nosocomial pathogens responsible for a variety of human infections worldwide [1]. Resistance to antimicrobial agents in clinical isolates of *S. aureus* has continued to evolve, beginning with penicillin in 1942, meticillin in 1961 [2], vancomycin in 2002 [3] and most recently linezolid and daptomycin in the last decade [4].

Treatment of serious MRSA infections has relied primarily on vancomycin. However, recent studies have reported increasing treatment failures against *S. aureus* isolates displaying elevated vancomycin minimum inhibitory concentration (MIC) results (i.e. ≥1.5 mg/L) [5], which are still considered as susceptible based on current breakpoints [6,7]. Recent recommendations by the Infectious Diseases Society of America (IDSA) suggest alternative therapeutic agents for the management of infections due to MRSA isolates with reduced susceptibility to vancomycin [8]. In addition, streptococcal isolates exhibiting a multidrug-resistant (MDR) phenotype, primarily *Streptococcus pneumoniae*, have become more common [9–11].

Dalbavancin was recently approved in the USA (May 2014) [12] and Europe (March 2015) [13] for the treatment of adults with acute bacterial skin and skin-structure infections (ABSSSIs) caused by susceptible isolates of *S. aureus*, including meticillin-susceptible *S. aureus* and MRSA isolates, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* and *Streptococcus anginosus* group.

Data from this study were presented in part at the 25th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), 25–28 April 2015, Copenhagen, Denmark [abstract P0706].

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Dalbavancin belongs to the lipoglycopeptide class of antimicrobials that act by interrupting bacterial cell wall synthesis resulting in bacterial cell death. Dalbavancin possesses unique pharmacokinetic properties allowing for a two-dose intravenous (i.v.) dosing regimen (1000 mg i.v. on Day 1 followed by 500 mg i.v. on Day 8) [12,14]. In addition, a recent clinical study demonstrated non-inferiority between a single 1500 mg i.v. dosing regimen of dalbavancin to the two-dose i.v. regimen for the treatment of ABSSSI [15], which led to the US Food and Drug Administration (FDA) approval of a single-dose option [12].

A newly published dalbavancin surveillance study [16] consisting predominantly of clinical isolates from the USA responsible for causing ABSSSIs confirmed the potent in vitro activity of this compound. This study herein evaluated the in vitro antibacterial activity of dalbavancin and relevant comparator agents against a large collection of *S. aureus* and streptococcal isolates (including MDR phenotypes) responsible for a variety of infection types collected from hospitalised patients at 57 medical centres in 19 European countries and surrounding regions during 2011–2013.

2. Materials and methods

2.1. Bacterial isolates

A total of 9303 *S. aureus*, 1777 β-haemolytic streptococci (βHS) and 893 viridans group streptococci (VGS) were collected from 57 medical centre sites in Europe (19 countries; Belgium, Bulgaria, Croatia, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Ukraine and the UK) as well as Russia, Turkey and Israel. Bacterial isolates were determined to be clinically significant based on local guidelines and were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, IA) as part of the 2011–2013 SENTRY Antimicrobial Surveillance Program. Bacterial isolates were initially identified by the participating laboratory, with confirmation of these identifications at the reference monitoring laboratory employing standard testing algorithms and supported by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) (Bruker Daltonik GmbH, Bremen, Germany).

2.2. Susceptibility testing

Bacterial isolates were tested for susceptibility to dalbavancin and comparator antimicrobials using the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method [17]. MIC testing was performed using panels manufactured by Thermo Fisher Scientific Inc. (Cleveland, OH). Quality assurance was performed by concurrent testing of CLSI-recommended quality control reference strains, including *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619; all results were within published limits [6].

2.3. Data analysis and interpretation

Data were analysed according to organism group and susceptibility profile. Multidrug resistance was defined as an isolate displaying a resistance phenotype to three or more drug classes [18]. Briefly, an MRSA isolate was categorised as MDR if it had, in addition to oxacillin resistance, a resistant phenotype (non-susceptibility to daptomycin was applied) to three or more of the following drug classes (CLSI criteria): macrolides (erythromycin, ≥8 mg/L); fluoroquinolones (ciprofloxacin, ≥4 mg/L); lincosamides (clindamycin, ≥4 mg/L); aminoglycosides (gentamicin, ≥16 mg/L); oxazolidinones (linezolid, ≥8 mg/L); tetracyclines (tetracycline HCl, ≥16 mg/L); folate pathway inhibitors (trimethoprim/sulfamethoxazole, ≥1/19 mg/L); or lipopeptides (daptomycin, ≥2 mg/L; resistance to glycopeptides was not observed). A streptococcal isolate was categorised as MDR if it had a resistant phenotype (CLSI criteria) to three or more of the following drug classes (drug class probe): ceftriaxone (≥1 mg/L for βHS or ≥4 mg/L for VGS); macrolides (erythromycin, ≥1 mg/L); fluoroquinolones (levofloxacin, ≥8 mg/L); lincosamides (clindamycin, ≥1 mg/L); or tetracyclines (tetracycline HCl, ≥8 mg/L). Resistance phenotypes to other tested class comparator agents (i.e. oxazolidinones, glycopeptides or lipopeptides) were not observed.

Dalbavancin breakpoints approved by the European Medicines Agency (EMA)/European Committee on Antimicrobial Susceptibility Testing (EUCAST) were applied [7,13], as follows: *S. aureus*, ≤0.12 mg/L for susceptible; *S. anginosus* group (including *S. anginosus*, *Streptococcus intermedius* and *Streptococcus constellatus*), ≤0.12 mg/L

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

Pathogen/phenotype (no. tested/%)	MIC (mg/L)		No. (cumulative %) inhibited at MIC (mg/L)[a]			
	MIC_{50}	MIC_{90}	≤0.03	0.06	0.12	0.25
Staphylococcus aureus (9303)	0.06	0.06	2899 (31.2)	**5630 (91.7)**	773 (>99.9)	1 (100.0)
MRSA (2471/26.6)	0.06	0.06	871 (35.2)	**1434 (93.3)**	165 (>99.9)	1 (100.0)
MDR (1053/42.6)[b]	0.06	0.06	340 (32.3)	**618 (91.0)**	94 (99.9)	1 (100.0)
Non-MDR (1418/57.4)	0.06	0.06	531 (37.4)	**816 (95.0)**	71 (100.0)	
βHS (1777)[c]	≤0.03	0.06	**1580 (88.9)**	159 (97.9)	38 (100.0)	
MDR (125/7.0)[d]	≤0.03	0.06	**110 (88.0)**	9 (95.2)	6 (100.0)	
Non-MDR (1652/93.0)	≤0.03	0.06	**1470 (89.0)**	150 (98.1)	32 (100.0)	
VGS (893)[e]	≤0.03	0.06	**766 (85.8)**	117 (98.9)	10 (100.0)	
MDR (135/15.1)[d]	≤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)	

MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC that inhibits 50% and 90% of the isolates, respectively; MRSA, meticillin-resistant *S. aureus*; MDR, multidrug-resistant; βHS, β-haemolytic streptococci; VGS, viridans group streptococci.

[a] Modal MIC results are in bold.

[b] *Staphylococcus aureus* with a resistance phenotype to meticillin and at least three other classes of drugs (except for daptomycin; non-susceptible phenotypes were included) were categorised as MDR.

[c] Includes *Streptococcus agalactiae* (596 strains), *S. dysgalactiae* (143 strains), *S. equi* (1 strain), *S. equisimilis* (6 strains), *S. pyogenes* (846 strains), group C streptococci (54 strains), group F streptococci (4 strains), group G streptococci (126 strains) and unspeciated β-haemolytic streptococci (1 strain).

[d] Streptococci with a resistance phenotype to at least three drug classes were categorised as MDR.

[e] Includes *Streptococcus anginosus* (141 strains), *S. anginosus* group (19 strains), *S. australis* (7 strains), *S. bovis* group (28 strains), *S. constellatus* (72 strains), *S. cristatus* (8 strains), *S. equinus* (4 strains), *S. gallolyticus* (25 strains), *S. gordonii* (7 strains), *S. infantis* (15 strains), *S. intermedius* (9 strains), *S. mitis/oralis* (92 strains), *S. mitis* group (87 strains), *S. mutans* (3 strains), *S. oralis* (115 strains), *S. parasanguinis* (29 strains), *S. pasteurianus* (1 strain), *S. salivarius* (45 strains), *S. salivarius* group (3 strains), *S. sanguinis* (46 strains), *S. suis* (1 strain), *S. urinalis* (1 strain), *S. vestibularis* (3 strains), unspeciated streptococci (2 strains), unspeciated α-haemolytic streptococci (9 strains) and unspeciated viridans group streptococci (121 strains).