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Activity of dalbavancin against gram-positive cocci isolated from skin and soft tissue infections in Poland☆

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ABSTRACT

A total of 368 Gram-positive cocci from ABSSI were included in the study. *S. aureus* and *S. pyogenes* were susceptible to dalbavancin with MIC_{50} 0.016 mg/L and MIC_{90} 0.032 mg/L for MSSA and MIC_{50} 0.032 mg/L and MIC_{90} 0.047 mg/L for MRSA; MICs for *S. pyogenes* were ≤0.002–0.008 mg/L; for *E. faecalis* and *E. faecium,* ranging 0.016–0.12 mg/L and 0.012–≥32 mg/L, respectively; MICs for VRE were 0.032–0.125 mg/L.

Rapidly growing antibiotic resistance in major human bacterial pathogens has resulted in a global health crisis (ECDC, 2018; WHO 2014). Dalbavancin, represents a novel semisynthetic lipoglycopeptide with similar properties to vancomycin and teicoplanin spectrum of antibacterial activity. It received FDA and EMA authorization to treat acute skin and soft tissue infections in adults caused by Gram-positive pathogens..

The aim of this study was to evaluate the *in vitro* activity of dalbavancin against bacteria isolated from acute bacterial skin and soft tissue infections (ABSSI).

A total of 368 non-duplicate, non-consecutive randomly selected Gram-positive cocci recovered from ABSSI, collected between 2014 and 2017 in Poland and sent to the National Reference Laboratory for Antibiotic Susceptibility Testing for surveillance purposes, were included in the study. The isolates comprised *Staphylococcus aureus* (n = 202) including MSSA (n = 102) and MRSA (n = 100), *Enterococcus faecium* (n = 64), *E. faecalis* (n = 49) and *Streptococcus pyogenes* (n = 53). Two MSSA isolates with hGISA and GISA phenotype revealed by population analysis, were non-susceptible to vancomycin (MIC 4 mg/mL) and teicoplanin (MIC 4 and 8 mg/mL) (Żabicka et al. 2016). Enterococcal strains comprised 3 *E. faecalis* and 52 *E. faecium* with phenotype VanA, 11 *E. faecalis* and 10 *E. faecium* with VanB phenotype based on MICs values and 7 strains each of *E. faecalis* and *E. faecium* resistant to linezolid.

The following antibiotics were tested: ceftaroline, daptomycin, dalbavancin, linezolid, tedizolid, tigecycline, trimethoprim/sulfamethoxazole, teicoplanin, and vancomycin, using strips with concentration gradients of antimicrobial agents. To determine MLS_B mechanism in staphylococci and streptococci and resistance of enterococci to aminoglycosides (gentamicin and streptomycin) disc diffusion method was used. EUCAST and CLSI interpretation of susceptibility results was applied (CLSI 2018; *EUCAST: Breakpoint tables for interpretation of MICs and zone diameters* 2018).

S. aureus ATCC 29213, *S. aureus* NCTC 12493, *S. aureus* ATCC 43300, *S. aureus* ATCC 700698 (Mu3), *S. aureus* ATCC 700699 (Mu50), *E. faecalis* ATCC 29212, *E. faecalis* ATCC 51299, *S. pneumoniae* ATCC 49619 were used as controls.

All the *S. aureus* isolates were susceptible to dalbavancin with MIC_{50} 0.016 mg/L and MIC_{90} 0.032 mg/L for MSSA and MIC_{50} 0.032 mg/L and MIC_{90}–0.047 mg/L for MRSA. Two MSSA isolates non-susceptible to glycopeptides both with vancomycin MICs 4 mg/L and teicoplanin MICs 4 and 8 mg/L were susceptible to dalbavancin (MICs 0.032 and 0.064 mg/L).

☆ The work was performed at Department of Clinical Microbiology and Epidemiology, National Medicines Institute, Chełmska 30/34, 00-725 Warsaw, Poland

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Eight MRSA isolates with ceftaroline MIC 2 mg/mL (for all MRSA ceftaroline MIC_{50} = 0.5 mg/mL and MIC_{90} = 0.1 mg/L) were susceptible to dalbavancin (MICs 0.023 mg/L-0.032 mg/L). Twelve MRSA strains (12%) were resistant to trimethoprim/sulfamethoxazole (MIC_{50} 0.064 mg/L and MIC_{90} ≥ 32 mg/L) and they were susceptible to dalbavancin (MICs 0.016–0.047 mg/L). In 86 MRSA resistance to macrolides, lincosamides and streptogramin B was detected in 10 due to MLS_B ind. and in 76 MLS_B const. (n = 76). Four MRSA presented the MS_B phenotype.

All group A streptococci were susceptible to dalbavancin (MICs from ≤0.002 to 0.008 mg/L) including MLS_B resistance phenotype.

Table 1
MIC values [mg/L] of dalbavancin and the other antibiotics for *S. aureus* (MSSA i MRSA), *E. faecalis. E. faecium* and *S. pyogenes.*

Antimicrobial agents	Range of MICs [mg/L]	MIC_{50} [mg/L]	MIC_{90} [mg/L]	*In vitro* antibiotic susceptible strains [%]
Staphylococcus aureus MSSA (n = 102)				
Dalbavancin	0.016–0.06	0.016	0.032	100
Ceftaroline	0.06–0.5	0.125	0.25	100
Daptomycin	0.06–1	0.19	0.38	100
Clindamycin	0.016–≥ 256	0.047	0.094	96.1*
Linezolid	0.12–0.25	0.5	0.75	100
Tedizolid	0.032–0.5	0.094	0.19	100
Tigecycline	0.032–0.12	0.032	0.047	100
Teicoplanin	0.5–8	0.5	0.75	98
Vancomycin	0.12–4	0.5	0.75	98
Trimethoprim/Sulfamethoxazole	0.032–0.5	0.064	0.094	100
Staphylococcus aureus MRSA (n = 100)				
Dalbavancin	0.016–2	0.032	0.047	100
Ceftaroline	0..25–2	0.5	1	92
Daptomycin	0.032–1	0.38	0.5	100
Clindamycin	0.016–≥ 256	≥256	≥256	14*
Linezolid	0.25–2	0.5	1	100
Tedizolid	0.06–0.5	0.125	0.25	100
Tigecycline	0.032–0.12	0.032	0.064	100
Teicoplanin	0.5–1	0.75	1	100
Vancomycin	0.25–1	0.5	0.5	100
Trimethoprim/Sulfamethoxazole	0.32–32	0.064	≥32	88
Enterococcus faecalis (n = 49)				
Dalbavancin	0.016–0.12	0.06	0.12	na
Daptomycin	0.12–2	0.5	1	100**
Linezolid	0.5–64	2	2	90.2
Tedizolid	0.12–4	0.5	0.5	90.2**
Tigecycline	0.032–0.12	0.06	0.12	100
Teicoplanin	0.25–64	0.5	1	97.6
Vancomycin	0.12–≥256	1	8	87.8
Trimethoprim/Sulfamethoxazole	0.008–32	≥32	≥32	7.3
Enterococcus faecium (n = 64)				
Dalbavancin	0.008–32	0.12	≥32	na
Daptomycin	0.5–16	2	4	100**
Linezolid	1–32	2	4	93.8
Tedizolid	0.12–2	0.5	1	na
Tigecycline	0.032–0.12	0.06	0.06	100
Teicoplanin	0.5–≥ 256	32	256	20.3
Vancomycin	1–≥256	0.5	≥256	4.7
Trimethoprim/Sulfamethoxazole	0.032–64	≥32	≥32	1.6
Streptococcus pyogenes (n = 53)				
Dalbavancin	≤0.002–0.008	0.002	0.004	100
Ceftaroline	0.004–0.016	0.004	0.008	100 **
Daptomycin	0.032–0.12	0.06	0.12	100**
Clindamycin	0.016-- ≥ 256	0.12	0.25	88.7*
Linezolid		1	1	100
Linezolid	0.5–1	1	1	100
Tedizolid	0.12–0.5	0.25	0.5	100
Tigecycline	0.016–0.12	0.03	0.06	100
Teicoplanin	0.12–0.5	.,25	0.25	100
Vancomycin	0.12–0.5	0.25	0.25	100
Trimethoprim/Sulfamethoxazole	0.016–0.25	0.06	0.12	100

* Clinical interpretation including mechanisms of resistance to macrolides, lincosamides, streptogramins B, explanation in the text.
** CLSI recommendation; na = not applicable (no recommendation).

Dalbavancin exhibited low MICs for *E. faecalis* (0.016 mg/L to 0.12 mg/L). Eleven strains with VanB phenotype had dalbavancin MICs of 0.032–0.094 mg/L; 3 *E. faecalis* VanA strains with MICs 0.032–0.125 mg/L and 7 linezolid resistant *E. faecalis* with MICs -0.032 -0.064 mg/L.

Dalbavancin exhibited MICs for *E. faecium* ranging from 0.012 mg/L to ≥32 mg/L: for *E. faecium* VanA MICs were 0.012–≥32 mg/L, for VanB: 0.016–0.5 mg/L. Almost 40% (n = 25) of the *E. faecium* exhibited high level resistance to gentamicin with dalbavancin MICs of 0.008–≥32 mg/L. Seven (6,2%) of linezolid resistant *E. faecium* (MICs 8–32 mg/L) were susceptible to dalbavancin (MICs 0.023–0.032 mg/L).

Two strains of *E. faecium* by CLSI criteria were intermediate (MIC 4 mg/L), whereas, by the EUCAST, were sensitive with dalbavancin MICs 0.008 and 0.023 mg/L.

A detailed analysis of antibiotics susceptibility of study isolates is presented in Table 1.

ABSSI are among the most common bacterial infections (Jones et al. 2003; Miller et al. 2015; ECDC, 2016). Our study demonstrated a very good *in vitro* activity of dalbavancin against MSSA and MRSA isolates with MIC_{50} values of 0.016 mg/L and 0.032 mg/L respectively. MSSA strains with vancomycin 4 mg/L were susceptible to dalbavancin (MIC 0.03 mg/L). Our results are similar to those obtained by Biedenbach et al. and Sader et al. in a broad studies of worldwide collection of Gram-positive cocci isolated from skin structures (Biedenbach and Jones 2009; Sader et al. 2018). They are also in agreement with a study of Fernández et al. that obtained similar to us MIC_{50} and MIC_{90} values of dalbavancin, and they also showed good dalbavancin activity against *S. aureus* biofilm isolates from prosthetic joint infections (Fernández et al. 2016). It may open new possibilities to treat infections in orthopedic surgery of which *S. aureus* is often leading etiology (Arena et al. 2017; Kussmann et al. 2018). Therapeutic efficacy of dalbavancin was shown in other infections although further studies are required (Barber and Tirmizi 2017; Guest et al. 2017; McCurdy et al. 2015). The results of other researchers suggest that dalbavancin in combination with linezolid may show a high synergistic effect compared to the action of both drugs individually (Aktas and Derbentli 2017).

No EUCAST recommendations for clinical interpretation of enterococcal susceptibility to dalbavancin, but according to CLSI recommendations all vancomycin susceptible *E. faecalis* tested in our study were susceptible with MICs 0.016–0.12 mg/L and low MIC values for both Van B and VanA isolates,0.032–0.094 mg/L and 0.032–0.125 mg/L, respectively. However, MICs obtained for *E. faecium* were higher for both Van B and VanA isolates 0.016–0.5 mg/L and 0.012–≥32 mg/L, respectively. These data are in agreement with the results obtained previously (Biedenbach and Jones 2009; Jones et al. 2013) which showed that dalbavancin is inactive against VanA enterococci but remains active against VanB strains. Important information also resulting from our study is a good activity of dalbavancin against linezolid resistant both *E. faecalis* and *E. faecium*, which may be of clinical importance since the percentage of enterococci resistant to linezolid is increasing (Bi et al. 2018).

In conclusion our study proved that dalbavancin has a good *in vitro* activity against major Gram-positive cocci responsible for ABSSI including multidrug resistant strains and thus, provides a good therapeutic alternative.

Ethical approval

The authors declare that the ethical approval was not required.

Declaration of interest

No potential conflict of interest.

Submission declaration

The authors declare that the work described has not been published previously. The results of the study are accepted as a poster to be presented at 29th European Congress of Clinical Microbiology and Infectious Diseases (2019), in Amsterdam, Netherlands.

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