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Activity of Dalbavancin Tested against Gram-positive Clinical Isolates Causing Skin and Skin Structure Infections in Pediatric Patients from USA Hospitals (2014 - 2015)

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ABSTRACT

Background

Dalbavancin is approved for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults. Current trials will further define dalbavancin therapeutic use, including for the treatment of ABSSSI in pediatric patients. This study provides an *in vitro* analysis of dalbavancin activity against isolates causing SSSI in children.

Methods

770 *S. aureus*, 167 β-hemolytic streptococci (BHS), 42 coagulase-negative staphylococci (CoNS), 25 *E. faecalis* and 13 viridans group streptococci (VGS) causing SSSI were collected from children (<18 years old) in the USA (2014 - 2015). Bacteria were identified by standard algorithms and MALDI-TOF-MS. Susceptibility testing was performed by CLSI methods (M07-A10); interpretation of MICs used CLSI criteria.

Results

Dalbavancin had $MIC_{50/90}$ values of 0.03/0.06 µg/mL against *S. aureus* and CoNS, including methicillin-resistant (MRSA) and -susceptible (MSSA) *S. aureus* subsets. When tested against MRSA, dalbavancin MICs were 8- to 32-fold lower than those of daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL), vancomycin ($MIC_{50/90}$, 0.5/1 µg/mL) and linezolid ($MIC_{50/90}$, 1/1 µg/mL). These agents showed 100.0% susceptibility against MRSA, and clindamycin also had a high (92.7%) susceptibility rate. Dalbavancin ($MIC_{50/90}$, 0.03/0.06 µg/mL) and daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL) were the most active agents against CoNS, and dalbavancin was up to 32-fold more active than ampicillin ($MIC_{50/90}$, ≤0.5/1 µg/mL), daptomycin ($MIC_{50/90}$, 1/1 µg/mL), linezolid ($MIC_{50/90}$, 1/2 µg/mL) and vancomycin ($MIC_{50/90}$, 1/2 µg/mL) against *E. faecalis.* Dalbavancin ($MIC_{50/90}$, 0.008/0.03 µg/mL), ceftriaxone ($MIC_{50/90}$, ≤0.06/≤0.06 µg/mL) and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 µg/mL) were the most active against BHS, and most other tested agents also showed susceptibility rates >90.0%. All VGS isolates were susceptible to dalbavancin (MIC_{100}, 0.03 µg/mL) with MIC results 32- to 64-fold lower than daptomycin ($MIC_{50/90}$, 0.5/0.5 µg/mL), linezolid ($MIC_{50/90}$, 0.5/1 µg/mL) and vancomycin ($MIC_{50/90}$, 0.5/0.5 µg/mL).

Conclusions

Approved agents available for treatment of ABSSSI in children are limited. Dalbavancin demonstrated potent *in vitro* activity against these Gram-positive isolates causing SSSI in children. Development of dalbavancin for treatment of ABSSSI in children is warranted, provided safety and tolerability are satisfactory.

INTRODUCTION

Dalbavancin was approved in the United States (USA; 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 (MRSA) *S. aureus, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus* group and vancomycin-susceptible *Enterococcus faecalis*. Dalbavancin allows for very convenient administrations, which can be a single dose of 1500 mg or a dose of 1000 mg followed by 500 mg a week later. Moreover, current trials will further define dalbavancin therapeutic use, including for the treatment of ABSSSI in pediatric patients.

During pre-clinical development, dalbavancin has demonstrated potent *in vitro* activity against *S. aureus* (including MRSA), streptococci and vancomycin–susceptible enterococci. *In vitro* activity has also been demonstrated against heterogeneous vancomycin–intermediate (hVISA; MIC range, 0.12 – 0. 5 µg/mL) and vancomycin–intermediate *S. aureus* (VISA; 0.5 – 2 µg/mL), and other Gram–positive isolates less often recovered from human clinical specimens. This report describes dalbavancin in vitro activity and potency when tested against a contemporary (2014 – 2015) collection of Gram–positive isolates responsible for SSSI recovered from a pediatric patient population in USA medical centers.

METHODS

Bacterial isolates

A total of 770 *S. aureus*, 167 β-hemolytic streptococci (BHS), 42 coagulase-negative staphylococci (CoNS), 25 *E. faecalis* and 13 viridans group streptococci (VGS) causing SSSI were collected from children (<18 years old) in the USA (2014 - 2015). 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 **I**nternational **D**albavancin **E**valuation of **A**ctivity (IDEA) Surveillance Program. Isolates were initially identified by the participating laboratory and bacterial identifications were 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 CLSI M07-A10 document. Testing was performed using reference 96-well panels manufactured by JMI Laboratories (North Liberty, Iowa, USA). Quality assurance was performed by concurrent testing of CLSI–recommended QC reference strains (*S. aureus* ATCC 29213, *E. faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619). All QC results were within published acceptable ranges. The dalbavancin breakpoints approved by the Food and Drug Administration (FDA) for indicated species were applied (i.e. ≤0.25 µg/mL). Breakpoint criteria for comparator agents were those from the CLSI (M100-S26).

RESULTS

- Dalbavancin had $MIC_{50/90}$ values of 0.03/0.06 µg/mL against *S. aureus* and CoNS, including the MRSA and MSSA subsets (**Table 1**). When tested against MRSA, dalbavancin MIC results were 8- to 32-fold lower than those of daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL), vancomycin ($MIC_{50/90}$, 0.5/1 µg/mL) and linezolid ($MIC_{50/90}$, 1/1 µg/mL; **Table 2**).
- All tested agents showed *in vitro* activity against MSSA and MRSA (92.7 - 100.0% susceptible), except for erythromycin (72.9% susceptible) against MSSA, and erythromycin (17.1% susceptible) and levofloxacin (46.7% susceptible) against MRSA (**Table 2**).
- A total of 42.9% of CoNS isolates were oxacillin-resistant (**Table 2**). Dalbavancin MIC results were 8- to 16-fold lower than those of daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL), levofloxacin ($MIC_{50/90}$, 0.25/1 µg/mL) and linezolid ($MIC_{50/90}$, 0.5/1 µg/mL) against CoNS. Moreover, dalbavancin was 32-fold more active than vancomycin ($MIC_{50/90}$, 1/2 µg/mL; **Table 2**).
- All *E. faecalis* isolates were inhibited by dalbavancin ($MIC_{50/90}$, 0.03/0.06 µg/mL) at ≤0.06 µg/mL, except for one vancomycin-resistant isolate (**Table 1**). Other tested agents (92.0 – 100.0% susceptible) were also active against *E. faecalis*, with the exception of tetracycline (24.0% susceptible; **Table 2**).
- Dalbavancin was up to 32-fold more active than ampicillin ($MIC_{50/90}$, ≤0.5/1 µg/mL), daptomycin ($MIC_{50/90}$, 1/1 µg/mL), linezolid ($MIC_{50/90}$, 1/2 µg/mL), levofloxacin ($MIC_{50/90}$, 1/2 µg/mL) and vancomycin ($MIC_{50/90}$, 1/2 µg/mL) against the *E. faecalis* population (**Table 2**).
- Dalbavancin was very active against BHS ($MIC_{50/90}$, 0.008/0.03 µg/mL) and VGS ($MIC_{50/90}$, 0.008/0.015 µg/mL), inhibiting 100% of these isolates at ≤0.06 and ≤0.03 µg/mL, respectively (**Tables 1** and **2**).
- Dalbavancin ($MIC_{50/90}$, 0.008/0.03 µg/mL), ceftriaxone ($MIC_{50/90}$, ≤0.06/≤0.06 µg/mL) and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 µg/mL) were the most active agents against BHS, although other tested agents also showed susceptibility rates >90.0%, except for tetracycline (84.4%; **Table 2**).
- All VGS isolates were susceptible to dalbavancin (MIC_{100}, 0.03 µg/mL) with MIC results 32- to 64-fold lower than daptomycin ($MIC_{50/90}$, 0.5/0.5 µg/mL), linezolid ($MIC_{50/90}$, 0.5/1 µg/mL) and vancomycin ($MIC_{50/90}$, 0.5/0.5 µg/mL; **Table 2**).
- Other agents, such as ceftriaxone (84.6% susceptible), clindamycin (76.9% susceptible), erythromycin (46.2% susceptible), penicillin (69.2% susceptible) and tetracycline (53.8% susceptible) showed limited activity against VGS (**Table 2**).

Table 1. Activity and spectrum of dalbavancin against contemporary Gram-positive isolates causing SSSIs in children in the USA.

Pathogens[a] (no. tested)	MIC (µg/mL)		Number (cumulative %) inhibited at MIC (µg/mL)[b]							
	50%	90%	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	>0.25
S. aureus (770)	0.03	0.06	0 (0.0)	3 (0.4)	45 (6.2)	**540 (76.4)**	181 (99.9)	1 (100.0)		
MSSA (455)	0.03	0.06	0 (0.0)	2 (0.4)	27 (6.4)	**316 (75.8)**	109 (99.8)	1 (100.0)		
MRSA (315)	0.03	0.06	0 (0.0)	1 (0.3)	18 (6.0)	**224 (77.1)**	72 (100.0)			
CoNS (42)	0.03	0.06	0 (0.0)	1 (2.4)	11 (28.6)	**19 (73.8)**	8 (92.9)	2 (97.6)	0 (97.6)	1 (100.0)
E. faecalis (25)	0.03	0.06	0 (0.0)	0 (0.0)	4 (16.0)	**14 (72.0)**	6 (96.0)	0 (96.0)	0 (96.0)	1 (100.0)
BHS (167)	0.008	0.03	42 (25.1)	**60 (61.1)**	45 (88.0)	18 (98.8)	2 (100.0)			
VGS (13)	0.008	0.015	4 (30.8)	3 (53.8)	**5 (92.3)**	1 (100.0)				

a. MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; CoNS = coagulase-negative staphylococci; BHS = β-hemolytic streptococci; VGS = viridans group streptococci.
b. Dalbavancin modal MIC results are in bold. One CoNS and one vancomycin-resistant (VanA) *E. faecalis* had dalbavancin MIC values of >0.25 µg/mL and >2 µg/mL, respectively.

Table 2. Antimicrobial activity of dalbavancin and comparator agents against contemporary Gram-positive isolates causing SSSIs in children in the USA.

Organism/Group[a] (no.) Antimicrobial agent[b]	MIC (µg/mL): MIC_{50}	MIC_{90}	Range	%Susceptible/%Intermediate/%Resistant[c]		
MSSA (455)						
Dalbavancin	0.03	0.06	0.008 — 0.12	100.0	-	-
Clindamycin	≤0.25	≤0.25	≤0.25 — >2	97.4	0.0	2.6
Daptomycin	0.25	0.5	≤0.12 — 1	100.0	-	-
Erythromycin	0.25	>8	≤0.12 — >8	72.9	5.1	22.0
Levofloxacin	≤0.12	0.25	≤0.12 — >4	94.7	0.0	5.3
Linezolid	1	1	0.25 — 2	100.0	-	0.0
Tetracycline	≤0.5	≤0.5	≤0.5 — >8	94.7	0.2	5.1
TMP-SMX	≤0.5	≤0.5	≤0.5 — >4	99.6	-	0.4
Vancomycin	0.5	1	≤0.12 — 1	100.0	0.0	0.0
MRSA (315)						
Dalbavancin	0.03	0.06	0.008 — 0.06	100.0	-	-
Clindamycin	≤0.25	≤0.25	≤0.25 — >2	92.7	0.3	7.0
Daptomycin	0.25	0.5	≤0.12 — 1	100.0	-	-
Erythromycin	>8	>8	≤0.12 — >8	17.1	2.5	80.3
Levofloxacin	4	>4	≤0.12 — >4	46.7	1.3	52.1
Linezolid	1	1	0.25 — 1	100.0	-	0.0
Tetracycline	≤0.5	1	≤0.5 — >8	93.0	1.6	5.4
TMP-SMX	≤0.5	≤0.5	≤0.5 — >4	97.8	-	2.2
Vancomycin	0.5	1	≤0.12 — 1	100.0	0.0	0.0
CoNS (42)[d]						
Dalbavancin	0.03	0.06	0.008 — >0.25	-	-	-
Oxacillin	0.5	>2	≤0.25 — >2	57.1	-	42.9
Clindamycin	≤0.25	>2	≤0.25 — >2	78.6	2.4	19.0
Daptomycin	0.25	0.5	≤0.12 — 1	100.0	-	-
Erythromycin	0.25	>8	≤0.12 — >8	50.0	0.0	50.0
Levofloxacin	0.25	1	≤0.12 — >4	90.5	0.0	9.5
Linezolid	0.5	1	≤0.12 — 1	100.0	-	0.0
Tetracycline	≤0.5	1	≤0.5 — >8	92.9	0.0	7.1
TMP-SMX	≤0.5	≤0.5	≤0.5 — 4	95.2	-	4.8
Vancomycin	1	2	≤0.12 — 2	100.0	0.0	0.0
E. faecalis (25)						
Dalbavancin	0.03	0.06	≤0.015 — >2	96.0[e]	-	-
Ampicillin	≤0.5	1	≤0.5 — 1	100.0	-	0.0
Daptomycin	1	1	0.5 — 2	100.0	-	-
Levofloxacin	1	2	≤0.5 — >4	92.0	0.0	8.0
Linezolid	1	2	0.5 — 2	100.0	0.0	0.0
Tetracycline	>8	>8	≤1 — >8	24.0	0.0	76.0
Vancomycin	1	2	≤0.5 — >16	96.0	0.0	4.0
BHS (167)[f]						
Dalbavancin	0.008	0.03	≤0.002 — 0.06	100.0	-	-
Ceftriaxone	≤0.06	≤0.06	≤0.06 — 0.12	100.0	-	-
Clindamycin	≤0.25	≤0.25	≤0.25 — >2	94.6	0.0	5.4
Daptomycin	0.12	0.25	≤0.06 — 0.5	100.0	-	-
Erythromycin	≤0.12	≤0.12	≤0.12 — >4	91.6	0.0	8.4
Levofloxacin	0.5	1	0.12 — >4	99.4	0.0	0.6
Linezolid	1	1	0.5 — 1	100.0	-	-
Penicillin	≤0.06	≤0.06	≤0.06 — 0.12	100.0	-	-
Tetracycline	≤0.5	>8	≤0.5 — >8	84.4	1.2	14.4
Vancomycin	0.25	0.5	0.12 — 0.5	100.0	-	-
VGS (13)[g]						
Dalbavancin	0.008	0.015	≤0.002 — 0.03	100.0	-	-
Ceftriaxone	0.12	2	≤0.06 — 4	84.6	7.7	7.7
Clindamycin	≤0.25	>2	≤0.25 — >2	76.9	0.0	23.1
Daptomycin	0.5	0.5	0.12 — 1	100.0	-	-
Erythromycin	2	>4	≤0.12 — >4	46.2	0.0	53.8
Levofloxacin	1	2	0.25 — 2	100.0	0.0	0.0
Linezolid	0.5	1	≤0.06 — 1	100.0	-	-
Penicillin	≤0.06	1	≤0.06 — >4	69.2	23.1	7.7
Tetracycline	≤0.5	>8	≤0.5 — >8	53.8	7.7	38.5
Vancomycin	0.5	0.5	0.12 — 1	100.0	-	-

a. MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; CoNS = coagulase-negative staphylococci; BHS = β-hemolytic streptococci; VGS = viridans group streptococci.
b. TMP-SMX = Trimethoprim-sulfamethoxazole.
c. Dalbavancin FDA-approved breakpoint for primary indicated species (all ≤0.25 µg/mL). Breakpoint criteria for comparator agents were those from CLSI (2016), as available. "-" breakpoint not available.
d. Includes: *Staphylococcus caprae* (2), *S. epidermidis* (17), *S. haemolyticus* (3), *S. hominis* (7), *S. intermedius* (1), *S. lugdunensis* (7), *S. pseudintermedius* (1), *S. simulans* (1), *S. warneri* (3).
e. 96.0% susceptible when including a vancomycin-resistant isolate (not indicated), or 100.0% susceptible against indicated vancomycin-susceptible *E. faecalis*.
f. Includes: *Streptococcus agalactiae* (16), *S. dysgalactiae* (5), *S. pyogenes* (146).
g. Includes: *Streptococcus anginosus* (2), *S. constellatus* (2), *S. cristatus* (1), *S. gordonii* (1), *S. intermedius* (1), *S. mitis* group (1), *S. mitis/oralis* (2), *S. oralis* (2), *S. parasanguinis* (1).

CONCLUSIONS

- Approved agents available for treatment of ABSSSI in children are limited. Staphylococcal isolates comprised the majority of pathogens responsible for SSSI in children in the USA and a great proportion of these organisms were oxacillin-resistant (41.7%).
- Dalbavancin demonstrated potent *in vitro* activity against these Gram-positive isolates causing SSSI in children, and all indicated species were susceptible to dalbavancin when applying the FDA breakpoints.
- These data warrant further development of dalbavancin for treatment of SSSI in children, provided safety and tolerability are satisfactory.

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DISCLOSURES

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