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Antimicrobial activity of dalbavancin tested against Gram-positive clinical isolates from Latin American medical centres

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ABSTRACT

The activity of dalbavancin, a new semi-synthetic lipoglycopeptide antibiotic, was evaluated in comparison with other antibacterial agents against 1229 Gram-positive organisms collected from medical centres in Latin America. Dalbavancin was the most potent compound tested against isolates of *Staphylococcus aureus* (MIC_{50}, 0.06 mg/L) and coagulase-negative staphylococci (MIC_{50}, 0.03 mg/L), independently of methicillin susceptibility. Dalbavancin inhibited all *Streptococcus pneumoniae* isolates at ≤0.06 mg/L. Dalbavancin also demonstrated excellent activity against β-haemolytic (MIC_{50}, ≤ 0.008 mg/L) and viridans group (MIC_{50}, 0.016 mg/L) streptococci. All vancomycin-susceptible *Enterococcus* spp. isolates were inhibited by dalbavancin at ≤0.25 mg/L, but some vancomycin-resistant *Enterococcus* spp. isolates were only inhibited by dalbavancin levels of ≥8 mg/L. Dalbavancin exhibited excellent activity against isolates of *Corynebacterium* spp. and *Listeria* spp. Dalbavancin may provide an important therapeutic option for Gram-positive infections, excluding those caused by enterococci with VanA-type resistance.

Keywords Dalbavancin, enterococci, Gram-positive cocci, Latin America, staphylococci, streptococci

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INTRODUCTION

Staphylococci are major causes of both community-and hospital-acquired infections. Since methicillin (oxacillin) resistance was first reported in 1961, rates of resistance to penicillinase-resistant penicillins among isolates of *Staphylococcus aureus* and coagulase-negative staphylococci have increased greatly worldwide [1,2]. In many Latin American hospitals, methicillin-resistant *S. aureus* (MRSA) strains have become endemic and are increasingly resistant to many other antimicrobial agents [3]. Data from the SENTRY Antimicrobial Surveillance Program have demonstrated that methicillin resistance rates vary widely, from 8.6% to 45.3%, among *S. aureus* isolates collected from different Latin American medical centres [2].

Glycopeptides such as vancomycin and teicoplanin have been the drugs of choice for treatment of methicillin-resistant staphylococcal infections [2]. These agents have also been used successfully as therapeutic agents against life-threatening *Enterococcus* spp. and cephalosporin-resistant *Streptococcus pneumoniae* infections [4,5]. However, the emergence of vancomycin resistance among enterococci initiated the glycopeptide resistance era. Resistance, including high-level glycopeptide resistance, is now quite common in enterococci. Reduced susceptibility to vancomycin in isolates of *S. aureus* occurs infrequently, and rare instances of high-level vancomycin resistance in *S. aureus* have also been detected following acquisition of the *vanA* operon [6,7]. Compounds such as quinupristin–dalfopristin and linezolid have been developed to overcome emerging glycopeptide resistance. However, resistance to

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these agents has also been detected in *Enterococcus faecium* and *S. aureus* [8,9]. This fact has accentuated the need for additional new antimicrobial compounds.

Dalbavancin is a novel semi-synthetic amide derivative of the lipoglycopeptide A40926. Like other glycopeptides, it interferes with bacterial cell wall biosynthesis [10]. Dalbavancin has a wide spectrum of activity against Gram-positive organisms, including both aerobic and anaerobic species [10–12]. In addition, it is extremely potent against multiresistant bacteria, including MRSA, coagulase-negative staphylococci and penicillin-resistant *Strep. pneumoniae*. Dalbavancin has also demonstrated excellent activity in several animal models of infection, including acute septicaemia in mice, lobar pneumonia in rats, and endocarditis in rats and rabbits [10,13]. As it has a long elimination half-life in humans (*c.* 7 days), a dosage interval of 1 week has been tested for treatment of complicated skin and soft tissue infections [14]. To evaluate the potential efficacy of dalbavancin against Gram-positive organisms isolated in Latin America, the present study determined its comparative in-vitro activity against 1229 clinical isolates collected recently from this geographical region.

MATERIALS AND METHODS

Bacterial strains

In total, 1229 Gram-positive organisms, collected from ten Latin American medical centres between January and December 2003, were studied. The species distribution was as follows: *S. aureus*, 536 isolates; coagulase-negative staphylococci, 251; *Strep. pneumoniae*, 208; *Enterococcus* spp., 157; β-haemolytic streptococci, 53; viridans group streptococci, 13; *Listeria* spp., 6; *Corynebacterium* spp., 3; and *Micrococcus* spp., 2. Organisms were isolated from diverse body sites of hospitalised patients, but only a single isolate/patient was included in this study. The participating medical centres were located in nine cities in five countries: Brasília, Florianópolis, São Paulo and Porto Alegre in Brazil; Buenos Aires and San Isidro in Argentina; Santiago in Chile (two sites); Mexico City in Mexico; and Caracas in Venezuela.

Susceptibility testing

Antimicrobial susceptibility testing was performed using the NCCLS reference broth microdilution method [15]. Dalbavancin powder was obtained from Vicuron Pharmaceuticals (King of Prussia, PA, USA). Powders of comparator antimicrobial agents were provided by the respective manufacturers or purchased from Sigma Chemicals (St Louis, MO, USA). Validated dry-form broth microdilution trays were prepared by TREK Diagnostics (Cleveland, OH, USA). Susceptibility testing results were interpreted according to NCCLS criteria, except for dalbavancin, for which susceptibility and resistance breakpoints have not yet been established [16]. Quality control was performed by testing *Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 29213, and *Strep. pneumoniae* ATCC 49619.

RESULTS

The in-vitro activities of dalbavancin, compared to those of 11 other antimicrobial agents, against 787 staphylococcal isolates, 274 streptococcal isolates, 157 enterococcal isolates and 11 uncommon Gram-positive organisms isolated from patients in Latin American medical centres are shown in Table 1. Against *S. aureus*, dalbavancin (MIC_{50}, 0.06 mg/L) was, respectively, 32-, 16- and eight-fold more potent than linezolid (MIC_{50}, 2 mg/L), vancomycin (MIC_{50}, 1 mg/L) and quinupristin–dalfopristin (MIC_{50}, 0.5 mg/L). Dalbavancin inhibited all *S. aureus* isolates at ≤ 0.25 mg/L. No *S. aureus* isolate was resistant to vancomycin, teicoplanin, linezolid or quinupristin–dalfopristin. Among coagulase-negative (CoNS) isolates, dalbavancin (MIC_{50}, 0.03 mg/L) was 64-fold more potent than teicoplanin, 32-fold more potent than vancomycin and linezolid, and eight-fold more potent than quinupristin–dalfopristin. Only vancomycin and linezolid inhibited 100% of CoNS isolates at the NCCLS susceptibility breakpoints [16]. Among staphylococci, 26.7% of *S. aureus* isolates and 76.9% of CoNS isolates were methicillin-resistant. In addition, 2.0% of CoNS isolates were resistant to teicoplanin. No difference in dalbavancin activity was observed between oxacillin-susceptible and oxacillin-resistant *S. aureus* (Table 2). However, a slight trend toward higher dalbavancin MICs was observed among oxacillin-resistant CoNS isolates; thus, 100% of oxacillin-susceptible CoNS isolates were inhibited by dalbavancin 0.12 mg/L, compared to only 92.2% of oxacillin-resistant CoNS isolates.

Against *Strep. pneumoniae*, dalbavancin (MIC_{50}, 0.016 mg/L) was 16- and 32-fold more potent than vancomycin and linezolid, respectively. Among *Strep. pneumoniae* isolates, the lowest susceptibility rate was observed for trimethoprim–sulphamethoxazole (57.7%), followed by penicillin (73.1%), erythromycin (84.5%) and tetracycline (86.1%). Dalbavancin inhibited all pneumococcal isolates at ≤ 0.06 mg/L, regardless of the degree of penicillin susceptibility. Indeed, all penicillin-resistant *Strep. pneumoniae* isolates (0.016 mg/L)

Table 1. In-vitro activities of dalbavancin, compared to those of 11 other antimicrobial agents, against 787 staphylococcal isolates, 274 streptococcal isolates and 157 enterococcal isolates from patients in Latin American medical centres (2003)

	MIC (mg/L)			Percentage by category[a]	
Organism/antimicrobial (no. tested)	**Range**	**50%**	**90%**	**Susceptible**	**Resistant**
Staphylococcus aureus (536)					
Dalbavancin	≤ 0.008–0.25	0.06	0.06	–[a]	–
Teicoplanin	≤ 2–8	≤ 2	≤ 2	100.0	0.0
Vancomycin	0.5–2	1	1	100.0	0.0
Linezolid	0.25–2	2	2	100.0	–
Erythromycin	0.12 – > 8	0.5	> 8	65.9	33.6
Clindamycin	≤ 0.06 – > 8	0.12	> 8	74.1	25.9
Quinupristin–dalfopristin	≤ 0.25–1	0.5	0.5	100.0	0.0
Oxacillin	≤ 0.06 – > 2	0.5	> 2	73.3	26.7
Ceftriaxone	0.5 – > 32	4	> 32	73.1	24.8
Ciprofloxacin	0.06 – > 4	0.25	> 4	70.7	28.9
Tetracycline	≤ 2 – > 8	≤ 2	> 8	83.2	15.9
Trimethoprim–sulphamethoxazole	≤ 0.5 – > 2	≤ 0.5	> 2	84.3	15.7
Coagulase-negative staphylococci (251)[b]					
Dalbavancin	≤ 0.008–1	0.03	0.12	–	–
Teicoplanin	≤ 2 – > 16	≤ 2	8	92.4	2.0
Vancomycin	0.25–4	1	2	100.0	0.0
Linezolid	0.5–2	1	1	100.0	–
Erythromycin	≤ 0.06 – > 8	> 8	> 8	40.2	59.8
Clindamycin	≤ 0.06 – > 8	0.12	> 8	58.6	41.0
Quinupristin–dalfopristin	≤ 0.25–2	≤ 0.25	0.5	99.6	0.0
Oxacillin	≤ 0.06 – > 2	> 2	> 2	23.1	76.9
Ceftriaxone	≤ 0.25 – > 32	8	> 32	50.2	15.9
Ciprofloxacin	0.06 – > 4	0.5	> 4	57.4	38.6
Tetracycline	≤ 2 – > 8	≤ 2	> 8	79.6	19.6
Trimethoprim–sulphamethoxazole	≤ 0.5 – > 2	2	> 2	55.4	44.6
β-Haemolytic streptococci (53)[c]					
Dalbavancin	≤ 0.008–0.06	≤ 0.008	0.06	–	–
Teicoplanin	≤ 2	≤ 2	≤ 2	–	–
Vancomycin	0.25–1	0.25	0.5	100.0	–
Linezolid	0.25–1	1	1	100.0	0.0
Erythromycin	≤ 0.06–2	≤ 0.06	≤ 0.06	98.1	1.9
Clindamycin	≤ 0.06–0.12	≤ 0.06	≤ 0.06	100.0	0.0
Quinupristin–dalfopristin	≤ 0.25–0.5	≤ 0.25	0.5	100.0	0.0
Penicillin	≤ 0.016–0.12	≤ 0.016	0.06	100.0	–
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25	100.0	–
Levofloxacin	0.12–1	0.5	0.5	100.0	0.0
Tetracycline	≤ 2 – > 8	≤ 2	> 8	58.5	41.5
Trimethoprim–sulphamethoxazole	≤ 0.5–2	≤ 0.5	≤ 0.5	–	–
Viridans group streptococci (13)[d]					
Dalbavancin	≤ 0.008–0.03	0.016	0.016	–	–
Teicoplanin	≤ 2	≤ 2	≤ 2	–	–
Vancomycin	0.25–1	0.5	1	100.0	–
Linezolid	0.5–1	1	1	100.0	–
Erythromycin	≤ 0.06–2	≤ 0.06	1	73.3	20.0
Clindamycin	≤ 0.06	≤ 0.06	≤ 0.06	100.0	0.0
Quinupristin–dalfopristin	≤ 0.25–1	0.5	0.5	100.0	0.0
Penicillin	≤ 0.016–8	0.06	4	53.3	20.0
Ceftriaxone	≤ 0.25–8	≤ 0.25	2	86.7	6.7
Levofloxacin	0.5–4	1	4	86.7	0.0
Tetracycline	≤ 2 – > 8	≤ 2	> 8	73.3	26.7
Trimethoprim–sulphamethoxazole	≤ 0.5 – > 2	≤ 0.5	> 2	–	–
Streptococcus pneumoniae (208)					
Dalbavancin	≤ 0.008–0.06	0.016	0.016	–	–
Teicoplanin	≤ 2	≤ 2	≤ 2	–	–
Vancomycin	≤ 0.12–0.5	0.25	0.5	100.0	–
Linezolid	0.12–2	1	1	100.0	–
Erythromycin	≤ 0.25 – > 8	≤ 0.25	8	84.5	15.0
Clindamycin	≤ 0.25 – > 8	≤ 0.25	≤ 0.25	95.1	4.9
Quinupristin–dalfopristin	0.5–1	≤ 0.5	≤ 0.5	100.0	0.0
Penicillin	≤ 0.03 – > 4	≤ 0.03	2	73.1	13.9
Ceftriaxone	≤ 0.008–2	0.12	1	99.5	0.0
Levofloxacin	0.25–2	1	2	100.0	0.0
Tetracycline	≤ 2 – > 8	≤ 2	> 8	86.1	12.0
Trimethoprim–sulphamethoxazole	≤ 0.5 – > 2	≤ 0.5	> 2	57.7	30.3
Enterococci (157)[e]					
Dalbavancin	≤ 0.008 – > 16	0.03	0.12	–	–
Teicoplanin	≤ 2 – > 16	≤ 2	≤ 2	95.5	3.8
Vancomycin	0.5 – > 16	2	2	94.3	4.5
Linezolid	1–2	2	2	100.0	0.0
Quinupristin–dalfopristin	≤ 0.25 – > 2	> 2	> 2	10.2	81.5
Ampicillin	≤ 1 – > 16	2	16	89.8	10.2
Chloramphenicol	≤ 2 – > 16	8	> 16	71.3	26.8
Gentamicin (HL)	≤ 500 – > 1000	≤ 500	> 1000	66.4	33.6
Streptomycin (HL)	≤ 1000 – > 2000	≤ 1000	> 2000	72.6	27.4

Table 1. Continued

Organism/antimicrobial (no. tested)	MIC (mg/L)			Percentage by category[a]	
	Range	50%	90%	Susceptible	Resistant
Ciprofloxacin	0.5 – > 4	1	> 4	54.1	38.2
Tetracycline	≤ 2 – > 8	> 8	> 8	32.5	67.5
Trimethoprim–sulphamethoxazole	≤ 0.5 – > 2	≤ 0.5	> 2	–	–

[a]Susceptibility interpretations according to NCCLS criteria [16].
[b]Includes *S. auricularis* (one isolate), *S. capitis* (one), *S. epidermidis* (46), *S. haemolyticus* (16), *S. hominis* (six), *S. lugdunensis* (one), *S. saprophyticus* (six), *S. simulans* (two), *S. warnerii* (five) and unspeciated (167).
[c]Includes group A (33 isolates), group B (15), group C (3), group G (1) and unspeciated (1).
[d]Includes *Strep. anginosus* (one isolate), *Strep. mitis* (five), *Strep. oralis* (one), *Strep. salivarius* (one), *Strep. sanguis* (two) and unspeciated (three).
[e]Includes: *E. avium* (one isolate), *E. faecalis* (136), *E. faecium* (16), *E. gallinarum* (one), *E. hirae* (one) and *Enterococcus* spp. (two).
HL, high-level resistance; indicates that no criteria have been established.

Table 2. Influence of various resistance profiles on the MICs of dalbavancin against 1152 isolates from Latin American medical centres

Organism	Resistance phenotype (no. tested)	Dalbavancin MICs (mg/L)		
		Range	50%	90%
Staphylococcus aureus	Oxacillin-susceptible (393)	≤ 0.008–0.25	0.06	0.06
	Oxacillin-resistant (143)	0.016–0.12	0.06	0.06
Coagulase-negative staphylococci	Oxacillin-susceptible (58)	≤ 0.008–0.12	0.03	0.06
	Oxacillin-resistant (193)	≤ 0.008–1	0.03	0.12
Streptococcus pneumoniae	Penicillin-susceptible (152)	≤ 0.008–0.06	0.016	0.016
	Penicillin-intermediate (27)	≤ 0.008–0.06	0.016	0.016
	Penicillin-resistant (29)	≤ 0.008–0.016	0.016	0.016
Enterococci	Vancomycin-susceptible (148)	≤ 0.008–0.25	0.03	0.06
	Vancomycin-resistant (9)	0.06 to > 16	16	–

were inhibited at lower dalbavancin concentrations than penicillin-susceptible isolates (0.06 mg/L; Table 2). Against 53 β-haemolytic streptococcal isolates, dalbavancin (MIC_{50}, ≤ 0.008 mg/L) was highly active and exhibited greater activity than vancomycin (MIC_{50}, 0.25 mg/L) and linezolid (MIC_{50}, 1 mg/L). This group of organisms was susceptible to most antimicrobial agents, except tetracycline (58.5% susceptible) and erythromycin (98.1% susceptible). In contrast, only 53.3% of streptococcal isolates belonging to the viridans group were susceptible to penicillin. Dalbavancin also showed excellent in-vitro activity against this group of streptococci, and inhibited all isolates at ≤ 0.03 mg/L.

Dalbavancin (MIC_{50}, 0.03 mg/L) was 64-fold more potent than vancomycin (MIC_{50}, 2 mg/L) and linezolid (MIC_{50}, 2 mg/L) against *Enterococcus* spp. isolates. Most (86.6%) of the isolates were *E. faecalis*, and were therefore mostly ampicillin-susceptible and quinupristin–dalfopristin-resistant. All vancomycin-susceptible *Enterococcus* spp. were inhibited by ≤ 0.25 mg/L dalbavancin. Although vancomycin-non-susceptible *Enterococcus* spp. isolates showed higher dalbavancin MIC values (MIC_{50}, 16 mg/L), two isolates of *Enterococcus* spp. and one *E. faecium* isolate that exhibited the VanC and VanB resistance phenotypes were inhibited at dalbavancin concentrations ≤ 0.12 mg/L. Only VanA isolates were not inhibited by low concentrations of dalbavancin.

Dalbavancin was also very active against uncommonly isolated Gram-positive organisms such as *Corynebacterium* spp., *Listeria* spp., and *Micrococcus* spp. (Table 3). Against *Listeria* spp. and *Corynebacterium* spp., the dalbavancin MICs ranged from 0.03 to 0.12 mg/L. Lower MICs (0.016 mg/L) were observed for two isolates of *Micrococcus* spp.

DISCUSSION

Vancomycin and teicoplanin are still the only glycopeptide antibiotics available for use in man. Emergence of resistance in enterococci and staphylococci has led to increasing restriction of their use to treatment of severe infections caused by Gram-positive bacteria for which no alternative agents are acceptable (because of resistance or allergy). Considerable efforts have been made to produce semi-synthetic glycopeptides, such as dalbavancin, with improved pharmacokinetic and pharmacodynamic properties, and with activity against resistant strains [5,17]. In the present

Table 3. In-vitro activity of dalbavancin against uncommonly isolated Gram-positive organisms

Organism (no. tested)	Cumulative percentage inhibited at MIC (mg/L)					
	≤ 0.008	0.016	0.03	0.06	0.12	0.25
Corynebacterium spp. (3)[a]	0	0	2	0	1	0
Listeria spp. (6)[b]	0	0	1	2	3	0
Micrococcus spp. (2)	0	2	0	0	0	0

[a]Includes *C. afermentans* (two isolates) and *C. jeikeium* (one).
[b]Includes *L. monocytogenes* (two isolates) and unspeciated (four).

study, dalbavancin showed excellent in-vitro activity against staphylococci, streptococci and vancomycin-susceptible enterococci isolated from patients in Latin America. As found in previous studies [10,11,18], dalbavancin activities against these Gram-positive pathogens, including methicillin-resistant staphylococci, penicillin-resistant pneumococci and viridans streptococci, and multiresistant organisms, was superior to those of vancomycin, teicoplanin, quinupristin–dalfopristin and linezolid (Table 1). The present study also demonstrated excellent activity of dalbavancin against uncommonly isolated bacteria such as *Listeria* spp. and *Corynebacterium* spp., which is also consistent with previous reports [12,18].

Dalbavancin showed decreased activity against vancomycin-resistant *Enterococcus* spp. possessing the VanA phenotype [10,11,18]. In Latin America, most vancomycin-resistant *Enterococcus* isolates belong to the species *E. faecalis* and carry *vanA*. Fortunately, the rates of vancomycin resistance among enterococci isolated from this geographical region were $<5.0\%$, and most vancomycin-resistant *Enterococcus* isolates remain susceptible to ampicillin [4,19].

Although no glycopeptide-intermediate *S. aureus* isolate was found in this study, emergence of glycopeptide-intermediate *S. aureus* has been reported previously in Latin America [20]. In addition, there has been a preliminary report of linezolid resistance in MRSA isolated from Brazilian cystic fibrosis patients [21]. Thus, antimicrobial agents active against strains with these phenotypes of resistance are desirable. Dalbavancin has shown superior potency to conventional glycopeptides in animal models of endocarditis caused by MRSA, with and without reduced susceptibility to vancomycin and teicoplanin [10,13]. In addition, in the rat granuloma pouch infection model, dalbavancin demonstrated greater efficacy than vancomycin or linezolid against methicillin-susceptible or methicillin-resistant *S. aureus*, even when it was administrated less frequently and at lower dosages than the comparators [22]. Dalbavancin has also been effective in models of penicillin-susceptible and penicillin-resistant pneumococcal pneumonia in immunocompetent and neutropenic rats [10].

In phase 1 studies in man, dalbavancin was well-tolerated, and bactericidal activity persisted in human plasma for 7 days after an intravenous dose of 500 mg [23]. Given the long dalbavancin half-life, single doses of ≥ 500 mg maintained concentrations above the minimal bactericidal level for at least 1 week [23]. A recent phase II clinical study demonstrated that a once-weekly dose of dalbavancin was successful for the treatment of deep skin and soft tissue infections [14], and dalbavancin was found to be as effective as the standard practice comparators (clindamycin, ceftriaxone, vancomycin or cefazolin) [14].

In conclusion, the present study showed that dalbavancin has potent in-vitro activity against important Gram-positive bacteria isolated from Latin American patients, similar to results described for bacteria from other diverse geographical areas. Its antimicrobial potency, pharmacokinetic properties and tolerability in patients mean that dalbavancin could represent an important therapeutic option against infections caused by Gram-positive cocci, excluding those caused by enterococci with the VanA phenotype.

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