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In Vitro Activity of Telavancin against Gram-Positive Clinical Isolates Recently Obtained in Europe[▽]

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The in vitro activity of telavancin was tested against 620 gram-positive isolates. For staphylococci, MICs at which 50 and 90% of isolates were inhibited (MIC_{50} and MIC_{90}) were both 0.25 μg/ml, irrespective of methicillin resistance. MIC_{50} and MIC_{90} were 0.25 and 0.5 μg/ml for vancomycin-susceptible enterococci and 1 and 2 μg/ml for vancomycin-resistant enterococci, respectively. *Streptococcus pneumoniae*, group A and B beta-hemolytic streptococci, and viridans streptococci were inhibited by ≤0.12 μg/ml.

The antimicrobial resistance of important gram-positive pathogens, such as *Staphylococcus aureus*, enterococci, and *Streptococcus pneumoniae*, to existing antibiotics is an increasing health concern. The emergence of enterococci and *S. aureus* strains resistant to "last-resort" antibiotics such as vancomycin and other glycopeptides (1, 11) has prompted the development of new, effective antibacterial agents.

Telavancin is a novel semisynthetic lipoglycopeptide with a broad spectrum of activity against aerobic and anaerobic gram-positive bacteria, including methicillin-resistant *S. aureus* (MRSA), and strains with reduced susceptibility to glycopeptides, such as some vancomycin-resistant enterococci (VRE) (3, 5, 6). Telavancin has been shown to be rapidly bactericidal against *S. aureus*, a feature that has been attributed to its multiple mechanisms of action, including inhibition of cell wall synthesis and disruption of cell membrane functional integrity (4).

The objective of this study was to test telavancin against recent, clinically relevant gram-positive isolates from 25 European hospitals in 12 European countries and to compare its activity with that of other antibacterial agents.

A total of 620 bacterial isolates were tested, comprising 100 *S. aureus* strains, 80 coagulase-negative staphylococci (CoNS), 80 *Enterococcus faecalis* strains, 80 *Enterococcus faecium* strains, 100 *S. pneumoniae* strains, 60 group A beta-hemolytic streptococci, 60 group B beta-hemolytic streptococci, and 60 viridans streptococci (Table 1). The strains were isolated mainly from bloodstream, respiratory tract, skin and soft tissue, and urinary tract infection clinical specimens. Only one isolate per patient was included.

The antimicrobial agents tested are listed in Table 1. MICs were determined by broth microdilution methodology according to CLSI guidelines (2). Trek Diagnostics prepared microtiter plates containing frozen serial dilutions of the antibiotics (TREK Diagnostic Systems, Ltd., West Sussex, England). For staphylococci and enterococci, cation-adjusted Mueller-Hinton broth was used. For testing of streptococci and pneumococci, the broth was supplemented with 5% lysed horse blood. The inoculum was adjusted to 5×10^5 CFU/ml. Plates were read after incubation for 20 to 24 h at 35°C in ambient air. MICs were recorded as the lowest concentration that inhibited visible growth. The following reference strains were used for quality control and yielded results within CLSI-approved limits: *E. faecalis* ATCC 29212 (MIC range, 0.12 to 0.5 μg/ml), *S. aureus* ATCC 29213 (MIC range, 0.12 to 1 μg/ml), and *S. pneumoniae* ATCC 49619 (MIC range, 0.004 to 0.03 μg/ml).

The results of testing of susceptibilities to telavancin and the comparator agents are shown in Table 1, presented as the range of MICs and the MICs at which 50% or 90% of isolates are inhibited (MIC_{50} or MIC_{90}, respectively). Telavancin was highly active against *S. aureus* and CoNS; all strains were inhibited by 0.5 μg/ml. No difference was observed in activity against methicillin-susceptible versus methicillin-resistant strains (MIC_{50} and MIC_{90}, both 0.25 μg/ml for both types of strains). Based on the MIC_{90}, telavancin was the most active agent against MRSA: twice as active as daptomycin, 4 times more active than vancomycin, and 8 and 16 times more active than linezolid and teicoplanin, respectively. Similar results have been obtained in other studies (5, 7).

Telavancin showed high potency against vancomycin-susceptible enterococci, with MICs ranging from ≤0.015 to 0.5 μg/ml. Its activity against *E. faecium* was comparable to that against *E. faecalis* (MIC_{50} and MIC_{90}, 0.12 and 0.25 μg/ml versus 0.25 and 0.5 μg/ml, respectively), confirming the results of King et al. (5). VRE were less susceptible to telavancin (MIC range, 0.12 to 8 μg/ml). Overall, the MIC_{50} and MIC_{90} for VRE were 4 times higher than those of non-VRE (1 and 2 μg/ml versus 0.25 and 0.5 μg/ml). Of the 28 VRE strains tested, 20 exhibited the VanA phenotype (vancomycin MICs, 256 to >512 μg/ml; teicoplanin MICs, 8 to >128 μg/ml) and 8 expressed the VanB phenotype (vancomycin MICs, 8 to 64 μg/ml; teicoplanin MICs, 0.06 to 0.5 μg/ml). Telavancin showed more-potent activity against VanB strains (MIC range, 0.12 to 1 μg/ml) than against VanA strains (MIC range, 0.5 to 8 μg/ml).

Telavancin was the most active agent tested against vancomycin-resistant *E. faecium* (MIC_{50} and MIC_{90}, 1 and 2 μg/ml, respectively), followed by daptomycin and linezolid (MIC_{50} and MIC_{90}, both 2 μg/ml for both agents). Against vancomy-

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TABLE 1. In vitro activities of telavancin and comparators against gram-positive bacteria

Organism (no. of strains) and antimicrobial agent	MIC (mg/liter)		
	Range	50%	90%
Staphylococcus aureus			
Methicillin susceptible (60)			
Telavancin	0.06–0.5	0.25	0.25
Vancomycin	0.5–2	0.5	1
Teicoplanin	0.25–4	0.5	1
Daptomycin	0.12–0.5	0.25	0.5
Oxacillin	≤0.06–2	0.25	0.5
Erythromycin	≤0.12–>16	0.5	>16
Telithromycin	0.06–>8	0.12	0.12
Clindamycin	≤0.5–>4	≤0.5	≤0.5
Quinupristin-dalfopristin	≤0.12–0.5	0.25	0.25
Linezolid	≤0.5–4	2	2
Ciprofloxacin	0.12–>8	0.25	1
Trimethoprim-sulfamethoxazole	≤0.5–2	≤0.5	≤0.5
Gentamicin	≤0.06–>16	0.25	1
Methicillin resistant (40)			
Telavancin	0.06–0.5	0.25	0.25
Vancomycin	0.5–2	1	1
Teicoplanin	≤0.12–4	0.5	4
Daptomycin	0.12–1	0.5	0.5
Oxacillin	4–>4	>4	>4
Erythromycin	≤0.12–>16	>16	>16
Telithromycin	≤0.03–>8	0.12	>8
Clindamycin	≤0.5–>4	≤0.5	>4
Quinupristin-dalfopristin	≤0.12–>4	0.25	0.5
Linezolid	≤0.5–4	2	2
Ciprofloxacin	0.25–>8	>8	>8
Trimethoprim-sulfamethoxazole	≤0.5–>4	≤0.5	>4
Gentamicin	0.12–>16	0.5	>16
CoNS			
Methicillin susceptible (30)			
Telavancin	0.12–0.25	0.25	0.25
Vancomycin	0.5–2	1	2
Teicoplanin	≤0.12–16	2	8
Daptomycin	0.12–1	0.5	1
Oxacillin	≤0.06–0.25	0.12	0.12
Erythromycin	≤0.12–>16	0.25	>16
Telithromycin	≤0.03–>8	0.06	0.5
Clindamycin	≤0.5–>4	≤0.5	≤0.5
Quinupristin-dalfopristin	≤0.12–0.25	≤0.12	0.25
Linezolid	1–2	1	2
Ciprofloxacin	0.12–>8	0.12	0.25
Trimethoprim-sulfamethoxazole	≤0.5–>4	≤0.5	>4
Gentamicin	≤0.06–>16	≤0.06	≤0.06
Methicillin resistant (50)			
Telavancin	0.12–0.5	0.25	0.25
Vancomycin	0.5–4	1	2
Teicoplanin	≤0.12–16	2	8
Daptomycin	0.12–>1	0.5	0.5
Oxacillin	0.5–>4	>4	>4
Erythromycin	≤0.12–>16	>16	>16
Telithromycin	0.06–>8	0.12	>8
Clindamycin	≤0.5–>4	≤0.5	>4
Quinupristin-dalfopristin	≤0.12–>4	0.25	0.5
Linezolid	1–4	2	2
Ciprofloxacin	≤0.06–>8	2	>8
Trimethoprim-sulfamethoxazole	≤0.5–>4	2	>4
Gentamicin	≤0.06–>16	8	>16
Enterococcus faecalis			
Vancomycin susceptible (73)			
Telavancin	≤0.015–0.5	0.25	0.5

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TABLE 1—*Continued*

Organism (no. of strains) and antimicrobial agent	MIC (mg/liter)		
	Range	50%	90%
Vancomycin	≤0.5–4	2	2
Teicoplanin	≤0.03–0.25	0.12	0.25
Daptomycin	≤0.015–4	1	2
Ampicillin	≤0.25–8	1	2
Linezolid	1–4	2	2
Quinupristin-dalfopristin	0.5–32	8	16
Ciprofloxacin	0.5–>32	1	>32
Vancomycin resistant (7)			
Telavancin	0.25–8	4	8
Vancomycin	64–>512	512	>512
Teicoplanin	0.06–>128	32	>128
Daptomycin	0.5–2	0.5	2
Ampicillin	1–4	1	4
Linezolid	1–2	2	2
Quinupristin-dalfopristin	8–16	8	16
Ciprofloxacin	0.5–>32	1	>32
Enterococcus faecium			
Vancomycin susceptible (59)			
Telavancin	0.03–0.5	0.12	0.25
Vancomycin	≤0.5–2	1	1
Teicoplanin	≤0.03–2	0.25	0.5
Daptomycin	0.03–4	2	4
Ampicillin	0.5–>128	64	128
Linezolid	1–4	2	2
Quinupristin-dalfopristin	0.25–4	1	4
Ciprofloxacin	0.25–>32	>32	>32
Vancomycin resistant (21)			
Telavancin	0.12–8	1	2
Vancomycin	8–>512	512	512
Teicoplanin	0.12–>128	32	128
Daptomycin	0.25–4	2	2
Ampicillin	1–>128	128	128
Linezolid	1–2	2	2
Quinupristin-dalfopristin	0.25–4	1	4
Ciprofloxacin	0.5–>32	32	>32
Streptococcus pneumoniae			
Penicillin susceptible (42)			
Telavancin	0.008–0.06	0.015	0.03
Vancomycin	0.25–0.5	0.25	0.5
Daptomycin	0.06–0.5	0.12	0.25
Penicillin	≤0.06–≤0.06	≤0.06	≤0.06
Cefuroxime	≤0.12–0.25	≤0.12	≤0.12
Ceftriaxone	≤0.015–0.12	0.03	0.03
Erythromycin	≤0.015–>1	0.03	0.06
Telithromycin	0.004–0.25	0.008	0.008
Clindamycin	≤0.03–>0.25	0.06	0.06
Levofloxacin	0.25–1	0.5	1
Trimethoprim-sulfamethoxazole	0.12–>4	0.25	1
Linezolid	0.5–1	1	1
Tetracycline	≤0.06–>8	0.12	0.25
Penicillin intermediate (36)			
Telavancin	0.008–0.06	0.015	0.03
Vancomycin	0.25–0.5	0.25	0.5
Daptomycin	≤0.03–0.5	0.12	0.25
Penicillin	0.12–1	0.5	1
Cefuroxime	≤0.12–>4	0.5	4
Ceftriaxone	0.03–1	0.12	1
Erythromycin	≤0.015–>1	0.03	>1
Telithromycin	≤0.002	0.008	0.25
Clindamycin	≤0.03–>0.25	0.06	>0.25

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TABLE 1—*Continued*

Organism (no. of strains) and antimicrobial agent	MIC (mg/liter)		
	Range	50%	90%
Levofloxacin	0.5–2	0.5	1
Trimethoprim-sulfamethoxazole	0.12–>4	4	>4
Linezolid	0.5–2	1	1
Tetracycline	≤0.06–>8	0.25	>8
Penicillin resistant (22)			
Telavancin	0.015–0.03	0.015	0.03
Vancomycin	0.25–0.5	0.25	0.5
Daptomycin	0.06–0.25	0.12	0.12
Penicillin	2–>2	2	2
Cefuroxime	4–>4	>4	>4
Ceftriaxone	0.5–2	1	2
Erythromycin	0.03–>1	>1	>1
Telithromycin	0.008–0.5	0.015	0.03
Clindamycin	0.06–>0.25	>0.25	>0.25
Levofloxacin	0.5–8	0.5	4
Trimethoprim-sulfamethoxazole	0.12–>4	4	>4
Linezolid	0.5–1	1	1
Tetracycline	0.12–>8	0.25	>8
Streptococcus group A (60)			
Telavancin	0.03–0.06	0.03	0.06
Vancomycin	0.25–0.5	0.25	0.5
Daptomycin	≤0.03–0.5	0.06	0.06
Penicillin	≤0.06–≤0.06	≤0.06	≤0.06
Cefuroxime	≤0.12–≤0.12	≤0.12	≤0.12
Ceftriaxone	≤0.015–0.06	0.03	0.03
Erythromycin	0.03–>1	0.03	0.06
Telithromycin	0.008–>4	0.015	0.015
Clindamycin	≤0.03–>0.25	≤0.03	0.06
Levofloxacin	≤0.12–1	0.5	0.5
Trimethoprim-sulfamethoxazole	≤0.06–0.25	≤0.06	0.25
Linezolid	0.5–1	1	1
Tetracycline	0.12–>8	0.12	>8
Streptococcus group B (60)			
Telavancin	0.03–0.12	0.06	0.06
Vancomycin	0.25–1	0.5	0.5
Daptomycin	0.06–0.5	0.25	0.25
Penicillin	≤0.06–≤0.06	≤0.06	≤0.06
Cefuroxime	≤0.12–0.5	≤0.12	≤0.12
Ceftriaxone	0.03–0.12	0.06	0.06
Erythromycin	0.03–>1	0.03	0.5
Telithromycin	0.008–0.12	0.015	0.015
Clindamycin	≤0.03–>0.25	0.06	0.06
Levofloxacin	0.25–1	0.5	1
Trimethoprim-sulfamethoxazole	≤0.06–0.25	≤0.06	0.12
Linezolid	0.5–1	1	1
Tetracycline	0.12–>8	>8	>8
Viridans streptococci (60)			
Telavancin	0.015–0.12	0.06	0.06
Vancomycin	0.25–1	0.5	1
Daptomycin	≤0.03–>1	0.5	1
Penicillin	≤0.06–>2	≤0.06	2
Cefuroxime	≤0.12–>4	≤0.12	2
Ceftriaxone	≤0.015–4	0.12	2
Erythromycin	≤0.015–>1	0.03	>1
Telithromycin	≤0.002–0.25	0.008	0.12
Clindamycin	≤0.03–>0.25	≤0.03	>0.25
Levofloxacin	0.25–>8	0.5	1
Trimethoprim-sulfamethoxazole	≤0.06–>4	0.25	2
Linezolid	0.25–2	1	1
Tetracycline	≤0.06–>8	0.5	>8

cin-resistant *E. faecalis*, daptomycin showed the highest activity (MIC_{50} and MIC_{90}, 0.5 and 2 μg/ml, respectively), followed by linezolid (MIC_{50} and MIC_{90}, both 2 μg/ml).

Telavancin exhibited potent in vitro activity against both penicillin-susceptible and non-penicillin-susceptible *S. pneumoniae* strains; all strains were inhibited by ≤0.06 μg/ml. Telavancin was also highly active against beta-hemolytic streptococci of groups A and B and against viridans streptococci (MIC_{90}, 0.06 μg/ml for each), and it was at least eight times more active than vancomycin against these species.

The results of our in vitro investigation confirm the broad spectrum of activity of telavancin against gram-positive bacteria, which has been determined previously using smaller collections of isolates from only one hospital in Great Britain (5). Telavancin reaches adequate levels in plasma (peak concentration, 96.7 μg/ml at 7.5 mg/kg of body weight/day) (8) and is approximately 90% protein bound (S. D. Brown and M. M. Traczewski, presented at the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 2006). Due to its favorable pharmacokinetic profile and in vitro potency, telavancin clearly has potential as a useful agent for the treatment of infections due to gram-positive bacteria. Phase 3 clinical studies suggest that telavancin may have a role in treating complicated skin and soft tissue infections, particularly those involving MRSA (9, 10).

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