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In Vitro Antimicrobial Activity of Telavancin against Methicillin-resistant *Staphylococcus aureus* Clinical Isolates from Japan (2006)

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Abstract *In vitro* antimicrobial activity of telavancin, a rapidly bactericidal lipoglycopeptide, was evaluated against 1500 strains of MRSA recently isolated in Japan. Telavancin had potent activity, with MIC values that ranged from 0.12 μg/ml to 0.5 μg/ml and a MIC_{90} value of 0.5 μg/ml. The MIC_{90}s of vancomycin and linezolid were 1.0μg/ml and 2 μg/ml, respectively. No vancomycin intermediate resistant or vancomycin-resistant MRSAs were detected in this surveillance study.

Keywords telavancin, *S. aureus*, MRSA, surveillance, vancomycin, Japan, lipoglycopeptide

The global emergence of severe infections caused by Gram-positive pathogens with resistance or reduced susceptibility to antibiotics has become a major public health concern. Importantly, among *Staphylococcus aureus* isolates, the frequency with which methicillin-resistant strains (MRSA) are isolated is rising [1]. In addition, MRSA strains with reduced susceptibility to vancomycin, teicoplanin and linezolid are reported with increasing frequency [2～4]. Failure of vancomycin to effectively treat serious staphylococcal infections has been reported and many experts believe that this may be due to its limited bactericidal activity [5, 6].

Telavancin (Fig. 1), a novel lipoglycopeptide antibiotic with a unique, multifunctional mechanism of action and rapid, concentration-dependent bactericidal activity, has completed two Phase III trials for complicated skin and skin structure infections, and is currently under evaluation for the treatment of hospital-acquired pneumonia [7]. Unlike vancomycin and teicoplanin, telavancin disrupts bacterial cell membrane integrity in addition to inhibiting peptidoglycan synthesis [8]. This dual mechanism of action may be the reason for the potent bactericidal activity observed with telavancin, which may also be a factor in limiting the emergence of resistance [8～10]. Additionally,

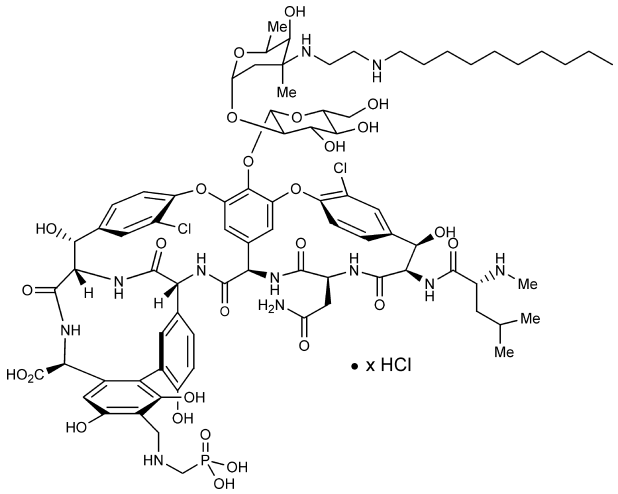

Fig. 1 Structure of telavancin.

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this rapid bactericidal activity may provide greater efficacy, a reduction in the duration of therapy and a decrease in the relapse rate, compared with standard therapy.

In order to evaluate the potential efficacy of telavancin as an anti-MRSA agent in Japan, we determined its *in vitro* activity against 1,500 recent clinical isolates. The majority (69%) of strains were isolated from the sputum, nasal cavity, accessory nasal sinus or pharynges, indicating that a large proportion of isolates were from patients with hospital-acquired pneumonia. MRSA strains were identified both by disk susceptibility testing (oxacillin inhibition zone diameter of ≤10 mm) and growth on MRSA Screen Agar (Nippon Becton Dickinson, Tokyo, Japan) [11]. Telavancin was supplied by Theravance, Inc. (South San Francisco, California, USA). Daptomycin (Cubicin®) was provided by Cubist Pharmaceuticals Inc., Lexington, Massachusetts, USA) and tigecycline (Tygacil®) by Wyeth Pharmaceuticals Inc., Philadelphia, Pennsylvania, USA). Susceptibility testing was performed according to the standards established by the Clinical and Laboratory

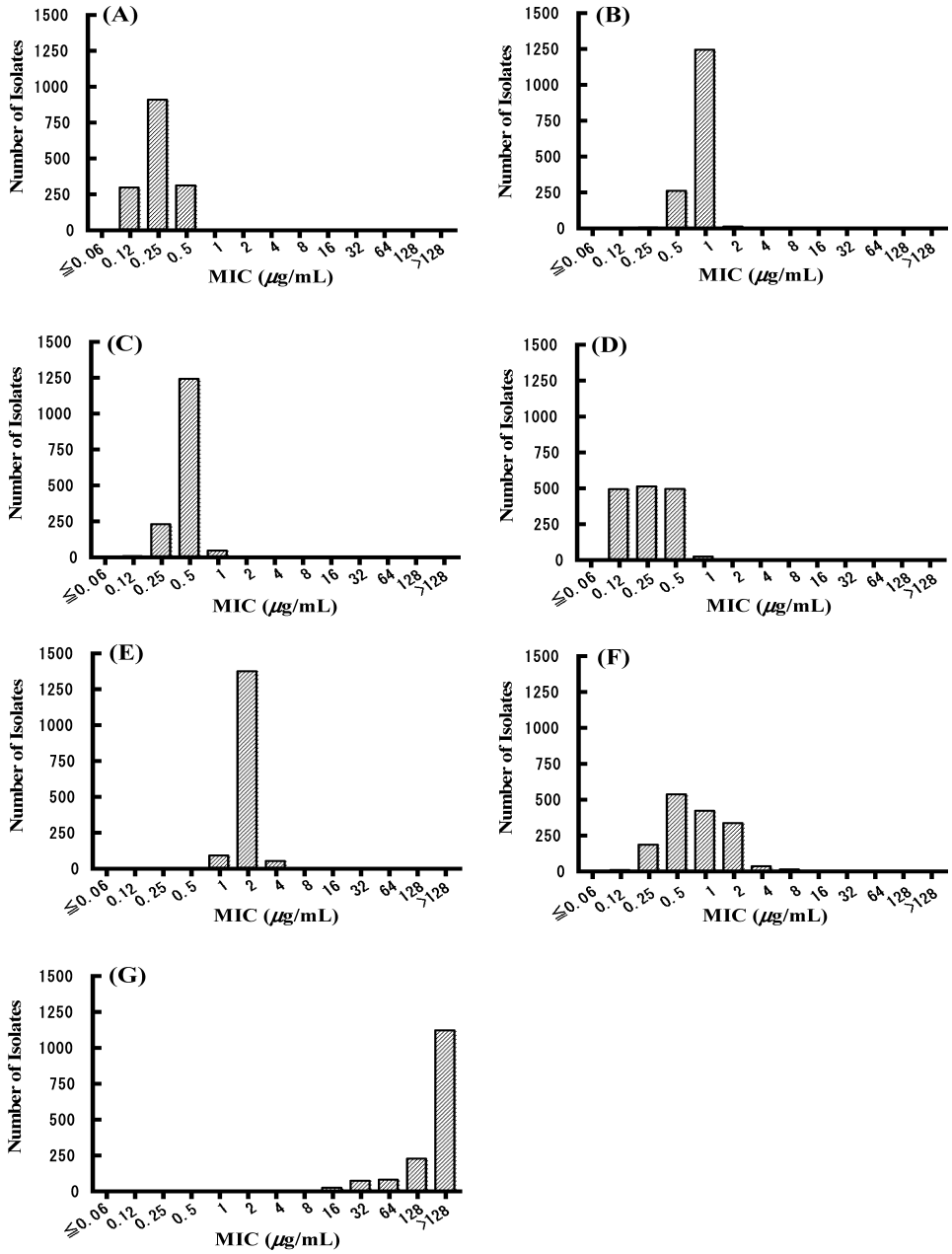

Fig. 2 MIC distributions of antibiotics tested against 1,500 MRSA clinical isolates from Japan.
(A) telavancin, (B) vancomycin, (C) daptomycin, (D) tigecycline, (E) linezolid, (F) arbekacin and (G) oxacillin.

Table 1 Antimicrobial activities of telavancin and comparators against 1,500 MRSA clinical isolates from Japan

Drugs	MIC (μg/ml)		
	Range	50%	90%
Telavancin	0.12～0.5	0.25	0.5
Vancomycin	0.25～2	1	1
Daptomycin	0.12～1	0.5	0.5
Tigecycline	0.12～1	0.25	0.5
Linezolid	1～4	2	2
Arbekacin	0.12～8	1	2
Oxacillin	16～>128	>128	>128

Standards Institute (CLSI) [12] using the broth microdilution method with cation-adjusted Mueller-Hinton broth. For testing daptomycin and oxacillin, the medium was supplemented with 50 μg/ml of Ca^{2+} and 2.0% NaCl, respectively [11]. Eiken Chemical Co., Ltd. (Tokyo, Japan) supplied vancomycin, linezolid, arbekacin and oxacillin powders and manufactured frozen MIC panels. Collection of clinical specimens, identification of organisms and MIC determinations were carried out by Mitsubishi Chemical Medience Corporation (Tokyo, Japan). Quality control testing was performed using *S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212. MIC and susceptibility were determined according to CLSI standards [11] for all antibiotics except arbekacin. For arbekacin, we used the quality control standard established by Mitsubishi Chemical Medience Corporation.

The *in vitro* antimicrobial activity of telavancin, compared with six other anti-MRSA agents, is summarised in Fig. 2 and Table 1. None of the strains grew on Vancomycin Screen Agar (Nippon Becton Dickinson, Tokyo, Japan), or had a MIC of >6 μg/ml as assessed with the Etest (AB Biodisk, Solna, Sweden) [2], indicating that there were no vancomycin-intermediate or -resistant organisms in the collection (data not shown). Over 90% of MRSA strains in this study had high resistance to oxacillin (MIC ≥128 μg/ml). Telavancin had potent antibacterial activity against these strains with a narrow MIC distribution (0.12 μg/ml to 0.5 μg/ml), and a MIC_{90} of 0.5 μg/ml. Telavancin was two to four times more potent than vancomycin by the microdilution method and was four-fold more potent than linezolid and arbekacin. No linezolid-nonsusceptible strains were identified in this surveillance study. MIC_{90}s for daptomycin and tigecycline, which have indication for the treatment of patients with infections such as complicated skin and skin structure infections (cSSSI) caused by microorganisms including MRSA in the USA and the EU but are not commercially available in Japan, were 0.5 μg/ml similar to telavancin. The results presented here are similar to those previously reported in global surveillance studies from the US (2004～2005) [13], and Europe and Israel (2005) [14].

Our surveillance study did not include vancomycin intermediate-resistant or linezolid-nonsusceptible strains. However, previous studies demonstrated that telavancin has potent activity against strains with reduced susceptibility to vancomycin [15～17], with MIC <4 μg/ml even against a MRSA strain with high-level vancomycin resistance (MIC >32 μg/ml). Similarly, telavancin is not cross-resistant with linezolid [18].

In conclusion, this surveillance study showed that telavancin has potent antimicrobial activity against *in vitro* MRSA strains isolated in Japan, suggesting that telavancin may represent an important therapeutic option for the treatment of severe infections caused by MRSA.

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