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Activity of Tedizolid (TR-700) against Well-Characterized Methicillin-Resistant *Staphylococcus aureus* Strains of Diverse Epidemiological Origins

Kenneth S. Thomson, Richard V. Goering

Creighton University, Omaha, Nebraska, USA

The *in vitro* activities of tedizolid and 10 antistaphylococcal agents were compared against 111 methicillin-resistant *Staphylococcus aureus* (MRSA) strains from 14 epidemiologically characterized groups. Tedizolid, tigecycline, and daptomycin were the most potent agents, with tedizolid 4-fold more potent than linezolid. Tedizolid, linezolid, and vancomycin were unaffected by epidemiological types. Tigecycline and daptomycin had reduced potency against ST80-MRSA-IV and ST239-MRSA-III, respectively. Overall, tedizolid was highly potent against all MRSA strain types, including those resistant to other classes of drugs.

Methicillin-resistant *Staphylococcus aureus* (MRSA)-associated infections have become increasingly common in the last 2 decades (1, 2). Better anti-MRSA therapeutic agents are needed to improve on the disadvantages of the traditionally used agent vancomycin, which has slow bactericidal activity, poor oral bioavailability and tissue penetration, nephrotoxicity, and diminished activity against some strains. Currently available alternative agents include linezolid, quinupristin-dalfopristin, daptomycin, telavancin, ceftaroline, and tigecycline. The oxazolidinone linezolid has good oral bioavailability and tissue penetration and is reported to be active against MRSA isolates with reduced vancomycin susceptibility (1, 3). Tedizolid (previously known as torezolid; TR-700) is a novel oxazolidinone with potent activity against MRSA (4). Previous reports have focused on activity against collections of MRSA strains that were not well characterized at the molecular level or were of limited or unknown epidemiological diversity (5). Therefore, a study was designed to compare the anti-MRSA activities of tedizolid and 10 other antistaphylococcal agents against 111 MRSA strains from 14 different epidemiologically well-characterized groups; i.e., they were not randomly chosen clinical isolates. The investigated isolates were chosen from an international clinical collection (R. Goering) characterized by pulsed-field gel electrophoresis (PFGE) and, in some instances, *spa* and multilocus sequence typing (MLST) (6–8).

MIC values were determined by a CLSI microdilution methodology (9) using Trek frozen microdilution panels containing tedizolid, linezolid, trimethoprim-sulfamethoxazole, tigecycline, levofloxacin, clindamycin, vancomycin, daptomycin, oxacillin, erythromycin, gentamicin, and ampicillin.

The results in Table 1 indicate that tedizolid, tigecycline (MIC_{90} = 0.5 μg/ml), and daptomycin ($MIC_{90} \leq 0.5$ μg/ml) were the most potent agents against all types of MRSA. Tedizolid was 4-fold more potent than the comparison oxazolidinone, linezolid. The MIC values of tedizolid, linezolid, and vancomycin were unchanged against all epidemiological types, whereas tigecycline ($MIC_{90} > 1$ μg/ml) and daptomycin (MIC_{90} = 1 μg/ml) exhibited reduced potency against the European community-associated ST80-MRSA-IV strains and the ST239-MRSA-III (Brazilian clone) strains, respectively. In particular, 3 of 10 European community-associated ST80-MRSA-IV strains had elevated tigecycline MIC values of ≥1 μg/ml, and 4 of 10 ST239-MRSA-III (Brazilian clone) strains had elevated daptomycin MIC values of ≥1 μg/ml. The other epidemiological groups were more susceptible to tigecycline and daptomycin.

Except for oxacillin and erythromycin, which were inactive, the MICs of the other agents varied with the different strain types. Specifically, the activity of trimethoprim-sulfamethoxazole against ST8-MRSA-IV (USA500) and ST239-MRSA-III (Brazilian clone) strains was compromised. Levofloxacin was most active agent against ST1-MRSA-IV (USA400), ST5-MRSA-IV (USA800), and ST80-MRSA-IV strains but had compromised activity against ST8-MRSA-IV (USA500), ST22-MRSA-IV (EMRSA15), ST247-MRSA-I (Iberian clone), and ST239-MRSA-III (Brazilian clone) strains. Erythromycin was inactive against most strains but was active against some ST22-MRSA-IV (EMRSA15) strains. Clindamycin was highly active against ST8-MRSA-IV (USA300), MRSA-IV (USA400), ST22-MRSA-IV (EMRSA15), and ST80-MRSA-IV strains ($MIC_{90} \leq 0.5$ μg/ml) and moderately active against ST5-MRSA-IV (USA800) (MIC_{50} 0.12 μg/ml) but had compromised activity against ST5-MRSA-II (USA100), ST36-MRSA-II (USA200/EMRSA16), ST8-MRSA-IV (USA500), ST247-MRSA-I (Iberian clone), and some ST239-MRSA-III (Brazilian clone) strains. The activity of gentamicin was compromised against ST247-MRSA-I (Iberian clone) and ST239-MRSA-III (Brazilian clone) strains and was variable against ST8-MRSA-IV (USA500) strains.

In conclusion, tedizolid was highly potent against all MRSA strain types, including those with reduced susceptibility to daptomycin and tigecycline. The narrow MIC range of tedizolid (0.12 to 0.5 μg/ml) indicated that its activity was not compromised by the resistance mechanisms present in this diverse collection of MRSA strains. Thus, tedizolid shows potential as a therapeutic agent

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Address correspondence to Kenneth S. Thomson, kstaac@creighton.edu.

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TABLE 1 Drug activity against all MRSA isolates and epidemiological groups[a]

Isolate(s)	Drug(s)	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
All isolates ($n = 111$)	Tedizolid	0.12 to 0.5	0.5	0.5
	Linezolid	0.5 to 4	2	2
	Trimethoprim/sulfamethoxazole	≤0.5/9.5 to >2/38	≤0.5/9.5	>2/38
	Tigecycline	0.06 to >1	0.25	0.5
	Levofloxacin	0.12 to >4	4	>4
	Clindamycin	0.06 to >16	0.12	>16
	Vancomycin	≤0.25 to 4	0.5	1
	Daptomycin	≤0.5 to 2	≤0.5	≤0.5
	Oxacillin	0.12 to >4	>4	>4
	Erythromycin	0.12 to >8	>8	>8
	Gentamicin	≤0.06 to >16	0.25	>16
ST5-MRSA-II (USA100) ($n = 10$)	Tedizolid	0.25 to 0.5	0.5	0.5
	Linezolid	1 to 2	2	2
	Trimethoprim/sulfamethoxazole	≤0.5/9.5	≤0.5/9.5	≤0.5/9.5
	Tigecycline	0.06 to 0.5	0.25	0.25
	Levofloxacin	4 to >4	4	>4
	Clindamycin	0.06 to >16	>16	>16
	Vancomycin	0.5	0.5	0.5
	Daptomycin	≤0.5	≤0.5	≤0.5
	Oxacillin	>4	>4	>4
	Erythromycin	>8	>8	>8
	Gentamicin	≤0.06 to 8	0.25	0.5
ST36-MRSA-II (USA200/EMRSA16) ($n = 10$)	Tedizolid	0.12 to 0.5	0.5	0.5
	Linezolid	0.5 to 4	2	2
	Trimethoprim/sulfamethoxazole	≤0.5/9.5	≤0.5/9.5	≤0.5/9.5
	Tigecycline	0.06 to 0.25	0.25	0.25
	Levofloxacin	0.12 to >4	>4	>4
	Clindamycin	0.12 to >16	>16	>16
	Vancomycin	≤0.25 to 0.5	0.5	0.5
	Daptomycin	≤0.5	≤0.5	≤0.5
	Oxacillin	>4	>4	>4
	Erythromycin	>8	>8	>8
	Gentamicin	0.12 to 0.25	0.25	>16
ST8-MRSA-IV (USA300) ($n = 10$)	Tedizolid	0.25 to 0.5	0.5	0.5
	Linezolid	2 to 4	2	4
	Trimethoprim/sulfamethoxazole	≤0.5/9.5	≤0.5/9.5	≤0.5/9.5
	Tigecycline	0.06 to 0.25	0.12	0.25
	Levofloxacin	0.12 to >4	0.25	4
	Clindamycin	0.06 to >16	0.12	0.12
	Vancomycin	0.5 to 1	0.5	1
	Daptomycin	≤0.5 to 0.5	≤0.5	≤0.5
	Oxacillin	>4	>4	>4
	Erythromycin	>8	>8	>8
	Gentamicin	≤0.06 to 1	0.25	0.5
ST1-MRSA-IV (USA400) ($n = 10$)	Tedizolid	0.5	0.5	0.5
	Linezolid	2 to 4	2	4
	Trimethoprim/sulfamethoxazole	≤0.5/9.5	≤0.5/9.5	≤0.5/9.5
	Tigecycline	0.12 to 0.5	0.25	0.25
	Levofloxacin	0.12 to 0.5	0.25	0.5
	Clindamycin	0.12 to 8	0.12	0.12
	Vancomycin	0.5 to 1	0.5	1
	Daptomycin	≤0.5	≤0.5	≤0.5
	Oxacillin	0.5 to >4	>4	>4
	Erythromycin	0.12 to >8	0.5	>8
	Gentamicin	0.25 to 1	0.25	0.5

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TABLE 1(Continued)

Isolate(s)	Drug(s)	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
ST8-MRSA-IV (USA500) (n = 10)	Tedizolid	0.25 to 0.5	0.5	0.5
	Linezolid	2	2	2
	Trimethoprim/sulfamethoxazole	≤0.5/9.5 to >2/38	≤0.5/9.5	>2/38
	Tigecycline	0.12 to 0.5	0.25	0.25
	Levofloxacin	>4	>4	>4
	Clindamycin	0.12 to >16	>16	>16
	Vancomycin	0.5 to 1	0.5	1
	Daptomycin	≤0.5 to 0.5	≤0.5	≤0.5
	Oxacillin	0.5 to >4	>4	>4
	Erythromycin	0.25 to >8	>8	>8
	Gentamicin	0.25 to >16	0.5	>16
ST5-MRSA-IV (USA800) (n = 10)	Tedizolid	0.25 to 0.5	0.5	0.5
	Linezolid	1 to 2	2	2
	Trimethoprim/sulfamethoxazole	≤0.5/9.5 to 0.5/9.5	≤0.5/9.5	≤0.5/9.5
	Tigecycline	0.06 to 0.25	0.12	0.25
	Levofloxacin	0.12 to 4	0.12	0.25
	Clindamycin	0.06 to >16	0.12	>16
	Vancomycin	0.5 to 1	0.5	1
	Daptomycin	≤0.5	≤0.5	≤0.5
	Oxacillin	1 to >4	>4	>4
	Erythromycin	0.25 to >8	>8	>8
	Gentamicin	0.12 to 0.5	0.25	0.5
ST22-MRSA-IV (EMRSA15) (n = 10)	Tedizolid	0.25 to 0.5	0.25	0.5
	Linezolid	1 to 2	2	2
	Trimethoprim/sulfamethoxazole	≤0.5/9.5	≤0.5/9.5	≤0.5/9.5
	Tigecycline	0.06 to 0.25	0.25	0.25
	Levofloxacin	0.12 to >4	>4	>4
	Clindamycin	0.12 to >16	0.12	0.12
	Vancomycin	0.5 to 1	0.5	0.5
	Daptomycin	≤0.5	≤0.5	≤0.5
	Oxacillin	0.12 to >4	>4	>4
	Erythromycin	0.25 to >8	>8	>8
	Gentamicin	0.12 to 1	0.25	0.25
ST80-MRSA-IV (European community associated) (n = 10)	Tedizolid	0.25 to 0.5	0.25	0.5
	Linezolid	2 to 4	2	2
	Trimethoprim/sulfamethoxazole	≤0.5/9.5	≤0.5/9.5	≤0.5/9.5
	Tigecycline	0.12 to >1	0.12	>1
	Levofloxacin	0.12 to >4	0.12	0.25
	Clindamycin	0.12 to >16	0.12	0.5
	Vancomycin	0.5 to 4	0.5	1
	Daptomycin	≤0.5	≤0.5	≤0.5
	Oxacillin	4 to >4	>4	>4
	Erythromycin	0.25 to >8	0.5	>8
	Gentamicin	0.12 to 2	0.25	1
ST247-MRSA-I (Iberian clone) (n = 11)	Tedizolid	0.25 to 0.5	0.25	0.25
	Linezolid	1 to 2	1	2
	Trimethoprim/sulfamethoxazole	≤0.5/9.5 to >2/38	≤0.5/9.5	≤0.5/9.5
	Tigecycline	0.12 to 1	0.25	0.5
	Levofloxacin	4 to >4	>4	>4
	Clindamycin	0.12 to >16	>16	>16
	Vancomycin	0.5 to 1	1	1
	Daptomycin	≤0.5 to 1	≤0.5	≤0.5
	Oxacillin	>4	>4	>4
	Erythromycin	0.5 to >8	>8	>8
	Gentamicin	>16	>16	>16

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TABLE 1(Continued)

Isolate(s)	Drug(s)	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
ST239-MRSA-III (Brazilian clone) ($n = 10$)	Tedizolid	0.12 to 0.5	0.25	0.5
	Linezolid	1 to 2	2	2
	Trimethoprim/sulfamethoxazolemethoxazole	≤0.5/9.5 to >2/38	>2/38	>2/38
	Tigecycline	0.12 to 0.5	0.25	0.5
	Levofloxacin	0.12 to >4	4	>4
	Clindamycin	0.12 to >16	>16	>16
	Vancomycin	1 to 4	1	1
	Daptomycin	≤0.5 to 2	≤0.5	1
	Oxacillin	1 to >4	>4	>4
	Erythromycin	>8	>8	>8
	Gentamicin	0.25 to >16	>16	>16

[a] Results for 4 epidemiological groups are not provided in the table because fewer than 10 isolates were tested. These were 1 isolate of ST45-MRSA-II (USA600), 3 isolates of ST72-MRSA-IV (USA700), 3 isolates of ST59-MRSA-IV (USA1000), and 3 isolates of ST30-MRSA-IV (USA1100).

against all MRSA types, including those strains that are less susceptible or resistant to currently available anti-MRSA agents.

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