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In Vitro Activity of the Glycylcycline Tigecycline Tested Against a Worldwide Collection of 10,127 Contemporary Staphylococci, Streptococci and Enterococci

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ABSTRACT

Background:
Tigecycline (TIG) is a novel glycylcycline with broad spectrum activity. Increasing reports of resistance (R) among commonly occurring Gram-positive cocci (GPC) that produce respiratory tract and skin and soft tissue infections has created a need for development of new antimicrobial agents. In this study the activity and potency of TIG, tetracycline (TC) and other comparator agents was evaluated using contemporary isolates of commonly-occurring species of GPC, including the presence of R organism subsets.

Methods:
The activity of TIG and 9 comparators was challenged with a collection of GPC including oxacillin (OXA)-susceptible (S; 3,196 strains) and -R (1,881 strains) *S. aureus* (SA); OXA-S (321 strains) and -R (1,111 strains) coagulase-negative staphylococci (CoNS); penicillin (PEN)-S (1,126 strains) and -non-susceptible (NS; 459 strains) *S. pneumoniae* (SPN); pen-S (161 strains) and -NS (51 strains) viridans group streptococci (VGS); ß-haemolytic streptococci (BHS; 405 strains); and vancomycin-S (1,294 strains) and -R (122 strains) enterococci (ENT). Broth microdilution susceptibility tests were performed and analyzed using NCCLS reference methods and interpretive criteria.

Results:
Whereas OXA-R subsets of both SA and CoNS displayed cross resistance to TC, macrolides, clindamycin and quinolones, no differences were seen with TIG (MIC50/90 being 0.25 and 0.5 mg/L, respectively). Among streptococci, all SPN and VGS (regardless of PEN-S), and BHS demonstrated TIG $MIC_{50/90}$ values of ≤ 0.12 mg/L (one exception being PEN-intermediate VGS with the MIC_{90} at 0.25 mg/L). TIG was also uniformly active against enterococcal isolates, with $MIC_{50/90}$ results of vancomycin-S and -R subsets being 0.25 and 0.5mg/L, and 0.12 and 0.25 mg/L, respectively. When using the NCCLS TC S breakpoint of ≤ 4mg/L, all 10,127 staphylococci, streptococci and enterococci tested would be classified as S to TIG.

Conclusions:
TIG displays a remarkable spectrum of activity and potency against S and R subsets of GPC with the highest MIC90 being only 0.5 mg/L. In addition to for use in treating community-acquired respiratory tract infections, TIG may also be a candidate for treatment of complicated skin and soft tissue infections and, possibly, urinary tract infections caused by GPC.

INTRODUCTION

The glycylcyclines constitute a novel class of synthetic antimicrobic with potent activity against a broad-spectrum of aerobic and anaerobic Gram-positive and -negative microorganisms, including commonly occurring resistant strains. Tigecycline is a 9-t-butylglycylamido derivative of minocycline and the first of this new class to enter clinical development. The compound inhibits protein synthesis by binding to the 30S ribosomal subunit and is stable to commonly occurring resistance mechanisms including efflux and ribosomal protection factors.

Tigecycline is currently undergoing advanced clinical evaluation as a parenteral agent because of its potent activity against contemporary resistant organisms including penicillin-resistant *S. pneumoniae*, oxacillin-resistant staphylococci, vancomycin-resistant enterococci, and extended-spectrum ß-lactamase producing strains of Enterobacteriaceae. The compound is also active against *Haemophilus influenzae*, *Neisseria gonorrhoeae,* and other Gram-negatives.

INTRODUCTION (Continued)

In this study we evaluated the in vitro activity of tigecycline against a total of 10,127 Gram-positive bacterial isolates recovered from patients with community-acquired respiratory tract infection (CARTI) or skin and soft tissue infections (SSTI).

MATERIALS AND METHODS

Specimen Collection. The collection consisted of consecutively acquired, non-duplicate, patient isolates submitted from 93 participating medical centers representing 29 countries in four continents (Asia-Pacific, Europe, Latin America and North America) and included: *S. aureus* (5,077 strains), *S. pneumoniae* (1,585 strains), coagulase negative staphylococci (1,432 strains), and *Enterococcus* spp. (1,416 strains), ß-haemolytic streptococci (405 strains), and viridans streptococci (212 strains). Isolates were initially identified by the submitting laboratory and subsequently shipped to the monitoring laboratory (The JONES Group/JMI Laboratories, Iowa, USA) where identifications were confirmed and antimicrobial susceptibility testing was performed.

Susceptibility Testing. MIC values for tigecycline and comparator agents were tested using validated dry-form broth microdilution panels (TREK Diagnostics, Cleveland, OH) with cation-adjusted Mueller-Hinton medium. Five percent lysed horse blood was added for testing of streptococci. Testing, incubation and MIC interpretation were performed using the manufacturers recommendations and procedures from the NCCLS. Quality control strains utilized included *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619 and *E. faecalis* ATCC 29212.

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RESULTS

Table 1. Antimicrobial activity of tigecycline and nine selected agents tested against a worldwide collection of 10,127 Gram-positive cocci (2000 + 2002) using reference MIC methods [NCCLS, 2003].

	MIC (mg/L)		% by category	
Org. (no. tested)/Drug	50%	90%	Sus.	Res.
S. aureus				
oxacillin-susceptible (3,196)				
Tigecycline	0.25	0.5	(100.0)[a]	-[b]
Tetracycline	≤4	≤4	94.1	5.4
Doxycycline	≤0.5	≤0.5	98.6	1.4
Erythromycin	0.25	>8	78.9	19.5
Clindamycin	0.12	0.12	95.9	3.9
Quinupristin/Dalfopristin	0.25	0.5	99.9	0.0
Ciprofloxacin	0.25	1	92.5	4.4
Chloramphenicol	8	8	96.3	0.8
Linezolid	2	2	100.0	-[b]
Vancomycin	1	1	100.0	0.0
oxacillin-resistant (1,881)				
Tigecycline	0.25	0.5	(100.0)[a]	-[b]
Tetracycline	≤4	>8	77.4	22.0
Doxycycline	≤0.5	>4	83.0	17.0
Erythromycin	>8	>8	7.7	92.1
Clindamycin	>8	>8	28.3	71.6
Quinupristin/Dalfopristin	0.5	1	99.4	0.3
Ciprofloxacin	>2	>2	9.8	89.4
Chloramphenicol	8	>16	75.9	10.6
Linezolid	2	2	99.9	-[b]
Vancomycin	1	2	100.0	0.0
Coagulase-negative staphylococci				
oxacillin-susceptible (321)				
Tigecycline	0.25	0.5	(100.0)[a]	-[b]
Tetracycline	≤4	>8	85.6	13.5
Doxycycline	≤0.5	2	94.7	5.3
Erythromycin	0.25	>8	65.4	33.7
Clindamycin	≤0.06	0.12	92.8	6.8
Quinupristin/Dalfopristin	0.25	0.5	100.0	0.0
Ciprofloxacin	≤0.25	>2	87.8	11.3
Chloramphenicol	4	8	99.1	0.9
Linezolid	1	1	100.0	-[b]
Vancomycin	1	2	100.0	0.0
oxacillin-resistant (1,111)				
Tigecycline	0.25	0.5	(100.0)[a]	-[b]
Tetracycline	≤4	>8	80.6	19.2
Doxycycline	1	>4	87.7	12.3
Erythromycin	>8	>8	23.8	76.7
Clindamycin	0.12	>8	54.5	45.2
Quinupristin/Dalfopristin	0.25	0.5	98.5	0.5
Ciprofloxacin	>2	>2	37.2	61.0
Chloramphenicol	4	>16	84.3	15.1
Linezolid	1	1	100.0	-[b]
Vancomycin	2	2	100.0	0.0
Enterococcus spp.				
vancomycin-susceptible (1,294)				
Tigecycline	0.25	0.5	(100.0)[a]	-[b]
Tetracycline	>8	>8	38.4	61.3
Doxycycline	>4	>4	45.8	54.2
Ampicillin	≤2	>16	88.8	11.2
Chloramphenicol	8	>16	83.8	13.7
Gentamicin	≤500	>1000	69.2	30.8
Streptomycin	≤1000	>2000	64.5	35.5
Quinupristin/Dalfopristin	>2	>2	12.5	79.1
Linezolid	2	2	99.8	0.0
Teicoplanin	≤2	≤2	100.0	0.0
vancomycin-resistant (122)				
Tigecycline	0.12	0.25	(100.0)[a]	-[b]
Tetracycline	>8	>8	45.0	54.2
Doxycycline	4	>4	50.0	50.0
Ampicillin	>16	>16	32.0	68.0
Chloramphenicol	8	>16	83.6	11.5
Gentamicin	1000	>1000	46.7	53.3
Streptomycin	>2000	>2000	36.1	63.9
Quinupristin/Dalfopristin	1	>8	62.3	29.5
Linezolid	2	2	99.2	0.8
Teicoplanin	>16	>16	26.2	66.4

	MIC (mg/L)		% by category	
Org. (no. tested)/Drug	50%	90%	Sus.	Res.
S. pneumoniae				
penicillin-susceptible (1,126)				
Tigecycline	≤0.12	≤0.12	(100.0)[a]	-[b]
Tetracycline	≤4	>8	87.3	12.7
Amoxicillin/Clavulanate	≤2	≤2	99.9	0.1
Ceftriaxone	≤0.25	≤0.25	99.6	0.1
Erythromycin	≤0.25	>8	87.7	11.1
Clindamycin	≤0.06	≤0.06	94.3	5.4
Quinupristin/Dalfopristin	0.5	0.5	100.0	0.0
Levofloxacin	1	1	98.9	1.1
Linezolid	1	1	100.0	-[b]
Vancomycin	0.25	0.5	100.0	-[b]
penicillin-intermediate (227)				
Tigecycline	≤0.12	≤0.12	(100.0)[a]	-[b]
Tetracycline	≤4	>8	62.4	37.4
Amoxicillin/Clavulanate	≤2	≤2	95.6	0.0
Ceftriaxone	≤0.25	0.5	99.6	0.4
Erythromycin	0.5	>32	49.8	47.1
Clindamycin	≤0.06	>8	74.6	25.0
Quinupristin/Dalfopristin	0.5	0.5	100.0	0.0
Levofloxacin	1	1	98.2	1.8
Linezolid	1	1	100.0	-[b]
Vancomycin	0.25	0.5	99.6	-[b]
penicillin-resistant (232)				
Tigecycline	≤0.12	≤0.12	(100.0)[a]	-[b]
Tetracycline	≤4	>8	47.0	53.0
Amoxicillin/Clavulanate	2	4	42.4	9.9
Ceftriaxone	1	1	91.8	3.4
Erythromycin	4	>32	28.9	69.8
Clindamycin	≤0.06	>8	65.9	32.3
Quinupristin/Dalfopristin	0.5	0.5	100.0	0.0
Levofloxacin	1	1	98.7	1.3
Linezolid	1	1	100.0	-[b]
Vancomycin	0.25	0.5	100.0	-[b]
viridans group streptococci				
penicillin-susceptible (161)				
Tigecycline	≤0.12	≤0.12	(100.0)[a]	-[b]
Tetracycline	≤4	>8	75.6	24.4
Amoxicillin/Clavulanate	≤2	≤2	100.0	0.0
Ceftriaxone	≤0.25	≤0.25	98.8	0.6
Erythromycin	≤0.06	>8	73.9	22.4
Clindamycin	≤0.06	0.25	90.6	6.2
Quinupristin/Dalfopristin	0.5	1	97.5	0.0
Levofloxacin	1	2	96.9	3.1
Linezolid	1	1	100.0	-[b]
Vancomycin	0.5	1	100.0	-[b]
penicillin-intermediate (43)				
Tigecycline	≤0.12	0.25	(100.0)[a]	-[b]
Tetracycline	8	>8	46.5	53.5
Amoxicillin/Clavulanate	≤2	≤2	0.0	0.0
Ceftriaxone	0.5	2	81.4	7.0
Erythromycin	1	>8	41.9	53.5
Clindamycin	≤0.06	>8	76.7	20.9
Quinupristin/Dalfopristin	0.5	1	100.0	0.0
Levofloxacin	1	>4	86.0	11.6
Linezolid	1	1	100.0	-[b]
Vancomycin	0.5	1	100.0	-[b]
penicillin-resistant (8)				
Tigecycline	≤0.12	-	(100.0)[a]	-[b]
Tetracycline	≤4	-	50.0	50.0
Amoxicillin/Clavulanate	≤2	-	0.0	100.0
Ceftriaxone	4	-	25.0	62.5
Erythromycin	1	-	25.0	62.5
Clindamycin	≤0.06	-	87.5	12.5
Quinupristin/Dalfopristin	0.5	-	100.0	0.0
Levofloxacin	1	-	100.0	0.0
Linezolid	1	-	100.0	-[b]
Vancomycin	0.5	-	100.0	-[b]

	MIC (mg/L)		% by category	
Org. (no. tested)/Drug	50%	90%	Sus.	Res.
ß-haemolytic streptococci (405)				
Tigecycline	≤0.12	≤0.12	(100.0)[a]	-[b]
Tetracycline	>8	>8	45.8	54.2
Penicillin	≤0.016	0.06	99.8	-[b]
Ceftriaxone	≤0.25	≤0.25	100.0	-[b]
Erythromycin	≤0.06	2	82.7	16.8
Clindamycin	≤0.06	≤0.06	93.8	5.9
Quinupristin/Dalfopristin	0.25	0.5	100.0	0.0
Levofloxacin	0.5	1	98.0	1.2
Linezolid	1	1	100.0	-[b]
Vancomycin	0.5	0.5	100.0	-[b]

a. % susceptible if the tetracycline breakpoint was applied to tigecycline.
b. No breakpoints have been established by the NCCLS [2004].

Table 2. Tigecycline MIC distributions for a collection of 10,127 organisms (worldwide; 2000 + 2002).

	Occurrences (cumulative % inhibited) at MIC in mg/L:						
Organism (no. tested)	≤0.12	0.25	0.5	1	2	4	8
Staphylococcus aureus (5,077)	1858(36.6)	1755(71.2)	1372 (98.2)	90(99.9)	2(100.0)	-	-
Coagulase-negative staphylococci (1,432)	396(27.6)	447(58.8)	496 (93.4)	88(99.5)	7(100.0)	-	-
Enterococcus spp. (1,416)	687(48.5)	443(79.8)	278 (99.4)	7(99.9)	1(100.0)	-	-
Streptococcus pneumoniae (1,585)	1554(98.0)	19(99.2)	10 (99.9)	2(100.0)	-	-	-
ß-haemolytic streptococci (405)	389(96.0)	15(99.8)	1 (100.0)	-	-	-	-
viridans group streptococci (212)	199(93.9)	7(97.2)	5 (99.5)	1(100.0)			

- Both oxacillin-susceptible and –resistant subsets of *S. aureus* and coagulase-negative staphylococci remained fully suceptible to tigecycline, with MIC_{50} and MIC_{90} results remaining unchanged at 0.25 mg/L and 0.5 mg/L, respectively (Table 1). All staphylococci were inhibited at 2 µg/m or less of tigecycline.
- Co-resistance was observed, however, among tetracyclines, macrolides, clindamycin and fluoroquinolones within the subsets of oxacillin-resistant strains of staphylococci.
- Tigecycline was also the most active agent tested against both vancomycin-susceptible and -resistant strains of enterococci (MIC_{90}, 0.5 and 0.25 mg/L, respectively) with linezolid (MIC_{90}, 2 mg/L/susceptibility ≥99.2%) and chloramphenicol (MIC_{90}, >16 mg/L/susceptibility ≥83.6%) also remaining unchanged.
- MIC_{50} and MIC_{90} results for *S. pneumoniae* were ≤0.12 mg/L, with no co-resistance evident among penicillin-non-susceptible strains. Co-resistance, however, was evident with tetracycline, ß-lactams, erythromycin, and clindamycin, but was lacking for quinupristin/dalfopristin, levofloxacin, linezolid and vancomycin (all ≥ 98.2% susceptible).
- Tigecycline demonstrated potent activity against viridans group streptococci and ß-haemolytic streptococci with an MIC_{50} and MIC_{90} of ≤0.12 mg/L for both groups. In contrast, the corresponding MIC values for tetracycline were ≤4 and >8 mg/L. Co-resistance to tigecycline with penicillin non-susceptible strains was not observed.
- Tigecycline and linezolid were the only two agents that exhibited comprehensive coverage (100% of isolates susceptible) of all *S. pneumoniae*, viridans group streptococci and ß-haemolytic streptococci strains.

CONCLUSIONS

- Tigecycline displays a remarkable spectrum of activity and potency against susceptible and resistance subsets of staphylococci, streptococci and enterococci with the highest MIC_{90} being only 0.5 mg/L.
- Whereas the activity of tetracycline and doxycycline markedly decreased in various resistant organism subsets, tigecycline in vitro activity was unaffected and potent.
- These findings confirm that tigecycline retains the truly broad-spectrum of the tetracycline class while enhancing potency.
- Tigecycline also incorporates stability to the commonly occurring tetracycline resistance mechanisms, making it an attractive candidate for continued clinical development against these pathogens, including sampled isolates from Europe.