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Activity of Tigecycline Tested Against an International Collection (2000-2004) of Resistant Bacterial Pathogens

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AMENDED ABSTRACT

Objective:
To evaluate the activity and potency of tigecycline (TIG) when tested against a large international collection of common bacterial pathogens displaying increasing and worrisome resistance (R) profiles. TIG is a novel glycylcycline derivative of minocycline that has demonstrated activity against a variety of Gram-positive and -negative pathogens, making it an attractive candidate for treatment of community-acquired pneumonia, mixed aerobic/anaerobic infections and SSTI.

Methods:
Non-duplicate clinically-significant bacterial isolates (12,068 strains) were collected from 2000 to 2004 in >70 medical centers participating in the global TIG surveillance program. Isolates originated from North America (39%); Europe (41%); Latin America (18%); and Asia-Australia (2%). All isolates were tested using NCCLS broth microdilution methods against TIG and representative comparator agents including ciprofloxacin (CIP) and tetracycline (TET).

Results:
TIG results for the R organism subsets are in the Table:

	MIC (mg/L)		% inhibited at MIC (mg/L)		
Organism (no. tested)	50%	90%	≤1	≤2	≤4
S. aureus (SA)					
Oxacillin-R (3,867)	0.25	0.5	>99	100	-
TET-R (1,138)	0.25	0.5	>99	100	-
Coag neg staphylococci (CoNS)					
Oxacillin-R (2,557)	0.25	0.5	>99	100	-
TET-R (598)	0.25	0.5	>99	100	-
Enterococcus spp. (ESP)					
Van A (520)	≤0.12	0.25	100	-	-
Van B (95)	≤0.12	0.25	100	-	-
S. pneumoniae (SPN)					
Penicillin-R (570)	≤0.12	0.12	100	-	-
CIP-R (171)	≤0.12	0.25	100	-	-
TET R (733)	≤0.12	≤0.12	100	-	-
Viridans group streptococci (VGS)					
Penicillin-R (26)	≤0.12	≤0.12	100	-	-
Enterobacteriaceae (ENT)					
TET-R (2,829)	0.5	4	77	88	98
CIP-R (1,055)	0.25	2	82	91	98
E. coli ESBL (279)	0.25	0.5	>99	>99	100
Klebsiella spp. ESBL (317)	0.5	2	86	95	100
Total % Inhibited	-	-	94	97	>99

TIG was highly active (MIC$_{50}$ and $_{90}$, ≤ 0.25 and ≤ 0.5 mg/L, respectively) against all resistant SA, CoNS, ESP, SPN and VGS with >99% of strains inhibited by ≤ 2 mg/L. While potency of TIG against R subsets of ENT was less (MIC$_{50}$ and $_{90}$, ≤ 0.5 and ≤ 4 mg/L, respectively), the vast majority of TET-R isolates remained S to TIG (>98% of isolates were inhibited by ≤ 4 mg/L). No geographic differences in TIG potency among ESBL-producing, CIP-R or TET-R ENT strains were noted.

Conclusions:
Among R subsets of commonly occurring pathogens, 97% were inhibited by ≤ 2 mg/L of TIG and >99% were inhibited by ≤ 4 mg/L (the current NCCLS breakpoint for TET). TIG is highly stable to most TET-R determinants, including protected ribosomes and efflux mechanisms, and may represent a superior choice among parenteral agents for broad-spectrum coverage, including the most commonly occurring- and problematic-R phenotypes.

INTRODUCTION

The 9-t-butylglycylamido derivative of minocycline, tigecycline (formerly GAR-936), has become the sentinel representative of a new class known as the glycylcyclines. This agent is currently undergoing extensive clinical evaluation as a parenteral agent because of its potent activity against a broad range of commonly occurring species, including many resistant organisms such as penicillin-resistant *Streptococcus pneumoniae* (PRSP), oxacillin-resistant staphylococci (ORSA), vancomycin-resistant enterococci (VRE), and extended-spectrum ß-lactamase (ESBL) producing strains of Enterobacteriaceae. Tigecycline is also active against *Haemophilus influenzae, Moraxella catarrhalis*, pathogenic *Neisserias* and many other Gram-negative species.

Tigecycline offers important advantages to existing antimicrobials including enhanced spectrum of activity and stability against tetracycline resistance mechanisms (Tet A or B efflux determinants and Tet M or O ribosomal protection factors). Its mode of action on bacterial ribosomes shows identical and overlapping binding sites when compared to tetracycline, but the position 9 substitution of tigecycline provides additional steric hindrance features and resulting greater spectrum of activity.

In this study, we evaluated the in vitro activity of tigecycline against a total of over 12,000 Gram-positive and -negative bacterial isolates, collected between 2000 and 2004, recovered predominantly from patients with bloodstream, respiratory tract, skin and soft tissue and urinary tract infections. The collection consisted of those common pathogens displaying the most worrisome and increasingly recognized resistance profiles.

MATERIALS AND METHODS

To assess the spectrum of activity and potency of tigecycline, recent clinical isolates submitted to a reference laboratory (JMI Laboratories, North Liberty, IA) were examined. A total of 12,068 Gram-positive and –negative bacterial isolates recovered from patients were processed. Consecutively acquired, non-duplicate, patient isolates were submitted from > 70 participating medical centers representing 29 countries in Asia - Australia (2% of strains), Europe (41%), South America (18%) and North America (39%).

Isolates were identified by the submitting laboratory and confirmed by the monitoring facility using colonial characteristics on standard media, rapid tests (catalase, oxidase, coagulase, bile solubility, latex agglutination kits), and use of an automated identification system (Vitek bioMerieux, Hazelwood, MO), among others methods, as necessary. The collection consisted of those species and resistant subsets as specified in Table 1.

MIC values were determined for a variety of antimicrobials including tetracycline and tigecycline using validated, dry-form broth microdilution panels with cation-adjusted Mueller-Hinton medium (TREK Diagnostics Inc., Cleveland, OH). Antimicrobials tested included those classes and examples of drugs most commonly used for the empiric or directed treatment of the indicated infection. When testing *Streptococcus spp.*, supplemental lysed horse blood (2-5%) was added. Testing, incubation and MIC interpretation were performed using the manufacturers recommendations and/or recommendations from the Clinical Laboratory Standards Institute (CLSI; formerly NCCLS) [NCCLS, 2003; CLSI, 2005]. Quality control was performed using American Type Culture Collection (ATCC) strains including *Escherichia coli* ATCC 25922 and 35218, *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619.

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RESULTS

- Among a large collection of oxacillin-resistant staphylococci (*S. aureus* and coagulase-negative staphylococci), 100% of strains were inhibited by ≤ 2 mg/L; tigecycline and daptomycin were the most potent agents tested (MIC$_{50}$ and MIC$_{90}$ values, 0.25 and 0.5 mg/L) followed in rank order of decreasing potency by quinupristin/dalfopristin, vancomycin and linezolid (Tables 1 and 2).

- Tigecycline was the most potent compound tested against vancomycin-resistant *Enterococcus* spp. (MIC$_{50}$ and MIC$_{90}$ values, 0.06 - 0.12 and 0.25 mg/L, respectively) and was ≥ eight-fold more potent than daptomycin, quinupristin/dalfopristin and linezolid. Differentiation of enterococci by vancomycin-resistance phenotype (VanA or VanB) had little effect on potency of tigecycline (Table 2) and all isolates were inhibited by 0.5 mg/L.

- All penicillin-resistant *S. pneumoniae* and viridans group streptococci were inhibited by ≤ 1 mg/L of tigecycline, which also displayed the highest potency among tested agents (MIC$_{50}$ and MIC$_{90}$ values, 0.06 and 0.12 - 0.25 mg/L, respectively).

- The vast majority of tetracycline-resistant and/or ciprofloxacin-resistant Enterobacteriaceae were also susceptible to tigecycline (greater than 98% of isolates were inhibited by ≤ 4 mg/L), confirming the stability of tigecycline to the common tetracycline-resistance determinants.

- Tigecycline was also highly active against extended-spectrum ß-lactamase producing isolates of *E. coli* and *Klebsiella* spp. with ≥ 95% of isolates being inhibited by 2 mg/L and 100% being inhibited by 4 mg/L; only imipenem displayed greater potency against *Klebsiella* spp.

- Geographic differences in tigecycline potency among ESBL-producing, ciprofloxacin-resistant or tetracycline-resistant Enterobacteriaceae were not noted.

Table 1. Cumulative frequency distributions for Gram-positive and -negative resistant bacterial subsets (12,068 strains; 2000 - 2004) tested against tigecycline.

	MIC (mg/L)		% inhibited at MIC (mg/L)							
Organism (no. tested/% of total)	50%	90%	≤0.12	0.25	0.5	1	2	4	8	≥16
S. aureus (SA)										
Oxacillin-R (3,867)	0.25	0.5	44	81	98	99	100	-	-	-
Tetracycline-R (1,138)	0.25	0.5	34	75	97	99	100	-	-	-
Coag.-neg. staphylococci (CoNS)										
Oxacillin-R (3,867)	0.25	0.5	42	75	97	99	100	-	-	-
Tetracycline-R (1,138)	0.25	0.5	32	62	90	99	100	-	-	-
Enterococcus spp. (ESP)										
Van A (520)	≤0.12	0.25	75	98	100	-	-	-	-	-
Van B (95)	≤0.12	0.25	66	97	100	-	-	-	-	-
S. pneumoniae (SPN)										
Penicillin-R (570)	≤0.12	0.12	94	96	98	100	-	-	-	-
Ciprofloxacin-R (171)	≤0.12	0.25	88	93	98	100	-	-	-	-
Tetracycline-R (733)	≤0.12	≤0.12	95	98	99	100	-	-	-	-
viridans group streptococci (VGS)										
Penicillin-R (26)	≤0.12	≤0.12	92	100	-	-	-	-	-	-
Enterobacteriaceae (ENT)										
Tetracycline-R (2,829)	0.5	4	21	50	66	77	88	98	99	100
Ciprofloxacin-R (1,055)	0.25	2	18	51	70	82	91	98	99	100
E. coli ESBL (279)	0.25	0.5	28	76	98	99	99	100	-	-
Klebsiella spp. ESBL (317)	0.5	2	1	22	67	86	95	100	-	-

Table 2. Antimicrobial activity of tigecycline and selected comparators tested against various resistant bacterial subsets selected from a population of 12,068 strains (2000 - 2004).

	MIC (mg/L)			% category:[a]	
Organism (no. tested/antimicrobial agent	50%	90%	Range	Susceptible	Resistant
S. aureus					
Oxacillin-resistant (3,867)					
Tigecycline	0.25	0.5	≤0.12-2	-[b]	-[b]
Tetracycline	≤4	>8	≤4->8	80.1	19.2
Erythromycin	>8	>8	0.016->8	9.4	91.2
Clindamycin	>8	>8	≤0.06->8	32.3	67.5
Ciprofloxacin	>4	>4	≤0.25->4	9.9	89.7
Daptomycin	0.25	0.5	≤0.12-1	100.0	-[b]
Quinupristin/Dalfopristin	0.5	1	≤0.25->2	99.6	0.2
Linezolid	2	2	≤0.25-16	99.9	-[b]
Vancomycin	1	1	≤0.12-4	100.0	0.0
Coagulase-negative staphylococci					
Oxacillin-resistant (2,557)					
Tigecycline	0.25	0.5	≤0.12-2	-[b]	-[b]
Tetracycline	≤4	>8	≤4->8	81.8	17.8
Erythromycin	>8	>8	≤0.06->8	22.8	76.6
Clindamycin	0.25	>8	≤0.06->8	52.7	46.7
Ciprofloxacin	4	>4	≤0.25->4	32.3	63.9
Daptomycin	0.25	0.5	≤0.12-2	99.9	-[b]
Quinupristin/Dalfopristin	≤0.25	0.5	≤0.25->2	98.9	0.4
Linezolid	1	1	≤0.25-2	100.0	-[b]
Vancomycin	2	2	≤0.12-4	100.0	0.0
Enterococcus spp.					
VanA phenotype (520)					
Tigecycline	0.06	0.25	≤0.12-0.5	-[b]	-[b]
Tetracycline	>8	>8	≤4->8	38.3	60.6
Ampicillin	>16	>16	≤2->16	15.8	84.2
Chloramphenicol	8	8	≤2->16	91.5	6.2
Gentamicin	1000	>1000	≤500->1000	49.0	51.0
Streptomycin	>2000	>2000	≤1000->2000	28.1	71.9
Daptomycin	2	4	0.06-4	100.0	-[b]
Quinupristin/Dalfopristin	1	>2	≤0.25->2	79.8	16.9
Linezolid	2	2	0.5->8	98.5	1.2
VanB phenotype (95)					
Tigecycline	0.12	0.25	≤0.12-0.5	-[b]	-[b]
Tetracycline	4	>8	≤4->8	50.0	50.0
Ampicillin	2	>16	≤2->16	56.8	43.2
Chloramphenicol	8	>16	4->16	74.7	21.1
Gentamicin	1000	>1000	≤500->1000	48.4	51.6
Streptomycin	>2000	>2000	≤1000->2000	33.7	76.3
Daptomycin	1	2	0.12-4	100.0	-[b]
Quinupristin/Dalfopristin	>2	>2	≤0.25->2	45.3	53.7
Linezolid	1	2	0.5-2	100.0	0.0
S. pneumoniae					
Penicillin-resistant (570)					
Tigecycline	0.06	0.12	≤0.12-1	-[b]	-[b]
Tetracycline	8	>8	≤4->8	43.8	50.3
Amoxicillin/Clavulanate	2	8	≤2->8	69.6	16.7
Ceftriaxone	1	2	≤0.25->32	88.6[c]	4.4[c]
Erythromycin	4	>32	≤0.25->8	32.3	77.0
Clindamycin	≤0.25	>2	≤0.25->2	61.5	36.9
Levofloxacin	1	1	0.5->4	99.3	0.7
Quinupristin/Dalfopristin	≤0.5	≤0.5	≤0.5-1	100.0	0.0
Linezolid	1	1	≤0.25-2	100.0	-[b]
Vancomycin	0.25	0.5	0.12-1	100.0	-[b]
viridans group streptococci					
Penicillin-resistant (26)					
Tigecycline	0.06	0.25	≤0.12-0.25	-[b]	-[b]
Tetracycline	4	>8	≤4->8	46.2	30.8
Ceftriaxone	4	8	≤0.25-16	19.2	61.5
Erythromycin	1	4	≤0.06->8	19.2	69.2
Clindamycin	≤0.06	>8	≤0.06->8	88.5	11.5
Levofloxacin	1	2	0.25-2	100.0	0.0
Quinupristin/Dalfopristin	0.5	1	≤0.25-2	96.2	0.0
Linezolid	1	1	0.12-2	100.0	-[b]
Vancomycin	0.5	1	0.25-1	100.0	-[b]

a. Categorical breakpoints those of CLSI (formerly NCCLS) M100-S15 [2005].
b. Breakpoints have not been established by CLSI.
c. Defined by CLSI [2005] as ceftriaxone or ceftazidime or aztreonam MIC values of ≥ 2 mg/L.

	MIC (mg/L)			% category:[a]	
Organism (no. tested/antimicrobial agent	50%	90%	Range	Susceptible	Resistant
E. coli					
ESBL-phenotype (279)[c]					
Tigecycline	0.25	0.5	0.03-4	-[b]	-[b]
Tetracycline	>8	>8	≤2->8	30.8	68.8
Minocycline	2	>8	≤0.25->8	70.2	19.1
Ceftazidime	8	>16	≤1->16	52.0	30.1
Ceftriaxone	32	>32	≤0.25->32	40.5	49.5
Cefepime	4	>16	≤0.12->16	59.1	33.0
Piperacillin/Tazobactam	8	>64	≤0.5->64	77.4	10.4
Aztreonam	16	>16	≤0.12->16	47.3	44.4
Imipenem	0.5	0.5	≤0.5-8	99.3	0.0
Ciprofloxacin	>4	>4	≤0.03->4	38.7	61.3
Gentamicin	≤2	>8	≤2->8	57.0	39.4
Klebsiella spp.					
ESBL-phenotype (317)[c]					
Tigecycline	0.5	2	0.12-4	-[b]	-[b]
Tetracycline	4	>8	≤2->8	57.4	36.3
Minocycline	4	>8	≤0.25->8	61.0	25.0
Ceftazidime	16	>16	≤1->16	38.5	49.8
Ceftriaxone	>32	>32	≤0.25->32	24.0	52.7
Cefepime	8	>16	≤0.12->16	57.7	34.4
Piperacillin/Tazobactam	32	>64	≤0.5->64	48.3	42.3
Aztreonam	>16	>16	≤0.12->16	27.1	63.7
Imipenem	≤0.5	≤0.5	≤0.5->8	98.4	1.3
Ciprofloxacin	0.5	>4	≤0.03->4	57.3	34.5
Gentamicin	>8	>8	≤2->8	38.3	66.0

CONCLUSIONS

- Among resistant subsets of staphylococci, streptococci, enterococci and Enterobacteriaceae, 97% of the 12,068 strains were inhibited by ≤ 2 mg/L of tigecycline and > 99% were inhibited by ≤ 4 mg/L (the current CLSI breakpoint for tetracycline).

- Tigecycline remains highly stable to most tetracycline-resistance determinants, including protected ribosomes and efflux mechanisms that are found in both Gram-positive and –negative pathogens.

- This agent, currently under FDA consideration for approval (with Priority Review status), may represent a superior choice among parenteral agents for broad-spectrum coverage in cases of skin and soft tissue infection and intra-abdominal infection, including the most commonly occurring - and problematic – resistance phenotypes.