

Tigecycline In Vitro Activity in an Out-patient vs. In-patient Global Population

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REVISED ABSTRACT

Background: Tigecycline, a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent broad spectrum activity against most commonly encountered species responsible for community and hospital acquired infections. The T.E.S.T. program determined the in vitro activity of tigecycline compared to most commonly prescribed broad spectrum antimicrobials against gram negative and gram positive species collected from hospitals globally throughout 2004-2006. **Methods:** A total of 25,134 clinical isolates were identified to the species level at each site and confirmed by the central laboratory. Minimum Inhibitory Concentration (MICs) were determined by each site using supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results:** Results are in the table as follows*:

Enterobacteriaceae				Acinetobacter spp.			
In patients	Out patients	In patients	Out patients	In patients	Out patients	In patients	Out patients
(n=7,879)	(n=1,984)	(n=1,391)	(n=278)	%S	MIC ₅₀	%S	MIC ₅₀
Tigecycline	96.1	97.4	1	98.5	1	99.3	1
Amikacin	98.9	4	99.3	4	77.1	>64	89.2
Cefepime	95.2	4	97.6	1	47.4	>32	66.2
Ceftazidime	84.8	32	91.1	8	46.7	>32	66.5
Imipenem	100.0	1	99.0	1	83.0	16	92.4
Levofloxacin	85.3	8	88.4	4	49.7	>8	68.0
Minocycline	85.0	8	86.1	8	89.1	8	92.8
PipTazo	89.0	32	93.9	8	56.6	>128	76.3

*Tigecycline susceptibility defined according to FDA package insert (Tygactl[®], 2005) where available. Tigecycline Acinetobacter susceptibility breakpoint defined as ≤ 2 mcg/mL for comparative purposes only.

Conclusion: Tigecycline's in vitro activity was comparable to or greater than most commonly prescribed antimicrobials without any demonstrable change in activity between in- and out-patient bacterial study strains. The presented data suggest that tigecycline may be an effective and reliable therapeutic option against nosocomial or community pathogens.

INTRODUCTION

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycylcyclines. This synthetic analogue of the tetracyclines exhibits significant antibacterial activity that is both bacteriostatic and, in certain instances, bactericidal with killing activity that is as much as fourfold better than vancomycin and daptomycin [1, 2]. The development of tigecycline is important in that tigecycline and other glycylcyclines are active against bacterial strains carrying either or both of the two major forms of tetracycline resistance: efflux and ribosomal protection. Certain substituents at the 9-position of the tetracycline molecule restored activity against bacteria harboring genes encoding either or both efflux and ribosomal protection. A single chemical modification of tigecycline overcomes the two molecularly distinct forms of resistance while maintaining activity against susceptible gram-positive, gram-negative, aerobic, and anaerobic bacteria [3]. Furthermore, resistance to tigecycline is difficult to produce even in the laboratory.

Previous studies have demonstrated excellent in vitro activity for tigecycline against clinical and laboratory strains of Gram-positive and -negative bacteria with minimum inhibitory concentrations for the 90th percentile inhibited at or below 2 mcg/mL, including difficult to treat methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococci* (VRE) and extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* [4-6]. This study was undertaken to document the in vitro activity of tigecycline against significant numbers of clinical isolates collected worldwide from in-patient and out-patient populations. This study is part of the larger ongoing Global Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program.

MATERIALS & METHODS

All isolates were derived from blood, respiratory tract, urine, skin, wound, body fluids and other defined sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected and tested between 2004 to 2006 from 150 study centers

in 27 countries. Isolates were identified to the species level and tested at each site by the participating laboratory. Organism collection, transport, confirmation of organism identification, as well as, development and management of a centralized database was coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc. located in Schaumburg, IL, USA.

All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age or gender. All sites identified each study isolate utilizing local laboratory site criteria. Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [7]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturer, MicroScan (Dade Behring Inc., Sacramento, CA, USA). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in mcg/mL): amikacin (0.5-64); amoxicillin/clavulanic acid (0.12/0.06-32/16); ampicillin (0.5-32, Gram-negative panel) and (0.06-16, Gram-positive panel); cefepime (0.5-32); ceftioxone (0.06-64); ceftazidime (8-32); imipenem (0.06-16); linezolid (0.5-8); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16); penicillin (0.06-8); piperacillin/tazobactam (0.06/4-128/4) and vancomycin (0.12-32). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [8] and recent US Food and Drug Administration packaging insert for tigecycline [9], where applicable.

Escherichia coli, *Klebsiella pneumoniae* and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftioxone were >1 mcg/ml using broth microdilution panels. ESBL activity was confirmed using the CLSI (2005) phenotypic confirmatory disk test (Oxoid, Ogdensburg, NY, USA) on Mueller-Hinton agar (Remel Inc., Lenexa, KS, USA) according to CLSI (2005) guidelines. ESBL presence was confirmed by testing the following antibiotic disks: cefotaxime (30-mcg), cefotaxime/clavulanic acid (30/10-mcg) and ceftazidime (30-mcg), ceftazidime/clavulanic acid (30/10-mcg). Antimicrobial disks were manufactured by Oxoid, Inc. (Ogdensburg, NY, USA). Mueller-Hinton agar used in testing was manufactured by Remel, Inc. (Lenexa, KS, USA). An organism was interpreted as containing an ESBL if there was an increase of >5 mm in the inhibition zone of the combination disk when compared to that of the cephalosporin alone.

Quality controls (QC) were performed by each testing site on each day of testing using the corresponding ATCC control strains: *E. coli* ATCC 25922; *E. coli* ATCC 35218; *H. influenzae* ATCC 49766; *H. influenzae* ATCC 49247; *S. aureus* ATCC 29213; *Pseudomonas aeruginosa* ATCC 27853; *Enterococcus faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2005) guidelines [8].

REFERENCES

- Hoellman, D.B., et al. *Antipneumococcal activities of GAR-936 (a new glycylcycline) compared to those of nine other agents against penicillin-susceptible and -resistant pneumococci*. Antimicrob Agents Chemother, 2000, 44(4): p. 1085-8.
- Labithavikul, P., P.J. Petersen, and P.A. Bradford. *In vitro activity of tigecycline against Staphylococcus epidermidis growing in an adherent-cell biofilm model*. Antimicrob Agents Chemother, 2003, 47(12): p. 3967-9.
- Projan, S.J., *Preclinical pharmacology of GAR-936, a novel glycylcycline antibiostat agent*. Pharmacotherapy, 2000, 20(9 Pt 2): p. 219S-223S; discussion 224S-228S.
- Gales, A.C. and R.N. Jones. *Antimicrobial activity and spectrum of the new glycylcycline, GAR-936 tested against 1,203 recent clinical bacterial isolates*. Diagn Microbiol Infect Dis, 2000, 36(1): p. 19-36.
- CLSI. *Performance Standards for Antimicrobial Susceptibility Testing*, in Document M100-S15, 2005 Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
- Patel, R., et al. *In vitro activity of GAR-936 against vancomycin-resistant enterococci, methicillin-resistant Staphylococcus aureus and penicillin-resistant Streptococcus pneumoniae*. Diagn Microbiol Infect Dis, 2000, 38(3): p. 177-9.
- Rupp, M.E. and P.D. Fey. *Extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae: considerations for diagnosis, prevention and drug treatment*. Drugs, 2003, 63(4): p. 353-65.
- CLSI. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*. Approved Standard-Sixth Edition, in Document M7-A6, 2005. Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
- Tygactl[®] Product Insert, 2005. Wyeth Pharmaceuticals, Inc., Philadelphia, PA, USA.

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RESULTS

Table 1. In Vitro Activity of Tigecycline and Comparative Antimicrobial Agents against Gram-Positive Clinical Pathogens Isolated from In-Patients and Out-Patients - Worldwide results.

Organism (N)	Drug	In-Patients		Out-Patients	
		MIC ₅₀	%Sus ^a	MIC ₅₀	%Sus ^a
<i>E. faecalis</i> In-Patient (n=1,024) Out-Patient (n=162)	Tigecycline	0.12	99.1	0.12	97.9
	AmoxClav	0.5	1	0.5	1
	Ampicillin	1	2	1	100.0
	Ceftioxone	>64	>64	na	>64
	Ceftazidime	>32	99.1	>32	60.5
	Linezolid	2	98.3	2	97.4
	Minocycline	8	43.8	8	38.5
	Penicillin	2	4	2	4
	PipTazo	2	4	2	na
	Vancomycin	1	2	95.9	1
Vancomycin Resistant <i>E. faecalis</i> In-Patient (n=28) Out-Patient (n=6)	Tigecycline	0.06	100.0	0.06	100.0
	AmoxClav	0.5	2	na	na
	Ampicillin	1	2	na	na
	Ceftioxone	>64	>64	na	na
	Levofloxacin	1	4	na	na
	Linezolid	1	2	100.0	na
	Minocycline	4	8	60.7	0.0
	Penicillin	2	8	100.0	na
	PipTazo	2	8	na	na
	Vancomycin	>32	>32	0.0	na
<i>E. faecium</i> In-Patient (n=408) Out-Patient (n=4)	Tigecycline	0.06	100.0	0.06	100.0
	AmoxClav	>64	>64	na	na
	Ampicillin	>64	>64	na	na
	Ceftioxone	>64	>64	na	na
	Levofloxacin	>32	>32	14.2	>32
	Linezolid	2	2	97.0	na
	Minocycline	>8	70.9	>25	73.5
	Penicillin	>8	15.6	>8	10.2
	PipTazo	>16	>16	na	na
	Vancomycin	4	4	90.1	23.2
<i>S. aureus</i> In-Patient (n=200) Out-Patient (n=26)	Tigecycline	0.06	100.0	0.06	100.0
	AmoxClav	>8	>8	na	na
	Ampicillin	>16	>16	na	na
	Ceftioxone	>64	>64	na	na
	Levofloxacin	>32	>32	1.5	>32
	Linezolid	2	2	97.0	2
	Minocycline	0.5	8	67.0	65.9
	Penicillin	>8	2.5	>8	na
	PipTazo	>16	>16	na	na
	Vancomycin	>32	>32	0.0	>32
<i>S. aureus</i> In-Patient (n=2,274) Out-Patient (n=437)	Tigecycline	0.12	99.1	0.12	99.2
	AmoxClav	1	99.2	1	99.7
	Ampicillin	16	87.1	16	10.8
	Ceftioxone	4	82.1	4	80.8
	Imipenem	0.25	8	86.5	93.1
	Linezolid	0.25	99.2	0.25	99.2
	Levofloxacin	2	4	100.0	2
	Minocycline	>25	95.9	>25	99.2
	Penicillin	>8	7.5	>8	7.3
	PipTazo	2	>16	66.8	>16
<i>S. aureus</i> , MRSA In-Patient (n=1,182) Out-Patient (n=170)	Tigecycline	0.12	99.4	0.12	98.9
	AmoxClav	1	2	99.2	1
	Ampicillin	4	16	16.8	na
	Ceftioxone	4	97.1	4	97.3
	Levofloxacin	0.25	99.4	0.25	99.5
	Linezolid	0.12	2	88.7	0.12
	Minocycline	>25	98.5	>25	98.9
	Penicillin	8	>8	14.0	8
	PipTazo	1	2	99.1	1
	Vancomycin	0.5	1	100.0	0.5
<i>S. aureus</i> , MRSA In-Patient (n=1,082) Out-Patient (n=307)	Tigecycline	0.12	98.1	0.12	98.6
	AmoxClav	8	>8	30.4	8
	Ampicillin	>16	>16	0.6	>16
	Ceftioxone	32	>64	9.2	>64
	Imipenem	0.5	>16	76.3	0.5
	Linezolid	0.25	4	92.8	0.25
	Levofloxacin	2	2	100.0	2
	Minocycline	>25	2	98.7	>25
	Penicillin	>8	0.5	>8	0.5
	PipTazo	16	>16	36.4	>16
<i>S. agalactiae</i> In-Patient (n=597) Out-Patient (n=44)	Tigecycline	0.03	100.0	0.03	100.0
	AmoxClav	0.06	100.0	0.06	100.0
	Ampicillin	0.12	100.0	0.06	100.0
	Ceftioxone	0.08	100.0	0.08	100.0
	Imipenem	>0.12	0.5	na	>0.12
	Levofloxacin	0.5	1	98.5	0.5
	Linezolid	1	1	100.0	1
	Minocycline	8	>8	na	>8
	Penicillin	0.06	0.12	100.0	0.06
	PipTazo	>25	>25	na	>25
<i>S. pneumoniae</i> In-Patient (n=1,124) Out-Patient (n=53)	Tigecycline	0.06	0.5	na	0.06
	AmoxClav	>0.03	2	95.2	>0.03
	Ampicillin	>0.06	2	na	>0.06
	Ceftioxone	>0.03	1	97.8	>0.03
	Imipenem	>0.12	0.5	80.4	>0.12
	Levofloxacin	0.5	1	99.9	0.5
	Linezolid	>0.5	1	100.0	>0.5
	Minocycline	>25	4	na	>25
	Penicillin	>0.06	2	63.3	>0.06
	PipTazo	>25	2	na	>25
Penicillin Resistant <i>S. pneumoniae</i> In-Patient (n=123) Out-Patient (n=75)	Tigecycline	0.03	0.5	na	0.03
	AmoxClav	2	8	59.2	2
	Ampicillin	4	8	58.7	4
	Ceftioxone	2	2	88.0	2
	Imipenem	0.5	1	0.0	0.5
	Linezolid	1	1	100.0	1
	Levofloxacin	0.5	1	100.0	0.5
	Minocycline	>25	8	na	>25
	Penicillin	0.25	1	100.0	0.25
	Vancomycin	0.25	2	na	0.25
<i>S. agalactiae</i> In-Patient (n=102) Out-Patient (n=12)	Tigecycline	0.03	0.5	na	0.03
	AmoxClav	2	8	58.7	2
	Ampicillin	4	8	58.7	4
	Ceftioxone	2	2	88.0	2
	Imipenem	0.5	1	0.0	0.5
	Linezolid	1	1	100.0	1
	Levofloxacin	0.5	1	100.0	0.5
	Minocycline	>25	8	na	>25
	Penicillin	0.25	2	na	0.25
	Vancomycin	0.25	2	na	0.25

^aMIC in mcg/mL.
^bInterpretive criteria as defined by CLSI, M100-S16 (2006), where available; Tigecycline susceptible breakpoint is according to FDA package insert (2005), where available [9]; Tigecycline FDA breakpoints (susceptible ≤ 0.25 mcg/mL) for *enterococci* are approved for vancomycin-susceptible *E. faecalis*, only; this criteria is applied to all *enterococci* for comparison purposes only; na = not available.
^cMIC₅₀ and MIC₉₀ values not calculated for species or phenotypic groups with n < 10. Species with aggregate n's < 20 are not shown.

Table 2. In Vitro Activity of Tigecycline and Comparative Antimicrobial Agents against Gram-Negative Clinical Pathogens Isolated from In-Patients and Out-Patients - Worldwide results.

Organism (N)	Drug	In-Patients		Out-Patients	
		MIC ₅₀	%Sus ^a	MIC ₅₀	%Sus ^a
Enterobacteriaceae In-Patient (n=7,879) Out-Patient (n=1,984)	Tigecycline	0.5	1	96.1	0.25
	Amikacin	2	4	98.9	2
	AmoxClav	16	>32	47.3	8
	Ampicillin	>32	>32	13.5	>32
	Cefepime	<0.5	4	95.2	<0.5
	Ceftazidime	<8	32	84.8	<8
	Ceftioxone	0.12	32	86.3	<0.6
	Imipenem	0.5	1	100.0	0.5
	Levofloxacin	0.06	8	86.3	0.06
	Minocycline	2	8	85.0	2
<i>E. aerogenes</i> In-Patient (n=538) Out-Patient (n=132)	Tigecycline	0.5	1	95.2	0.5
	Amikacin	2	4	99.4	2
	AmoxClav	>32	>32	4.1	>32
	Ampicillin	>32	>32	0.0	>32
	Cefepime	<0.5	2	96.3	<0.5
	Ceftazidime	<8	>32	75.5	<8
	Ceftioxone	0.12	16	87.7	