

Tigecycline Evaluation Surveillance Trial (T.E.S.T.) - In Vitro Antibacterial Activity against 9,063 Gram-positive and Gram-negative pathogens in the United States

#P 805

S. Bouchillon¹, T. Stevens¹, B. Johnson¹, J. Johnson¹, D. Hoban¹, A. Hsiung¹, M. Hackel¹, M. Person¹, M. Dowzicky²

¹International Health Management Associates, Schaumburg, IL, USA

²Wyeth Pharmaceuticals, Collegeville, PA, USA

IHMA, Inc.
2122 Palmer Dr.
Schaumburg, IL 60173
Tel: (847) 303-5003
Fax: (847) 303-5601
www.ihmainc.com

REVISED ABSTRACT

Background: Tigecycline, a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent expanded broad spectrum activity against most commonly encountered Gram-positive and Gram-negative species, including anaerobic pathogens responsible for community and hospital infections. The T.E.S.T. program determined the in vitro activity of tigecycline compared to amikacin, ampicillin, imipenem, cefepime, ceftazidime, ceftriaxone, levofloxacin, minocycline and piperacillin/tazobactam against Gram-negative strains in addition to linezolid, penicillin and vancomycin for the Gram-positive species. Isolates were collected from 44 hospitals in the United States throughout 2004. **Methods:** A total of 9,063 clinical isolates were identified to the species level at each participating site and confirmed by the central laboratory. Minimum Inhibitory Concentration (MICs) were determined by the local laboratory using supplied broth microdilution panels from Dade Behring and interpreted according to CLSI guidelines. **Results:** Tigecycline's activity was similar to imipenem against most *Enterobacteriaceae*. Tigecycline inhibited ESBL producers with a MIC equal or lesser than 2mcg/ml. Although similar to other classes of broad spectrum antimicrobial agents against non-fermenters, tigecycline was especially active against *Acinetobacter* spp. with the lowest MIC₉₀ of 1 mcg/ml. Tigecycline inhibited *S. aureus* with MIC₉₀ of 0.25 mcg/ml for both MSSA and MRSA isolates. Similar results were noticed against enterococci with a tigecycline MIC₉₀ of 0.12 mcg/mL that remained consistent regardless of vancomycin susceptibility. **Conclusion:** Tigecycline's in vitro activity was comparable or greater than most commonly prescribed antimicrobials against a broad spectrum of aerobic clinical pathogens. The presented data suggest that tigecycline may be an effective therapeutic option against many aerobic Gram-positive and Gram-negative pathogens, including ESBL, VRE and MRSA resistant phenotypes.

INTRODUCTION

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycylcyclines. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit. Although it is perceived to be bacteriostatic, its anti-bacterial activity is significant and has shown some bactericidal activity against key targeted pathogens [1,2]. Tigecycline was developed to provide activity against tetracycline and multi-drug-resistant Gram-positive pathogens and has demonstrated significant activity against aerobic and anaerobic Gram-positive and Gram-negative microorganisms [2-4].

Tigecycline resistance is very infrequent and is also difficult to induce in the laboratory [5, 6] with a selection frequency observed at less than 10⁻⁹ [3, 5, 7]. With the exception of *P. aeruginosa*, tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline [2-4, 7-11]. Tigecycline has shown to be a highly effective against multi-resistant *Acinetobacter* spp., particularly *A. baumannii* that are commonly associated with serious nosocomial infections. Similar activity has been observed against *Enterobacteriaceae*, even extended-spectrum β -lactamase (ESBL) producing strains [10]. Tigecycline has demonstrated MIC₉₀ values of \leq 0.5 mcg/ml against methicillin-resistant *Staphylococcus aureus* (MRSA) and other Gram-positive organisms [2, 4-6]. Tigecycline has shown potent activity against animal models infected with selected strains of multi-drug resistant *Enterococcus faecium* and *Enterococcus faecalis* [4, 5] with various genotypes van-A, -B and -C [6].

This study was designed to better define the in vitro activity of tigecycline in a large diverse population of clinical isolates collected from hospitals across the United States.

MATERIALS & METHODS

- All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, fluids and few other defined sources. Only one isolate per patient was accepted.
- 9,063 Clinical isolates were collected tested between January 2004 - December 2004 from 44 study centers in the United States.
- Custom broth microdilution panels were supplied by MicroScan (Dade MicroScan, Sacramento, CA, USA) with the following antimicrobial agents and concentrations (expressed in mcg/ml): amoxicillin/clavulanic acid (0.12-32); piperacillin/tazobactam (0.06-128); levofloxacin (0.008-8); ceftriaxone (0.06-64); ceftazidime (0.5-32); ampicillin (0.5-32); amikacin (0.5-64); minocycline (0.5-16); cefepime (8-32); tigecycline (0.008-16) and imipenem (0.06-16).
- MIC interpretive criteria followed published guidelines established by the CLSI where applicable [12]. Tigecycline tentative breakpoints (in units of mcg/mL) are defined as susceptible \leq 2; intermediate = 4; and resistant \geq 8.
- Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution.
- Quality control of broth microdilution panels followed manufacturer's and NCCLS guidelines using the following ATCC strains: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922; *Haemophilus influenzae* ATCC 49247; *Haemophilus influenzae* ATCC 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619 and *Pseudomonas aeruginosa* ATCC 27853.
- The collection and transportation of organisms and the confirmation of identification, as well as, construction and management of a centralized database were conducted and coordinated by Laboratories International for Microbiology Studies (LIMS), a subsidiary of International Health Management Associates, Inc. (IHMA, Schaumburg, IL).

ACKNOWLEDGEMENTS

This study was supported by a grant from Wyeth Pharmaceuticals. We gratefully acknowledge contributors to the T.E.S.T. study from the following participating institutions: Laboratory Sciences of Arizona, AZ; Scottsdale Healthcare - Shea, AZ; UCLA Medical Center, CA; Shands Hospital University of Florida, FL; Jackson Memorial, FL; Bayfront Medical Center, FL; Wellstar Kennestone Hospital, GA; Ochsner Clinic Foundation, LA; LSU HSC - S. LA; University of Maryland Medical Center, MD; University of Michigan Health System, MI; William Beaumont Hospital, MI; New Hanover Regional Medical Center, NC; Wake Forest University Baptist Medical Center, NC; University Hospital - Newark, NJ; The Valley Hospital - Microbiology, NJ; Albany Medical Center Hospital, NY; Brookdale Hospital Center, NY; Brookdale Hospital Center, NY; Columbia Presbyterian Medical Center, NY; Univ. of Rochester Medical Center, NY; Summa Health System, OH; University Hospitals of Cleveland, OH; CompNet Clinical Laboratories, OH; RML @ SMMC, OK; Memorial Hospital, TN; University of Tennessee Medical Center, TN; Memorial Hermann Hospital, TX; Scott & White Memorial Hospital, TX; LDS Hospital, UT; Hennepin County Medical Center, MN; Stanford University Medical Center, CA; Oregon Medical Laboratories, OR; The Methodist Hospital, TX; Clarian Health Partners, Inc./Methodist Hospital, IN; Charleston Area Medical Center, WV; Marshfield Laboratories, WI; Northside Hospital - Laboratory, GA; Cleveland Clinic Foundation, OH; Inova Fairfax Hospital, VA; Mercy Health Laboratory, PA; Hartford Hospital, CT and Fleisher Allen Health Care, VT

REFERENCES

- Sum, P. E. and P. Petersen, Synthesis and structure-activity relationship of novel glycylcycline derivatives leading to the discovery of GAR-936. *Bioorg Med Chem Lett*, 1999, 9(10): p. 1459-62.
- Abbanat, D., M. Macielag, and K. Bush, Novel antibacterial agents for the treatment of serious Gram-positive infections. *Expert Opin Invest Drugs*, 2003, 12(3): p. 379-99.
- Berlin, C., et al., In vitro activities of tigecycline (GAR-936) against recently isolated clinical bacteria in Spain. *Antimicrob Agents Chemother*, 2002, 46(3): p. 892-5.
- 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.
- Hawwood, C. J., et al., Antibiotic resistance among clinical isolates of *Acinetobacter* in the UK, and in vitro evaluation of tigecycline (GAR-936). *J Antimicrob Chemother*, 2002, 49(3): p. 479-87.
- Chopra, I., New developments in tetracycline antibiotics: glycylcyclines and tetracycline efflux pump inhibitors. *Drug Resist Update*, 2002, 5(3-4): p. 119-25.
- Projan, S. J., Preclinical pharmacology of GAR-936, a novel glycylcycline antibacterial agent. *Pharmacotherapy*, 2000, 20(9 Pt 2): p. 2195-2235; discussion 2245-2265.
- Biedenbach, D. J., M. L. Beach, and R. N. Jones, In vitro antimicrobial activity of GAR-936 tested against antibiotic-resistant gram-positive blood stream infection isolates and strains producing extended-spectrum beta-lactamases. *Diagn Microbiol Infect Dis*, 2001, 49(4): p. 173-7.
- 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.
- Petersen, P. J., et al., In vitro and in vivo antibacterial activities of a novel glycylcycline, the 9-t-butylglycylamide derivative of minocycline (GAR-936). *Antimicrob Agents Chemother*, 1999, 43(4): p. 738-44.
- Petersen, P. J., et al., In vitro and in vivo activities of tigecycline (GAR-936), daptomycin, and comparative antimicrobial agents against glycopeptide-intermediate *Staphylococcus aureus* and other resistant gram-positive pathogens. *Antimicrob Agents Chemother*, 2002, 46(6): p. 2599-601.
- National Committee for Clinical Laboratory Standards (NCCLS), Performance Standards for Antimicrobial Susceptibility Testing; Fourteenth Informational Supplement. NCCLS document M100-S14. Wayne, PA, 2004.

Table 1. In vitro activity of tigecycline and comparative agents against 5,012 strains of *Enterobacteriaceae*.

Organism Name ^a	Drug ^b	MICs (mcg/mL)				
		%SUS	%INT	%RES	MIC ₅₀	MIC ₉₀
<i>E. coli</i> (n=951)	Tigecycline	100	0	0	0.12	0.25
	Amikacin	99.5	0.4	0.1	2	4
	Amox-Clav	77.1	12.6	10.3	4	32
	Ampicillin	48.1	13	50.6	>32	>32
	Cefepime	98.5	0.3	1.2	\leq 0.5	\leq 0.5
	Ceftazidime	95.2	1.2	3.6	\leq 8	\leq 8
	Ceftriaxone	96.3	1.3	2.4	\leq 0.06	0.12
	Imipenem	99.7	0	0.3	\leq 0.25	0.5
	Levofloxacin	77.9	1.6	20.5	0.03	\leq 8
	Minocycline	85.8	8.2	5.9	1	8
	Pip-Tazo	96	1.7	2.3	1	4
<i>K. pneumoniae</i> (n=807)	Tigecycline	95.2	3.9	0.9	0.5	2
	Amikacin	97.9	1.9	0.2	2	4
	Amox-Clav	84.9	5.7	9.4	2	16
	Ampicillin	3.5	16.9	79.6	>32	>32
	Cefepime	94.7	0.7	4.6	\leq 0.5	2
	Ceftazidime	87.1	1.4	11.5	\leq 8	>32
	Ceftriaxone	90.7	4	5.3	\leq 0.06	8
	Imipenem	98.2	1.6	2.2	0.25	1
	Levofloxacin	88.2	1.1	10.7	0.06	8
	Minocycline	84.1	6.6	9.3	2	8
	Pip-Tazo	91	1.2	7.8	2	16
<i>K. oxytoca</i> (n=106)	Tigecycline	99.1	0.9	0	0.25	0.5
	Amikacin	100	0	0	2	4
	Amox-Clav	86.8	2.8	10.4	2	32
	Ampicillin	3.8	9.5	86.7	>32	>32
	Cefepime	100	0	0	\leq 0.5	1
	Ceftazidime	94.3	0	5.7	\leq 8	\leq 8
	Ceftriaxone	95.3	3.8	0.9	\leq 0.06	2
	Imipenem	99.1	0	0.9	\leq 0.25	0.5
	Levofloxacin	97.2	2.8	0	0.03	0.5
	Minocycline	92.5	6.6	0.9	1	4
	Pip-Tazo	91.5	0.9	7.6	1	16
ESBL producers (E. coli, K. pneumoniae, K. oxytoca) (n=87)	Tigecycline	94.3	4.6	1.1	0.5	2
	Amikacin	90.8	9.2	0	8	16
	Amox-Clav	27.6	31	41.4	16	>32
	Ampicillin	0	1.1	98.9	>32	>32
	Cefepime	60.9	4.6	34.5	8	>32
	Ceftazidime	10.3	2.4	86.3	>32	>32
	Ceftriaxone	25.3	31	43.7	>32	>64
	Imipenem	89.5	12.6	6.9	0.5	8
	Levofloxacin	23	4.6	72.4	\leq 8	\leq 8
	Minocycline	72.4	6.9	20.7	4	>16
	Pip-Tazo	59.2	4.6	40.2	16	>128
<i>E. aerogenes</i> (n=256)	Tigecycline	95.7	3.5	0.8	0.5	1
	Amikacin	98.4	1.6	0	2	4
	Amox-Clav	7	3.5	89.5	>32	>32
	Ampicillin	95.5	1.4	2.1	\leq 0.5	4
	Cefepime	98.4	0.8	0.8	\leq 0.5	1
	Ceftazidime	84.5	6.2	9.3	\leq 8	16
	Ceftriaxone	93.8	1.6	1.1	2	8
	Imipenem	98.4	0	1.6	1	2
	Levofloxacin	95	2.7	2.3	0.06	0.5
	Minocycline	89.8	5	5.1	2	8
	Pip-Tazo	89.5	6.6	3.9	2	32
<i>E. cloacae</i> (n=929)	Tigecycline	93.5	4.4	2.1	0.5	2
	Amikacin	99.2	0.5	0.3	2	4
	Amox-Clav	3.5	2.1	94.4	>32	>32
	Ampicillin	4.6	3	92.4	>32	>32
	Cefepime	95.5	1.4	2.1	\leq 0.5	4
	Ceftazidime	77.7	3.3	19	\leq 8	32
	Ceftriaxone	80	6.7	11.3	0.25	64
	Imipenem	98.7	0.2	1.1	0.5	4
	Levofloxacin	92.1	1.7	6.2	0.06	2
	Minocycline	85.2	6.2	8.6	2	8
	Pip-Tazo	84.1	8.3	7.6	2	64
<i>S. marcescens</i> (n=348)	Tigecycline	96	3.7	0.3	1	2
	Amikacin	100	0	0	2	4
	Amox-Clav	2.3	1.4	96.3	>32	>32
	Ampicillin	2.3	4.3	93.4	>32	>32
	Cefepime	96.6	1.7	1.1	\leq 0.5	1
	Ceftazidime	91.4	3.1	5.5	\leq 8	16
	Ceftriaxone	92	3.7	4.3	0.25	8
	Imipenem	98.2	0.6	0.6	0.25	2
	Levofloxacin	96.3	0.8	2.9	0.12	1
	Minocycline	89.9	6	4.1	4	8
	Pip-Tazo	95.1	2.6	2.3	1	8

^aOnly species with $n \geq 20$ are represented.
^bBreakpoints as defined by NCCLS where available (M100-S14), 2004. Tigecycline breakpoints defined as: susceptible \leq 2; intermediate = 4; and resistant \geq 8.

RESULTS

Table 2. In vitro activity of tigecycline and comparative agents against 1,318 *Acinetobacter* spp and *Pseudomonas aeruginosa*.

Organism Name ^a	Drug ^b	MICs (mcg/mL)				
		%SUS	%INT	%RES	MIC ₅₀	MIC ₉₀
<i>Acinetobacter</i> spp (n=516)	Tigecycline	98.5	1.5	0	0.5	1
	Amikacin	84.4	7.9	7.7	4	32
	Amox-Clav	na	na	na	>32	>32
	Ampicillin	na	na	na	>32	>32
	Cefepime	na	na	na	>32	>32
	Ceftazidime	45.4	16.2	38.4	16	>32
	Ceftriaxone	47.2	4.1	48.7	16	>32
	Imipenem	27.8	24.5	47.7	32	>64
	Levofloxacin	86.3	6.4	7.3	0.5	8
	Minocycline	46.5	5	46.5	4	>8
	Pip-Tazo	72.4	0	27.6	8	>128
<i>E. faecium</i> (n=138)	Tigecycline	100	0	0	0.06	0.12
	Amox-Clav	na	na	na	>8	>8
	Ampicillin	15.2	0	84.8	>16	>16
	Cefepime	na	na	na	>64	>64
	Imipenem	na	na	na	>16	>16
	Levofloxacin	65.5	0.7	82.8	>32	>32
	Minocycline	93.5	1.4	5.1	2	2
	Pip-Tazo	na	na	na	>16	>16
	Vancomycin	29.7	1.4	68.9	>32	>32
	Penicillin	10.1	0	89.9	>8	>8
	<i>A. baumannii</i> (n=467)	Tigecycline	98.3	1.7	0	0.5
Amikacin		82.9	8.7	8.4	4	32
Amox-Clav		na	na	na	>32	>32
Ampicillin		na	na	na	>32	>32
Cefepime		40.9	17.6	41.5	16	>32
Ceftazidime		44	3.2	52.8	32	>32
Ceftriaxone		24	24.2	51.8	64	>64
Imipenem		44.8	7.1	8.1	0.5	8
Levofloxacin		42.2	5.1	52.7	8	>8
Minocycline		59	9.2	2.8	\leq 0.5	8
Pip-Tazo		70	0	30	16	>128
<i>A. calcoaceticus</i> (n=29)	Tigecycline	100	0	0	0.25	2
	Amikacin	95	0	100	>32	>32
	Amox-Clav	na	na	na	>16	>32
	Ampicillin	na	na	na	>16	>32
	Cefepime	10	10	20	2	64
	Ceftazidime	75	10	15	\leq 8	32
	Ceftriaxone	30	50	20	16	>64
	Imipenem	100	0	0	0.25	1
	Levofloxacin	95	5	0	0.12	\leq 8
	Minocycline	88	9.2	2.8	\leq 0.5	8
	Pip-Tazo	80	0	20	16	>128
<i>A. baumannii</i> (n=28)	Tigecycline	100	0	0	0.12	0.12
	Amikacin	100	0			