

Variable Resistance Patterns among Tigecycline and 10 Comparators against Multi-Drug Resistant *Acinetobacter* from the T.E.S.T. Program

P 2052

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

M. Hackel¹, R. Badal¹, S. Bouchillon¹, B. Johnson¹, J. Johnson¹, D. Hoban¹, M. Dowzicky²

¹International Health Management Associates, Schaumburg, IL, USA
²Wyeth Pharmaceuticals, Collegeville, PA, USA

REVISED ABSTRACT

Background: Tigecycline (TIG), a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent expanded 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 TIG compared to piperacillin-tazobactam (PT), levofloxacin (LVX), ceftriaxone (CAX), cefepime (CPE), amikacin (AK), minocycline (MIN), ceftazidime (CAZ), and imipenem (IMP) against multi-drug resistant *Acinetobacter* strains collected from 320 investigational sites in 42 countries throughout 2004-2006. **Methods:** A total of 4,010 clinical *Acinetobacter* were identified to the species level at each participating site and confirmed by the central laboratory. Minimum Inhibitory Concentrations (MICs) were determined by the local laboratory using broth microdilution panels. Antimicrobial resistance was interpreted according to CLSI breakpoints where applicable. **Results:** Resistance rates to the comparator drugs against all *Acinetobacter* spp were CAX 33.8%, CAZ 42.9%, LVX 38.0%, CPE 33.8%, PT 26.3%, AK 15.4%, IMP 13.4%, MIN 2.5%. Strains were grouped by presence of resistance to 0, 1, 2, 3, 4, or >5 drug classes. TIG inhibited 90% of all 1,158 multi-drug resistant strains (resistant to 3 or more drug classes) at 2 mcg/ml. TIG MIC_{50/90} for Groups Resistant to 0 - >5 drug classes were 0.25/1, 0.5/1, 0.5/2, 1/2, 1/2 and 1/2 mcg/ml, respectively. **Conclusion:** It has been seen in some species that existing multi-drug resistant efflux pumps may also pump TIG. In spite of this, TIG remained effective although resistance to two or more drug classes increased the TIG MIC₉₀ by 2-fold, TIG remained active against the great majority (>90%) of the multi-drug resistant *Acinetobacter* strains at MIC values ≤ 2 mcg/ml. TIG's in vitro activity against multi-drug resistant *Acinetobacter* should prove useful in therapy of infections caused by such therapeutically challenging strains.

INTRODUCTION

Tigecycline is a broad-spectrum antimicrobial agent and first-in-class of the semisynthetic glycylcyclines to be approved for human use [1]. This synthetic analogue of the minocycline molecule 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 [2, 3]. 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 [4]. 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 gram-negative bacteria with minimum inhibitory concentrations for the 90th percentile inhibited at or below 2 mcg/ml, including difficult to treat methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci (VRE) and extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* [5-9]. This study was undertaken to document the in vitro activity of tigecycline against significant numbers of multi-drug resistant *Acinetobacter* worldwide. 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 January 2004 and December 2006 from 320 study centers in 42 countries globally. 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 [10]. 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): amoxicillin/clavulanic acid (0.12/0.06-32/16); ampicillin (0.06-16); ceftazidime (0.06-64); 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 [11] and recent US Food and Drug Administration packaging insert for tigecycline [12], where applicable.
- Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains where applicable: *Escherichia coli* ATCC 25922; *Escherichia coli* ATCC 35218; and *Pseudomonas aeruginosa* ATCC 27853. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2006) guidelines [11].

REFERENCES

- FDA, Tygacil (R), NDA No. N021821 http://www.fda.gov/cder/rdmt/ndaaps05cy.htm June 15, 2005, United States Federal Drug Administration (FDA), 5600 Fishers Lane, Rockville, MD, USA.
- 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.
- Lathiaukul, 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 antibacterial agent. Pharmacotherapy, 2000, 20(8 Pt 2): p. 2193-2205; discussion 2245-2265.
- 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.
- 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, 39(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. 363-65.
- Bouchillon, S.K., et al., In vitro Activity of Tigecycline Against 3,869 Gram-Negative and Gram-Positive Clinical Isolates from the Global Tigecycline Evaluation and Surveillance Trial (TEST Program), 2004. Diagn Microbiol Infect Dis, 2005, 52(3): p. 173-179.
- Hoban, D.J., et al., In Vitro Activity of Tigecycline Against 6,792 Gram-Negative and Gram-Positive Clinical Isolates from the Global Tigecycline Evaluation and Surveillance Trial (TEST Program), 2004. Diagn Microbiol Infect Dis, 2005, 52(3): p. 215-227.
- 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.
- CLSI. Performance Standards for Antimicrobial Susceptibility Testing, in Document M100-S16, 2006. Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
- Tygacil, Product Insert, 2005. Wyeth Pharmaceuticals, Inc., Philadelphia, PA, USA.

ACKNOWLEDGEMENTS

We gratefully acknowledge contributions of the investigators, laboratory personnel and all members of the T.E.S.T. program group. This study was supported by a grant from Wyeth Pharmaceuticals.

Table 1. In vitro activity of tigecycline and comparative agents against 4,010 *Acinetobacter* species collected Globally from 2004 through 2006.

Drug	MIC (mcg/ml)			%Sus ^a	%Res
	MIC ₅₀	MIC ₉₀	Range		
Tigecycline	0.25	1	≤ 0.008 - 8	na	na
Amikacin	4	64	≤ 0.5 - >64	77.5	15.4
Cefepime	8	>32	≤ 0.5 - >32	51.8	33.8
Ceftazidime	≤ 8	>32	≤ 8 - >32	50.4	42.9
Ceftriaxone	32	>64	≤ 0.06 - >64	33.3	42.8
Imipenem	0.5	16	≤ 0.06 - >16	84.5	13.4
Levofloxacin	1	>8	≤ 0.008 - >8	53.3	38
Minocycline	≤ 0.5	4	≤ 0.5 - >16	91.1	2.5
PipTazo	8	>128	≤ 0.06 - >128	59.3	26.3

^a Interpretive criteria as defined by CLSI, M100-S16 (2006), where applicable [10]; na=not available; Breakpoints are undefined for tigecycline against this species at the time of publication.

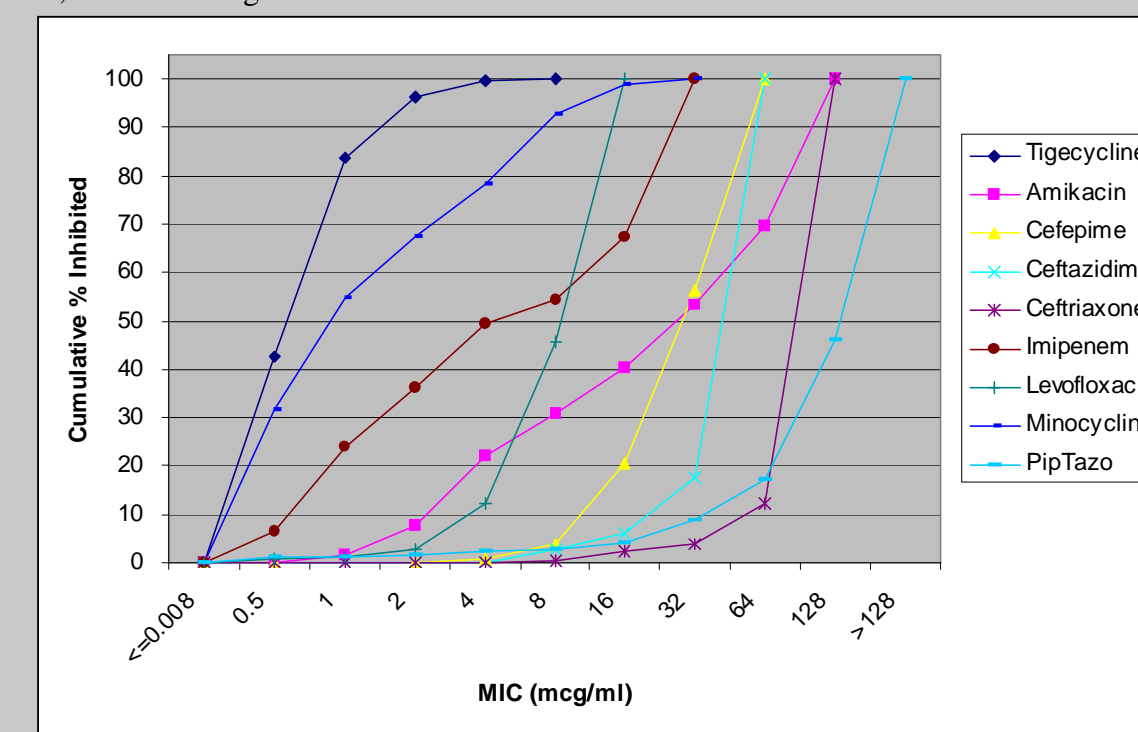
Table 2. In vitro activity of tigecycline and comparative agents against 1,158 multidrug-resistant *Acinetobacter*.

Organisms	Drug	MIC (mcg/ml)			%Sus ^a	%Res
		MIC ₅₀	MIC ₉₀	Range		
<i>Acinetobacter</i> spp (n=1,158) (includes all species below)	Tigecycline	1	4	≤ 0.008 - 8	na	na
	Amikacin	32	>64	≤ 0.5 - >64	40.2	46.6
	Cefepime	32	>32	≤ 0.5 - >32	3.6	79.5
	Ceftazidime	>32	>32	≤ 8 - >32	2.5	94
	Ceftriaxone	>64	>64	≤ 0.06 - >64	0.5	96.2
	Imipenem	8	>16	0.25 - >16	49.6	45.7
	Levofloxacin	>8	>8	0.12 - >8	2.6	88
	Minocycline	1	8	≤ 0.5 - >16	78.4	7.3
	PipTazo	>128	>128	≤ 0.06 - >128	4.2	83
	<i>Acinetobacter anitratus</i> (n=7)	Tigecycline	1	4	0.25 - 4	na
Amikacin		16	>64	4 - >64	71.4	28.6
Cefepime		32	>32	16 - >32	0	71.4
Ceftazidime		>32	>32	≤ 8 - >32	14.3	85.7
Ceftriaxone		>64	>64	>64 - >64	0	100
Imipenem		16	>16	1 - >16	42.9	57.1
Levofloxacin		>8	>8	4 - >8	0	85.7
Minocycline		4	16	≤ 0.5 - 16	57.1	14.3
PipTazo		>128	>128	128 - >128	0	100
<i>Acinetobacter baumannii</i> (n=1,121)		Tigecycline	1	2	≤ 0.008 - 8	na
	Amikacin	32	>64	≤ 0.5 - >64	40.1	46.7
	Cefepime	32	>32	≤ 0.5 - >32	3.7	79.2
	Ceftazidime	>32	>32	≤ 8 - >32	2.4	94.1
	Ceftriaxone	>64	>64	≤ 0.06 - >64	0.5	96.1
	Imipenem	4	>16	0.25 - >16	50.2	45
	Levofloxacin	>8	>8	0.12 - >8	2.3	88.2
	Minocycline	1	8	≤ 0.5 - >16	78.3	7.5
	PipTazo	>128	>128	≤ 0.06 - >128	4.2	82.8
	<i>Acinetobacter calcoaceticus</i> (n=6)	Tigecycline	1	4	0.5 - 4	na
Amikacin		4	64	2 - 64	50	33.3
Cefepime		>32	>32	16 - >32	0	83.3
Ceftazidime		>32	>32	16 - >32	0	83.3
Ceftriaxone		>64	>64	64 - >64	0	100
Imipenem		1	1	1 - 1	100	0
Levofloxacin		>8	>8	4 - >8	0	100
Minocycline		2	8	≤ 0.5 - 8	83.3	0
PipTazo		128	>128	≤ 0.06 - >128	16.7	83.3
<i>Acinetobacter lwoffii</i> (n=8)		Tigecycline	0.25	1	0.12 - 1	na
	Amikacin	16	>64	≤ 0.5 - >64	62.5	37.5
	Cefepime	>32	>32	16 - >32	0	87.5
	Ceftazidime	32	>32	≤ 8 - >32	12.5	75
	Ceftriaxone	>64	>64	>64 - >64	0	100
	Imipenem	>16	>16	2 - >16	25	62.5
	Levofloxacin	4	>8	0.12 - >8	37.5	50
	Minocycline	1	2	≤ 0.5 - 2	100	0
	PipTazo	>128	>128	4 - >128	12.5	62.5
	<i>Acinetobacter</i> , non-specified (n=16)	Tigecycline	1	2	0.25 - 4	na
Amikacin		64	>64	1 - >64	25	56.3
Cefepime		>32	>32	32 - >32	0	100
Ceftazidime		>32	>32	>32 - >32	0	100
Ceftriaxone		>64	>64	>64 - >64	0	100
Imipenem		>16	>16	0.5 - >16	13.3	86.7
Levofloxacin		8	>8	2 - >8	6.3	87.5
Minocycline		1	8	≤ 0.5 - 8	81.3	0
PipTazo		>128	>128	>128 - >128	0	100

^a Interpretive criteria as defined by CLSI, M100-S16 (2006), where applicable [10]; na=not available; Breakpoints are undefined for tigecycline against this species at the time of publication. Multidrug-resistant is defined as resistant to 3 or more CLSI drug classes.

RESULTS

Figure 1. Cumulative percents inhibited (%) of tigecycline and comparative agents against 1,158 multi-drug resistant *Acinetobacter*.



Multi-drug resistance is defined as resistant to 3 or more CLSI drug classes.

Table 3. In vitro activity of tigecycline and comparative agents against 4,010 *Acinetobacter* categorized by multiple drug class resistant groups.

Drug	MIC ₅₀ / MIC ₉₀ (mcg/ml)					
	MDR Group 0 (n=1923)	MDR Group 1 (n=380)	MDR Group 2 (n=549)	MDR Group 3 (n=539)	MDR Group 4 (n=420)	MDR Group 5+ (n=199)
Tigecycline	0.25/0.5	0.5/1	0.5/2	1/2	1/2	1/2
Amikacin	2/4	4/32	4/64	16/>64	32/>64	>64/>64
Cefepime	2/4	16/32	32/>32	32/>32	32/>32	>32/>32
Ceftazidime	$\leq 8/\leq 8$	16/>32	>32/>32	>32/>32	>32/>32	>32/>32
Ceftriaxone	8/16	32/>64	>64/>64	>64/>64	>64/>64	>64/>64
Imipenem	0.25/0.5	0.5/2	1/4	2/16	16/>16	>16/>16
Levofloxacin	0.12/0.5	4/8	8/>8	>8/>8	>8/>8	>8/>8
Minocycline	$\leq 0.5/\leq 0.5$	$\leq 0.5/4$	1/8	1/8	1/8	1/8
PipTazo	0.12/1	8/64	32/128	128/>128	>128/>128	>128/>128

Each MDR Group represents the number of resistant CLSI drug classes in that category. Drug class resistance is based on interpretive criteria as defined by CLSI, M100-S16 (2006).

CONCLUSIONS

- Tigecycline had the lowest in vitro MIC₉₀ of all study drugs against all strains of multidrug-resistant *Acinetobacter* at 2 mcg/ml. This value was 4- to 64-fold lower than amikacin, imipenem, levofloxacin, piperacillin-tazobactam and cefepime.
- The in vitro activity of tigecycline was superior to imipenem, cefepime, ceftazidime, ceftriaxone, levofloxacin, minocycline and piperacillin-tazobactam against all *Acinetobacter* resistant to three or more drug classes.
- It has been seen in some species that existing multi-drug resistant efflux pumps may also pump tigecycline. In spite of these mechanisms, tigecycline remains effective in the vast majority of *Acinetobacter* isolates. Although resistance to two or more drug classes increased the tigecycline MIC₉₀ by 2-fold, tigecycline remained active against more than 90% of the multi-drug resistant *Acinetobacter* strains at MIC values ≤ 2 mcg/ml.