

Tigecycline Evaluation Surveillance Trial (T.E.S.T.) Program – An Update on the In Vitro Antibacterial Activity Against Selected Species of Non-glucose Fermenting Gram negative Rods from Asia and the Pacific Rim – 2008

GN053

J. Johnson¹, R. Badal¹, S. Hawser¹, M. Hackel¹, S. Bouchillon¹, B. Johnson¹, D. Hoban¹, M. Renteria¹, M. Dowzicky²

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



IHMA, Inc.
2122 Palmer Dr.
Schaumburg, IL
60173
Tel: 847.303.5003
Fax: 847.303.5601

Revised Abstract

Objectives: Non-glucose fermenting Gram-negative rods are known to be highly resistant in hospital settings and have always been a challenge for clinicians and hospital infection control. The degree or type of resistance may be due to several sophisticated mechanisms such as production of extended spectrum β -lactamase, efflux pumps, altered membrane permeability therefore inactivating most classes of broad spectrum antimicrobials that are available for treatment. Tigecycline, the first member of a new class of antimicrobials (glycylcyclines), has been shown to have potent activity against most species of *Enterobacteriaceae* and selected species of non-fermenters. 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 members of *Acinetobacter* spp. and *Pseudomonas aeruginosa* collected from hospitals across Asia and the Pacific Rim. **Methods:** A total of 2009 clinical isolates (1174 *P. aeruginosa* and 835 *Acinetobacter* spp.) were collected throughout 2004-2008 from seventy-five centers and minimum inhibitory concentration (MICs) were determined by broth microdilution panels and interpreted according to CLSI guidelines. **Results:** All of the anti-pseudomonal agents ceftazidime, imipenem, piperacillin/tazobactam, cefepime, amikacin, and levofloxacin presented good inhibitory activity against *P. aeruginosa* with susceptibility rates above 60%. Tigecycline had an MIC₉₀ of >16 mcg/mL against *P. aeruginosa*. *A. baumannii* had the following susceptibility rates against the broad spectrum agents: cefepime 44%; amikacin 54%; ceftazidime 40%; levofloxacin 58%; imipenem 68%; pip/tazo 44%; minocycline 86%. Tigecycline had the lowest MIC₅₀/MIC₉₀ (0.5/2 mcg/ml) against *A. baumannii*. Performance of tigecycline was unaffected against multidrug-resistant isolates of *A. baumannii*. **Conclusions:** The presented data suggest that tigecycline may be an effective therapeutic option against multidrug-resistant nosocomial *Acinetobacter* spp. but ineffective against *Pseudomonas aeruginosa*.

Introduction

Tigecycline is a novel antimicrobial with an expanded broad-spectrum of activity from a new class of compounds, glycylcyclines. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit. Although it is perceived to be bacteriostatic, it 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 broad-spectrum 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]. The MIC₉₀ values for pseudomonal isolates are generally elevated, in the range of 8-16 mcg/ml due to synergism between outer membrane impermeability and efflux mechanisms [10]. However, tigecycline has been shown to be highly effective against multi-drug resistant *Acinetobacter* spp., particularly *A. baumannii* that are commonly associated with serious nosocomial infections [5].

This study prospectively compared the in vitro activity of tigecycline with comparative antimicrobial agents against *Acinetobacter* spp. and *P. aeruginosa* from Australia, China, Hong Kong, India, Indonesia, Korea, Pakistan, Philippines, Singapore and Taiwan.

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.
- Clinical isolates were collected tested between January 2004 – December 2008 from 75 study centers in Australia, China, Hong Kong, India, Indonesia, Korea, Pakistan, Philippines, Singapore and Taiwan.
- Custom broth microdilution panels were supplied by MicroScan (Dade Behring, 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); cefepime (0.5-32); ampicillin (0.5-32); amikacin (0.5-64); minocycline (0.5-16); ceftazidime (8-32); tigecycline (0.008-16); and imipenem (0.06-16).
- MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute where applicable [12]. Tigecycline tentative breakpoints (in units of mcg/mL) are defined as susceptible ≤ 2 ; intermediate = 4; and resistant ≥ 8 in this study for comparative purposes only.
- Isolates were identified to genus and species at each site by the local laboratory. Isolates were tested by the local laboratory.
- Quality control of broth microdilution panels followed manufacture's and CLSI guidelines using the following ATCC strains: *Pseudomonas aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 25922.
- The collection and transporting 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).

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 Investig Drugs, 2003, 12(5): p. 379-99.
- Betriu, 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.
- Henwood, 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 Updat, 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. 219S-223S; discussion 224S-225S.
- 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, 40(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-(4-butylglycylamido) 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(8): p. 2595-601.
- Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; Eighteenth Information Supplement. CLSI document M100-S18. Wayne, PA, 2008.

Acknowledgements

This study was supported by a grant from Wyeth Pharmaceuticals. We gratefully acknowledge contributions from all participants in the T.E.S.T. project who have helped make this program a success.

Results

Results are contained in the following Tables.

Table 1. In vitro activity of tigecycline and comparative agents against 2009 strains of *P. aeruginosa* and *Acinetobacter* spp. combined.

Organism (n)	Drug	MIC (mcg/mL)		
		MIC ₅₀	MIC ₉₀	Range
<i>P. aeruginosa</i> & <i>Acinetobacter</i> spp (n=2009)	Tigecycline	4	16	0.015 / >16
	Amikacin	4	>64	4 / >64
	Amox-Clav	>32	>32	>32 / >32
	Ampicillin	>32	>32	≤ 0.5 / >32
	Cefepime	8	>32	≤ 0.5 / >32
	Ceftazidime	≤ 8	>32	≤ 8 / >32
	Ceftriaxone	>64	>64	≤ 0.06 / >64
	Imipenem	1	>16	≤ 0.06 / >16
	Levofloxacin	2	>8	≤ 0.008 / >8
	Minocycline	8	>16	≤ 0.5 / >16
Pip-Tazo	4	>128	≤ 0.06 / >128	

*Breakpoints as defined by CLSI where available (M100-S18, 2008); na = not available when breakpoints are undefined by the CLSI. Tigecycline breakpoints defined as: susceptible ≤ 2 ; intermediate = 4; and resistant ≥ 8 for comparative purposes only.

Table 2. In vitro activity of tigecycline and comparative agents against 2009 Gram-negative non-fermenters.

Organism (n)	Drug *	MIC (mcg/mL)			%Sus
		Range	MIC ₅₀	MIC ₉₀	
<i>Acinetobacter</i> spp (n=835)	Tigecycline	0.015 / 8	0.5	2	95.8
	Amikacin	≤ 0.5 / >64	8	>64	55.8
	Amox-Clav	0.12 / >32	32	>32	na
	Ampicillin	≤ 0.5 / >32	>32	>32	na
	Cefepime	≤ 0.5 / >32	16	>32	44.9
	Ceftazidime	≤ 8 / >32	32	>32	40.8
	Ceftriaxone	≤ 0.06 / >64	64	>64	24.3
	Imipenem	0.12 / >16	1	>16	66.3
	Levofloxacin	≤ 0.008 / >8	4	>8	49.2
	Minocycline	≤ 0.5 / >16	≤ 0.5	8	86.9
	Pip-Tazo	≤ 0.06 / >128	64	>128	44.9
<i>Acinetobacter baumannii</i> (n=738)	Tigecycline	0.015 / 8	0.5	2	95.8
	Amikacin	≤ 0.5 / >64	8	>64	53.8
	Amox-Clav	0.12 / >32	>32	>32	na
	Ampicillin	≤ 0.5 / >32	>32	>32	na
	Cefepime	≤ 0.5 / >32	16	>32	43.4
	Ceftazidime	≤ 8 / >32	32	>32	39.6
	Ceftriaxone	≤ 0.06 / >64	64	>64	23.2
	Imipenem	0.12 / >16	1	>16	67.5
	Levofloxacin	≤ 0.008 / >16	4	>8	58.1
	Minocycline	≤ 0.5 / >16	≤ 0.5	8	86.3
	Pip-Tazo	≤ 0.06 / >128	64	>128	43.5
<i>Acinetobacter lwoffii</i> (n=33)	Tigecycline	0.03 / 4	0.25	1	97.0
	Amikacin	≤ 0.5 / >64	1	64	84.8
	Amox-Clav	≤ 0.12 / >32	4	32	na
	Ampicillin	32 / >32	32	>32	na
	Cefepime	≤ 0.5 / >32	1	8	90.9
	Ceftazidime	≤ 8 / >32	≤ 8	>32	66.7
	Ceftriaxone	1 / >64	8	>64	54.5
	Imipenem	0.12 / >16	0.25	1	92.3
	Levofloxacin	0.03 / >8	0.12	1	90.9
	Minocycline	≤ 0.5 / >16	0.5	>16	93.9
	Pip-Tazo	≤ 0.06 / >128	≤ 0.5	2	87.9
<i>Pseudomonas aeruginosa</i> (n=1174)	Tigecycline	≤ 0.06 / >16	8	>16	6.4
	Amikacin	≤ 0.5 / >64	4	>64	83.6
	Amox-Clav	0.25 / >32	>32	>32	na
	Ampicillin	≤ 0.5 / >32	>32	>32	na
	Cefepime	≤ 0.5 / >32	4	>32	68.7
	Ceftazidime	≤ 8 / >32	≤ 8	>32	69.8
	Ceftriaxone	≤ 0.06 / >64	64	>64	9.4
	Imipenem	≤ 0.06 / >16	1	16	81.9
	Levofloxacin	0.015 / >8	1	>8	62.4
	Minocycline	≤ 0.5 / >16	16	>16	na
	Pip-Tazo	≤ 0.06 / >128	8	>128	81.3

*Breakpoints as defined by CLSI where available (M100-S18, 2008); na = not available when breakpoints are undefined by the CLSI. Tigecycline breakpoints defined as: susceptible ≤ 2 ; intermediate = 4; and resistant ≥ 8 for comparative purposes only.

Conclusions

- Tigecycline inhibited 87.2% of *Acinetobacter* spp. tested in vitro at a MIC of 1 mcg/mL and 95.8% at an MIC of 2 mcg/mL.
- Tigecycline's MIC₉₀ of 2 mcg/mL against *Acinetobacter* spp. was the lowest among all broad spectrum antimicrobials tested.
- Tigecycline's limited activity against *P. aeruginosa* is similar to tetracyclines and their analog derivatives.
- The in vitro activity of tigecycline in this study suggests that tigecycline is a promising compound in the treatment of serious nosocomial infections caused by *Acinetobacter* spp.