

In Vitro Activity of Tigecycline and Comparators Against Nosocomial Pathogens in Italy from 2004-2008

#P 1595

M. Hackel¹, S. Bouchillon¹, B. Johnson¹, D. Hoban¹, M. Renteria¹, J. Johnson¹, R. Badal¹, S. Hawser², M. Dowzicky³

¹International Health Management Associates, Inc., Schaumburg, IL, USA
²International Health Management Associates Europe Sàrl, Epalinges, Switzerland
³Wyeth Pharmaceuticals, Collegeville, PA, USA

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

Revised Abstract

Background: Tigecycline has demonstrated potent activity against a range of pathogens encountered in hospitalized patients. The TEST program was designed to determine the *in vitro* activity of tigecycline and comparators to nosocomial pathogens isolated in Italy between 2004-2008. **Methods:** 5,933 clinical isolates were collected/identified from 54 sites and confirmed by the reference lab. Following CLSI guidelines, MICs were determined/interpreted using supplied broth microdilution panels. **Results:** The spectrum and potency of tigecycline against nosocomial pathogens is shown in the table below:

Organism (#)	Tigecycline		% Inhibited at MIC				
	%S	MIC ₉₀	≤0.25	0.5	1	2	4
<i>Acinetobacter</i> spp. (446)	NA	2	43	67	80	96	99
Enterobacteriaceae (2769)	90.5	1	42	75	91	96	99
ESBL producers ^a (258)	92.2	1	46	76	92	98	99
<i>Enterobacter</i> spp. (800)	85.6	2	22	66	86	93	99
<i>E. faecalis</i> (323)	99.7	0.25	99.7	100	-	-	-
<i>E. faecium</i> (126)	100	0.12	100	-	-	-	-
<i>H. influenzae</i> (309)	NA	1	65	89	98	100	-
<i>P. aeruginosa</i> (635)	NA	>16	0.3	1.3	2.5	6	23
<i>S. aureus</i> (MSSA) (487)	100	0.25	97.5	100	-	-	-
<i>S. aureus</i> (MRSA) (245)	99.6	0.25	94.3	99.6	100	-	-
<i>S. pneumoniae</i> (305)	NA	0.06	99.7	100	-	-	-
<i>S. agalactiae</i> (277)	100	0.12	100	-	-	-	-

^a ESBL producing *E. coli*, *K. oxytoca*, *K. pneumoniae*

Conclusions: Italian isolates of both gram positive & -negative hospital pathogens demonstrated excellent tigecycline MIC₉₀s excluding *P. aeruginosa*. For most resistant phenotypes tigecycline MIC₉₀s were 1 mg/L or less and the majority of isolates inhibited at MICs of 2 mg/L or less. All ESBLs isolated in Italy were inhibited by tigecycline at MICs of 8 or less with an MIC₉₀ of 1 mg/L.. Tigecycline promises expanded broad spectrum coverage against multiply resistant pathogens isolated in Italy.

Introduction

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycytyclines. This synthetic analogue of the tetracyclines exhibits 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 glycytyclines 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 restore 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].

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 mg/L, including difficult to treat methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and extended-spectrum β-lactamase (ESBL) producing *Enterobacteriaceae* [4-6]. This study was undertaken to document the *in vitro* activity of tigecycline against significant numbers of clinical pathogens collected in Italian laboratories. 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 (no more than 25% of all isolates), 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 2008 from 54 study centers across Italy. Isolates were identified to the species level and tested at each site by the participating laboratory.
- Organism collection, transport, confirmation of organism identification, and development and management of a centralized database, were 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 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 µg/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); ceftaxime (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 EUCAST where available. Where no breakpoints were available, the Clinical and Laboratory Standards Institute [8] and the recent US Food and Drug Administration package insert breakpoints for tigecycline [9], were used.
- Escherichia coli*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftaxime were >1 mg/L using broth microdilution panels. ESBL activity was confirmed using the CLSI (2006) 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), ceftazidime (30-mcg), and 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 (2006) guidelines [8].

References

- Hoellman, D.B., et al., *Antipneumococcal activities of GAR-936 (a new glycytycline) compared to those of nine other agents against penicillin-susceptible and -resistant pneumococci*. Antimicrob Agents Chemother. 2000, 44(4): p. 1085-9.
- Labthavikul, 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 glycytycline antibacterial 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 glycytycline, 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, 38(3): p. 177-9.
- Rupp, M.E. and P.D. Fey. *Extended spectrum β-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-A7. 2006: 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-S18. 2008: Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
- Tygaol. *Product Insert*. 2005: Wyeth Pharmaceuticals, Inc., Philadelphia, PA, USA.

Acknowledgements

We gratefully acknowledge the contributions of the investigators, laboratory personnel, and all members of the Tigecycline Evaluation Study Trials program group. This study was sponsored by a grant from Wyeth Pharmaceuticals.

Results

The results are listed in the following Tables.

Table 1. *In vitro* activity of tigecycline and comparative agents against 2,769 strains of *Enterobacteriaceae*.

Organism Name ^b	Drug	%SUS ^a	%INT	%RES	MIC (mg/L)	
					MIC ₅₀	MIC ₉₀
All Enterobacteriaceae (n=2,769)	Tigecycline	90.5	5.9	3.6	0.5	1
	Amikacin	92.4	3.8	3.8	2	8
	AmoxClav	29.4	11.5	59.2	16	>32
	Ampicillin	9.4	0.8	89.8	>32	>32
	Cefepime	74.2	14.0	11.8	≤0.5	16
	Ceftazidime	0.0	73.0	27.0	≤8	>32
	Ceftaxime	67.2	2.2	30.6	0.12	>64
	Imipenem	97.4	2.0	0.7	0.25	1
	Levofloxacin	73.0	2.0	25.0	0.06	>8
	Minocycline	76.6	10.3	13.0	2	16
	PipTazo	74.1	3.8	22.1	2	128
	<i>E. coli</i> (n=846)	Tigecycline	99.5	0.5	0.0	0.25
Amikacin		93.5	4.4	2.1	2	8
AmoxClav		38.3	24.8	36.9	8	>32
Ampicillin		30.5	2.1	67.4	>32	>32
Cefepime		79.1	8.2	12.8	≤0.5	32
Ceftazidime		0.0	86.2	13.8	≤8	16
Ceftaxime		78.7	0.9	20.3	≤0.06	>64
Imipenem		100.0	0.0	0.0	0.25	0.5
Levofloxacin		59.6	0.7	39.7	0.12	>8
Minocycline		73.8	10.4	15.8	2	16
PipTazo		84.2	3.9	11.9	1	32
<i>K. pneumoniae</i> (n=620)		Tigecycline	91.8	4.2	4.0	0.5
	Amikacin	87.7	4.2	8.1	2	16
	AmoxClav	54.5	11.6	33.9	4	32
	Ampicillin	0.0	0.2	99.8	>32	>32
	Cefepime	73.5	10.2	16.3	≤0.5	>32
	Ceftazidime	0.0	71.8	28.2	≤8	>32
	Ceftaxime	68.5	1.9	29.5	≤0.06	>64
	Imipenem	99.6	0.0	0.4	0.25	0.5
	Levofloxacin	80.2	1.1	18.7	0.06	>8
	Minocycline	75.8	5.5	18.7	2	>16
	PipTazo	74.7	3.5	21.8	2	>128
	<i>K. oxytoca</i> (n=30)	Tigecycline	94.3	3.4	2.3	0.25
Amikacin		99.4	0.0	0.6	2	4
AmoxClav		64.8	9.1	26.1	4	32
Ampicillin		0.0	0.0	100.0	>32	>32
Cefepime		88.6	8.0	3.4	≤0.5	2
Ceftazidime		0.0	90.3	9.7	≤8	≤8
Ceftaxime		82.4	2.3	15.3	≤0.06	8
Imipenem		100.0	0.0	0.0	0.25	0.5
Levofloxacin		92.6	1.1	6.3	0.06	0.5
Minocycline		88.1	4.5	7.4	2	8
PipTazo		83.5	0.6	15.9	2	128
ESBL-producing <i>E. coli</i> , <i>K. pneumoniae</i> , <i>K. oxytoca</i> (n=258)		Tigecycline	92.2	5.4	2.3	0.5
	Amikacin	71.3	12.4	16.3	4	>64
	AmoxClav	3.1	17.1	79.8	16	>32
	Ampicillin	0.0	0.0	100.0	>32	>32
	Cefepime	10.5	24.0	65.5	32	>32
	Ceftazidime	0.0	17.8	82.2	>32	>32
	Ceftaxime	2.3	1.9	95.7	>64	>64
	Imipenem	100.0	0.0	0.0	0.25	1
	Levofloxacin	26.4	2.3	71.3	>8	>8
	Minocycline	58.5	10.5	31.0	4	>16
	PipTazo	40.7	9.3	50.0	32	>128
	<i>E. aerogenes</i> (n=164)	Tigecycline	90.2	6.1	3.7	0.5
Amikacin		82.9	11.0	6.1	2	16
AmoxClav		1.2	3.0	95.7	>32	>32
Ampicillin		0.0	0.0	100.0	>32	>32
Cefepime		64.0	25.0	11.0	≤0.5	16
Ceftazidime		0.0	47.6	52.4	16	>32
Ceftaxime		40.9	4.9	54.3	4	>64
Imipenem		91.1	8.9	0.0	0.5	2
Levofloxacin		67.1	3.0	29.9	0.12	>8
Minocycline		79.3	13.4	7.3	2	8
PipTazo		56.7	9.1	34.1	8	>128
<i>E. cloacae</i> (n=606)		Tigecycline	84.0	7.9	8.1	0.5
	Amikacin	94.9	2.0	3.1	2	8
	AmoxClav	1.3	0.7	98.0	>32	>32
	Ampicillin	0.2	0.0	99.8	>32	>32
	Cefepime	59.2	28.4	12.4	≤0.5	16
	Ceftazidime	0.0	50.0	50.0	≤8	>32
	Ceftaxime	47.0	2.3	50.7	4	>64
	Imipenem	95.2	4.0	0.8	0.5	2
	Levofloxacin	73.9	2.0	24.1	0.06	>8
	Minocycline	75.4	12.5	12.0	4	16
	PipTazo	55.3	4.0	40.8	4	>128
	<i>S. marcescens</i> (n=47)	Tigecycline	73.4	22.8	3.8	1
Amikacin		94.1	4.1	1.7	2	8
AmoxClav		0.7	1.7	97.6	>32	>32
Ampicillin		0.3	1.0	98.6	>32	>32
Cefepime		85.9	8.3	5.9	≤0.5	4
Ceftazidime		0.0	85.2	14.8	≤8	>32
<i>S. pneumoniae</i> (n=305)	Ceftaxime	75.9	4.5	19.7	0.25	32
	Imipenem	93.1	3.1	3.8	0.5	2
	Levofloxacin	83.4	7.6	9.0	0.12	2
	Minocycline	79.0	17.6	3.4	4	8
	PipTazo	83.1	3.1	13.8	2	32

^a Interpretive criteria as defined by EUCAST where available. Where EUCAST breakpoints were not available CLSI [8] or FDA package insert breakpoints (Tygacil[®], 2005) were used [9].

^b Species with n < 10 were omitted.

Table 2. *In vitro* activity of tigecycline and comparative agents against *Acinetobacter* spp. and *P. aeruginosa*.

Organism Name	Drug	%SUS ^a	%INT	%RES	MIC (mg/L)	
					MIC ₅₀	MIC ₉₀
Acinetobacter spp. (n=446)	Tigecycline	na	na	na	0.5	2
	Amikacin	50.7	4.7	44.6	8	>64
	Cefepime	39.9	12.3	47.8	16	>32
	Ceftazidime	38.1	5.6	56.3	>32	>32
	Ceftaxime	30.7	11.2	58.1	>64	>64
	Imipenem	74.3	14.0	11.7	0.5	16
	Levofloxacin	39.7	3.6	56.7	4	>8
	Minocycline	93.9	4.9	1.1	≤0.5	4
	PipTazo	46.0	7.2	46.9	64	>128
	<i>P. aeruginosa</i> (n=635)	Tigecycline	na	na	na	8
Amikacin		80.9	8.0	11.0	4	32
Cefepime		64.7	0.0	35.3	8	>32
Ceftazidime		65.8	0.0	34.2	≤8	>32
Ceftaxime		13.9	24.4	61.7	>64	>64
Imipenem		74.9	11.5	13.6	2	16
Levofloxacin		45.0	7.6	47.4	2	>8
Minocycline		na	na	na	>16	>16
PipTazo		66.1	0.0	33.9	8	128

^a Interpretive criteria as defined by EU