OB004

The Activity of Tigecycline Against Minocycline Resistance Pathogens: A Global Perspective

B. Johnson[1], D. Hoban[1], M. Renteria[1], J. Johnson[1], R. Badal[1], S. Hawser[1], M. Hackel[1], S. Bouchillon[1], M. Dowzicky[2]

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

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

Revised Abstract

Objectives: Tigecycline, a new glycylcycline is an analogue of tetracycline that demonstrates activity against bacterial strains carrying tetracycline (minocycline) resistance mechanisms. This report documents the activity of TIG against minocycline resistant isolates collected worldwide, 2004-2008, as part of the Tigecycline Evaluation Surveillance Trial (TEST) study. **Methods**: Between 2004 and 2008, 1016 hospital sites in 53 countries collected significant pathogens associated with 8 specimen types, were identified to species level and MICs performed for each strain to a supplied panel of antibiotics and interpreted according to CLSI guidelines. **Results**: The table below illustrates the activity of tigecycline to minocycline-resistant clinical pathogens:

	Tigecycline MICs (mcg/ml)		
	MIC_{50}	MIC_{90}	Range
Acinetobacter spp (n=314)	1	4	0.03 – >16
Enterobacter spp (n=1484)	2	8	0.03 – >16
Enterococcus spp (n=1668)	0.12	0.25	≤0.008 – 1
VREs (n=121)	0.12	0.25	0.03-0.25
E. coli (n=1683)	0.25	0.5	≤0.008 – >16
Klebsiella spp (n=1858)	1	4	≤0.008 – 16
ESBLs (n=907)	0.5	4	0.06->16
P. aeruginosa (n=9695)	8	>16	≤0.008 - >16
Serratia spp (n=263)	2	4	≤0.008 - >16
H. influenzae (n=21)	0.5	0.5	0.015– 0.5
S. aureus (n=77)	0.25	0.5	0.06 – 0.5
MRSA (n=69)	0.5	0.5	0.12 – 0.5

Conclusions: Tigecycline MIC_{90}s were ≤0.5 mcg/ml for minocycline resistant Gram-positive pathogens such as *Enterococcus, H. influenza,* and *S. aureus* (including MRSA and VRE) and ≤8mcg/ml for minocycline-resistant Gram-negative pathogens such as *Enterobacteriaceae*, including ESBL producers. Tigecycline demonstrated minimal activity against *P. aeruginosa*. Tigecycline demonstrates enhanced activity to many minocycline-resistant pathogens.

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, 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].

Unlike the other members of the tetracycline family or derivatives, 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 active 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) and AmpC producing strains [10]. Tigecycline has demonstrated MIC_{90} values of ≤0.5 mcg/mL against methicillin-resistant *Staphylococcus aureus* (MRSA) and other Gram-positive organisms [2, 4-6].

This study was designed to better define the in vitro activity of tigecycline against minocycline-resistant clinical isolates collected from 1016 study centers worldwide.

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. More than 17,000 minocycline-resistant clinical isolates were collected and tested between 2004 to 2008 from 1016 investigative sites in 53 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, 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 [12]. Antimicrobial agents and concentrations tested (expressed in mcg/mL) were as follows: gram-positive panel: amoxicillin-clavulanic acid (0.03/0.015-8/4, tested using a 2:1 ratio of amoxicillin:clavulanic acid; reported concentrations refer to amoxicillin); ampicillin (0.06-16); ceftriaxone (0.03-64); imipenem (0.06-16, MicroScan panels only); meropenem (0.12-16, MicroScan and TREK panels); linezolid (0.5-8); levofloxacin (0.06-32); minocycline (0.25-8); tigecycline (0.008-16); penicillin (0.06-8); piperacillin-tazobactam (0.25/4-16/4) and vancomycin (0.12-32); gram-negative panel: amikacin (0.5-64); amoxicillin-clavulanic acid (0.12/0.06-32/16, tested using a 2:1 ratio of amoxicillin:clavulanic acid; reported concentrations refer to amoxicillin); ampicillin (0.5-32); cefepime (0.5-32); ceftriaxone (0.06-64); ceftazidime (8-32); imipenem (0.06-16, MicroScan panels only); meropenem (0.06-16, MicroScan and TREK panels); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16) and piperacillin-tazobactam (0.06/4-128/4). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [13] and the recent US Food and Drug Administration package insert for tigecycline [14], where applicable.
- 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, *K. pneumoniae* ATCC 700603 (ESBL pos) and *S. pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI guidelines [13].

References

1. 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.
2. Abbanat, D., M. Macielag, and K. Bush, *Novel antibacterial agents for the treatment of serious Gram-positive infections.* Expert Opin Investig Drugs, 2003. **12**(3): p. 379-99.
3. 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.
4. 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.
5. 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.
6. Chopra, I., *New developments in tetracycline antibiotics: glycylcyclines and tetracycline efflux pump inhibitors.* Drug Resist Updat, 2002. **5**(3-4): p. 119-25.
7. Projan, S.J., *Preclinical pharmacology of GAR-936, a novel glycylcycline antibacterial agent.* Pharmacotherapy, 2000. **20**(9 Pt 2): p. 219S-223S; discussion 224S-228S.
8. 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-
9. 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.
10. Petersen, P.J., et al., *In vitro and in vivo antibacterial activities of a novel glycylcycline, the 9-t-butylglycylamido derivative of minocycline (GAR-936).* Antimicrob Agents Chemother, 1999. **43**(4): p. 738-44.
11. 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.
12. CLSI, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Seventh Edition*, in *Document M7-A7*. 2007: Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
13. 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.
14. Tygacil®, 2005. Tigecycline FDA package insert.

Acknowledgements

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

Results

Table 1. In vitro activity of tigecycline and comparative agents against minocycline-resistant *Enterobacteriaceae*

		mcg/mL			
Organism	Drug	MIC_{50}	MIC_{90}	%Sus†	%Res
Enterobacter spp (n=1484)	Tigecycline	2	8	63.2	10.9
	Amikacin	2	32	88.6	7.6
	AmoxClav	>32	>32	1.3	95.5
	Ampicillin	>32	>32	0.1	97.6
	Cefepime	≤0.5	>32	74.9	17.5
	Ceftazidime	>32	>32	33.4	58.7
	Ceftriaxone	32	>64	36.9	44.9
	Imipenem	0.5	1	99	0.5
	Levofloxacin	2	>8	51.0	41.5
	Meropenem	0.12	1	95.5	3.0
	Minocycline	>16	>16	0	100
	PipTazo	32	>128	46.6	32.9
Escherichia coli (n=1683)	Tigecycline	0.25	0.5	99.6	0.2
	Amikacin	2	8	94.5	3.6
	AmoxClav	16	>32	37.4	30.5
	Ampicillin	>32	>32	10.1	89.3
	Cefepime	≤0.5	>32	81.1	14.9
	Ceftazidime	≤8	32	80.0	12.7
	Ceftriaxone	0.12	>64	70.8	23.9
	Imipenem	0.25	0.5	99.7	0.2
	Levofloxacin	8	>8	35.2	61.2
	Meropenem	≤0.06	0.12	98.9	0.7
	Minocycline	16	>16	0	100
	PipTazo	4	64	81.2	9.7
Klebsiella spp (n=1858)	Tigecycline	1	4	76.2	6.8
	Amikacin	2	32	86.8	8.4
	AmoxClav	16	>32	41.4	35.0
	Ampicillin	>32	>32	0	98.5
	Cefepime	1	>32	70.0	24.2
	Ceftazidime	≤8	>32	59.9	34.7
	Ceftriaxone	1	>64	58.4	32.7
	Imipenem	0.25	0.5	99.5	0.3
	Levofloxacin	1	>8	58.9	35.0
	Meropenem	≤0.06	2	91.9	6.7
	Minocycline	>16	>16	0	100.0
	PipTazo	16	>128	59	31.4
All ESBLs* (n=907)	Tigecycline	0.5	4	87.7	4.3
	Amikacin	8	>64	79.9	12.5
	AmoxClav	16	>32	15.8	45.8
	Ampicillin	>32	>32	0.1	99.7
	Cefepime	32	>32	35.2	51.9
	Ceftazidime	>32	>32	24.9	61.7
	Ceftriaxone	>64	>64	10.5	74.9
	Imipenem	0.25	1	99.5	0.0
	Levofloxacin	>8	>8	22.8	71.7
	Meropenem	≤0.06	2	91.7	6.6
	Minocycline	>16	>16	0.0	100.0
	PipTazo	16	>128	50.4	36.5
Serratia spp (n=263)	Tigecycline	2	4	68.4	8.4
	Amikacin	4	32	84.0	9.5
	AmoxClav	>32	>32	2.7	94.3
	Ampicillin	>32	>32	0.8	93.5
	Cefepime	≤0.5	32	84.0	12.9
	Ceftazidime	≤8	>32	73.4	20.5
	Ceftriaxone	2	>64	68.1	18.6
	Imipenem	0.5	2	100.0	0.0
	Levofloxacin	1	>8	66.9	22.4
	Meropenem	0.12	1	95.1	2.7
	Minocycline	16	>16	0.0	100.0
	PipTazo	4	128	76.8	12.9

* ESBL = extended spectrum beta-lactamase from *E. coli*, *K. oxytoca* and *K. pneumoniae*; VRE = vancomycin-resistant enterococci;
† Resistance phenotypes and drug susceptibilities as defined in CLSI document M100-S18, 2008; Tigecycline breakpoints defined by the FDA (Tygacil®, 2005).

Table 2. In vitro activity of tigecycline and comparative agents against minocycline-resistant *Haemophilus influenzae*.

		mcg/mL			
Organism	Drug	MIC_{50}	MIC_{90}	%Sus	%Res
Haemophilus influenzae (n=21)	Tigecycline	0.5	0.5	na	na
	AmoxClav	1	2	100	0
	Ampicillin	1	32	57.1	23.8
	Cefepime	≤0.5	≤0.5	95.2	4.8
	Ceftriaxone	≤0.06	≤0.06	100	0
	Levofloxacin	0.5	0.5	100	0
	Meropenem	≤0.06	0.12	100	0
	Minocycline	16	>16	0	100
	PipTazo	0.12	0.25	100	0

† Resistance phenotypes and drug susceptibilities as defined in CLSI document M100-S18, 2008; na=Tigecycline breakpoints not determined for this species.

Table 3. In vitro activity of tigecycline and comparative agents against minocycline-resistant Gram-positive pathogens.

		mcg/mL			
Organism	Drug	MIC_{50}	MIC_{90}	%Sus†	%Res
Enterococcus spp (n=1668)	Tigecycline	0.12	0.25	99.6	0.4
	Ampicillin	1	>16	84.8	15.2
	Levofloxacin	2	>32	47.6	52.4
	Linezolid	2	2	100	0
	Minocycline	>8	>8	0	100
	Penicillin	4	>8	83.6	16.4
	Vancomycin	1	4	91.5	8.1
All VREs [a] (n=121)	Tigecycline	0.12	0.25	100	0
	Ampicillin	>16	>16	15.7	81.8
	Levofloxacin	>32	>32	0	100
	Linezolid	2	2	100	0
	Minocycline	>8	>8	0	100
	Penicillin	>8	>8	15.7	84.3
	Vancomycin	>32	>32	0	100
Staphylococcus aureus (n=77)	Tigecycline	0.25	0.5	100	0.0
	AmoxClav	>8	>8	10.4	89.6
	Ampicillin	>16	>16	7.8	92.2
	Ceftriaxone	>64	>64	11.7	87.0
	Imipenem	16	>16	18.2	81.8
	Levofloxacin	8	32	14.3	81.8
	Linezolid	2	4	100	0.0
	Meropenem	>16	>16	13.6	84.8
	Minocycline	>8	>8	0.0	100.0
	Penicillin	>8	>8	7.8	92.2
	PipTazo	>16	>16	10.4	89.6
	Vancomycin	1	1	100.0	0.0
Staphylococcus aureus, MRSA [b] (n=69)	Tigecycline	0.5	0.5	100	0
	AmoxClav	>8	>8	0.0	100
	Ampicillin	>16	>16	0.0	100
	Ceftriaxone	>64	>64	1.4	97.1
	Imipenem	>16	>16	0.0	100.0
	Levofloxacin	8	32	5.8	89.9
	Linezolid	2	2	100	0
	Meropenem	>16	>16	5.0	93.3
	Minocycline	>8	>8	0.0	100.0
	Penicillin	>8	>8	0.0	100.0
	PipTazo	>16	>16	0.0	100.0
	Vancomycin	1	1	100.0	0.0

† Resistance phenotypes and drug susceptibilities as defined in CLSI document M100-S18, 2008; Tigecycline breakpoints defined by the FDA (Tygacil®, 2005). FDA breakpoints for tigecycline against vancomycin-susceptible *E. faecalis* are used against vancomycin-resistant enterococci (VRE) presented here for comparative purposes only.
[a] VRE = vancomycin-resistant enterococci
[b] MRSA = methicillin-resistant *S. aureus*

Table 4. In vitro activity of tigecycline and comparative agents against minocycline-resistant nonfermenting gram-negative pathogens.

		mcg/mL			
Organism	Drug	MIC_{50}	MIC_{90}	%Sus†	%Res
Acinetobacter baumannii (n=305)	Tigecycline	1	4	na	na
	Amikacin	16	>64	51.1	41.0
	AmoxClav	>32	>32	na	na
	Ampicillin	>32	>32	na	na
	Cefepime	32	>32	11.5	72.8
	Ceftazidime	>32	>32	8.5	89.2
	Ceftriaxone	>64	>64	6.9	87.5
	Imipenem	2	>16	70.4	27.8
	Levofloxacin	>8	>8	9.2	85.2
	Meropenem	>16	>16	30.5	65.0
	Minocycline	16	>16	0.0	100.0
	PipTazo	128	>128	14.1	70.5
Pseudomonas aeruginosa (n=9695)	Tigecycline	8	>16	na	na
	Amikacin	4	16	90.9	6.0
	Cefepime	4	32	71.3	14.9
	Ceftazidime	≤8	>32	76.5	15.6
	Ceftriaxone	64	>64	11.8	55.8
	Imipenem	1	16	81.1	10.5
	Levofloxacin	2	>8	58.2	34.2
	Meropenem	1	16	75.4	16.1
	Minocycline	>16	>16	0.0	100.0
	PipTazo	8	128	84.8	15.2

† Resistance phenotypes and drug susceptibilities as defined in CLSI document M100-S18, 2008; na=Tigecycline breakpoints not determined for this species. * Minocycline has no CLIS breakpoints for this species; Resistance is defined as ≥16 mcg/ml for *P. aeruginosa* for comparative purposes only.

Conclusions

- Tigecycline demonstrated minimal cross-resistant with minocycline and a variability that was species dependent. There was no cross-resistance of tigecycline with minocycline against *E. coli* and *Acinetobacter* species. Tigecycline MICs against minocycline-resistant *Klebsiella* and *Serratia* were 8- to more than 16-fold lower than minocycline. Neither tigecycline or minocycline demonstrated significant activity against *P. aeruginosa*.
- Tigecycline demonstrated potent in vitro activity against gram-positive strains that were resistant to minocycline. 100% of all minocycline-resistant staphylococci and 99.6% enterococci were inhibited by tigecycline at the defined susceptibility breakpoints of 0.5 and 0.25 mcg/mL, for staphylococci and enterococci (vancomycin-susceptible), respectively.
- The MIC_{90} value of tigecycline was 0.5 against the minocycline-resistant *H. influenzae.*
- Tigecycline exhibited potent in vitro activity against minocycline-resistant strains and may be considered in such cases where the tetracyclines and their analogs have been previously excluded.