#P-655

Acinetobacter Resistance In The United States: In Vitro Evaluation Of Tigecycline and Comparators Against Recent Isolates

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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 70 investigational sites in the United States throughout 2004-2005. **Methods:** A total of 921 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 with TIG susceptible and resistant breakpoints defined as ≤ 2 mcg/ml and ≥ 8 mcg/ml, respectively. **Results:** Resistance rates for comparator drugs were CAZ 49%, CAX 48%, LVX 47%, CPE 38%, PT 27%, AK 8%, IMP 6%, and MIN 2%. TIG inhibited >95% of all resistant isolates except those resistant to AK (92.2%), IMP (88.4%) and MIN (86.7%). There was only one strain found with a TIG-resistant MIC (≥8 mcg/mL). TIG $MIC_{50/90}$ for all resistant strains was 1/2 mcg/ml, except AK and IMP, which were 1/4 mcg/ml. The modal TIG MIC for these resistant strains was 1 mcg/ml compared to 0.12 mcg/ml for susceptible strains, indicating an 8-fold diminishment of activity. **Conclusions:** It has been seen in some species that existing multi-drug efflux pumps may also pump TIG. In spite of this, TIG remained effective and inhibited most *Acinetobacter* strains resistant to one or more other drugs in this study, although the higher TIG MICs seen for these strains suggests some linkage to resistance mechanisms for other drugs. TIG remained effective in inhibiting all strains of *Acinetobacter* spp. further broadening its wide spectrum of activity vs. difficult to treat pathogens.

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, 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 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 MIC_{90} 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 shown to be a 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 activity of tigecycline with comparative antimicrobial agents against clinical isolates *Acinetobacter* spp. 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.
- Clinical isolates were collected tested between January 2004 - October 2005 from 70 study centers in the United States.
- 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 against *Acinetobacter* spp (in units of mcg/mL) are defined as susceptible ≤2; intermediate =4; and resistant ≥8.
- 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

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 Allbanal, 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(4): p. 19-36.
5 Hernebol, 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. 173-7.
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 National Committee for Clinical Laboratory Standards (NCCLS), Performance Standards for Antimicrobial Susceptibility Testing; Fourteenth Informational Supplement. NCCLS document M100-S14. Wayne, PA, 2004.

ACKNOWLEDGEMENTS

This study was supported by a grant from Wyeth Pharmaceuticals. We gratefully acknowledge contributions to the T.E.S.T. study from the following participating institutions:

University of Alabama, Birmingham, AL; University Hospital of Arkansas Medical Center, Little Rock, AR; Scottsdale Memorial Hospital, Scottsdale, AZ; Laboratory Sciences of Arizona, Tempe, AZ; UCLA Medical Center, Los Angeles, CA; UCLA Medical Center, Los Angeles, CA; Stanford University Medical Center, Stanford, CA; Hartford Hospital, Hartford, CT; Yale - New Haven Hospital, New Haven, CT; Christiana Hospital Medical Center, Newark, DE; University of Florida, Gainesville, FL; Sacred Heart Hospital of Pensacola, Pensacola, FL; Emory Univ. Hospital, Atlanta, GA; Northside Hospital, Atlanta, GA; St. Joseph's Hospital, Atlanta, GA; Ingalls Memorial Hospital, Harvey, IL; Clarian Health Partners, Inc./Methodist Hospital, Indianapolis, IN; Via Christi Regional Medical Center, Wichita, KS; University of Louisville Hospital, Louisville, KY; Alton Ochsner Medical Foundation, New Orleans, LA; Boston Children's Hospital, Boston, MA; New England Medical Center, Boston, MA; Sinai Hospital of Baltimore, Baltimore, MD; University of Maryland Medical Center, Baltimore, MD; University of Michigan Medical Center, Ann Arbor, MI; Detroit Medical Center, Detroit, MI; William Beaumont Hospital, Royal Oak, MI; Hennepin County Medical Center, Minneapolis, MN; University Of Mississippi Medical Center, Jackson, MS; New Hanover Regional Medical Center, Wilmington, NC; Wake Forest University Baptist Medical Center, Winston Salem, NC; Dartmouth Medical Center, Hanover, NH; Mountainside Hospital, Montclair, NJ; University Hospital - Newark, Newark, NJ; Tricore Reference Laboratories, Albuquerque, NM; Albany Medical Center Hospital, Albany, NY; Montefiore Medical Center, Bronx, NY; Nassau University Medical Center, East Meadow, NY; New York Hospital Queens, Flushing, NY; Columbia Presbyterian Medical Center, New York, NY; St. Vincent's Hospital & Medical Center, New York, NY; Rochester General Hospital, Rochester, NY; Summa health System, Akron, OH; Cleveland Clinic Foundation, Cleveland, OH; University Hospitals of Cleveland, Cleveland, OH; Miami Valley Hospital, Dayton, OH; RML @ SJMC, Tulsa, OK; Oregon Medical Laboratories, Eugene, OR; Memorial Hospital, Chattanooga, TN; University of Tennessee Medical Center, Knoxville, TN; University of Tennessee Health Science Center, Memphis, TN; Memorial Hermann Hospital, Houston, TX; The Methodist Hospital, Houston, TX; Scott & White Clinic, Temple, TX; Inova Fairfax Hospital, Fairfax, VA; Marshfield Laboratories, Marshfield, WI; Charleston Area Medical Center, Charleston, WV.

RESULTS

Table 1. In vitro activity of tigecycline and comparative agents against 921 strains of *Acinetobacter* spp.

	MIC (mcg/mL)			
Drug	MIC_{50}	MIC_{90}	Range	%Sus[a]
Tigecycline	0.5	1	0.015 - 8	98.4
Amikacin	4	32	≤0.5 - >64	85
Cefepime	16	>32	≤0.5 - >32	47.8
Ceftazidime	16	>32	≤8 - >32	49.3
Ceftriaxone	32	>64	≤0.06 - >64	32.5
Imipenem	0.5	8	≤0.06 - >16	87
Levofloxacin	2	>8	≤0.008 - >8	50.4
Minocycline	≤0.5	8	≤0.5 - >16	88.7
PipTazo	8	>128	≤0.06 - >128	76.2

[a] Breakpoints as defined by CLSI where available (M100-S15), 2005. Tigecycline breakpoints defined as: susceptible <2 mcg/mL for comparative purposes only.

Table 2. In vitro activity of tigecycline and comparative agents against *Acinetobacter* categorized by species.

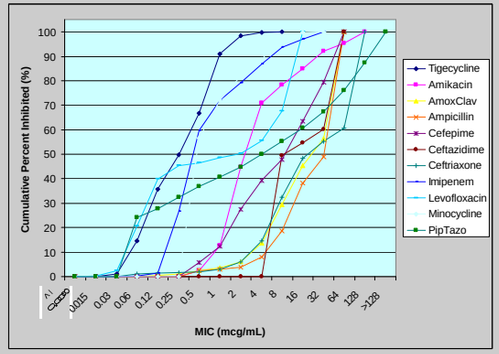
					MIC (mcg/mL)	
Organism	Drug	%Sus	%Int	%Res	MIC_{50}	MIC_{90}
A. baumannii (n = 855)	Tigecycline	98.2	1.6	0.1	0.5	1
	Amikacin	84	7.5	8.5	4	32
	Cefepime	44.9	16.6	38.5	16	>32
	Ceftazidime	46.9	5	48	16	>32
	Ceftriaxone	29.2	23.5	47.3	32	>64
	Imipenem	86.1	7.3	6.7	0.5	8
	Levofloxacin	47.6	5.3	47.1	4	>8
	Minocycline	88	9.7	2.3	≤0.5	8
	PipTazo	74.9	0	25.1	8	>128
A. calcoaceticus (n = 15)	Tigecycline	100	0	0	0.25	2
	Amikacin	93.3	0	6.7	2	8
	Cefepime	60	13.3	26.7	8	>32
	Ceftazidime	66.7	13.3	20	≤8	>32
	Ceftriaxone	40	33.3	26.7	16	>64
	Imipenem	100	0	0	0.5	1
	Levofloxacin	66.7	0	33.3	0.12	>8
	Minocycline	93.3	6.7	0	≤0.5	2
	PipTazo	86.7	0	13.3	4	128
A. lwoffii (n = 48)	Tigecycline	100	0	0	0.06	0.25
	Amikacin	100	0	0	1	4
	Cefepime	91.7	2.1	6.3	1	4
	Ceftazidime	83.3	8.3	8.3	≤8	16
	Ceftriaxone	85.4	8.3	6.3	4	32
	Imipenem	97.9	0	2.1	0.25	0.5
	Levofloxacin	91.7	4.2	4.2	0.12	1
	Minocycline	100	0	0	≤0.5	1
	PipTazo	95.8	0	4.2	≤0.06	4

[a] Breakpoints as defined by CLSI where available (M100-S15), 2005. Tigecycline breakpoints defined as: susceptible ≤2, intermediate =4 and resistant ≥8 mcg/mL for comparative purposes only. Species with n <10 are not shown.

Table 3. Frequency Distribution of tigecycline and comparators against 921 *Acinetobacter* spp. at each MIC (mcg/ml).

	MIC (mcg/mL)														
Drug	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Tigecycline		1	8	126	195	127	158	223	68	14	1					
Amikacin							22	95	295	241	69	61	64	31	43	
AmoxClav					5	4	14	10	22	71	146	145	103	401		
Ampicillin							22	7	6	39	98	179	98	471		
Cefepime							53	62	139	109	77	145	146	190		
Ceftazidime											453	49	51	365		
Ceftriaxone				10	2	2	3	10	28	78	166	146	65	49	362	
Imipenem				2	10	234	303	115	64	73	62	30	28			
Levofloxacin	1	2	20	167	177	50	12	20	15	47	112	298				
Minocycline							521	143	90	63	84	18	2			
PipTazo				223	32	44	40	36	37	48	50	49	61	82	104	115

Figure 1. Cumulative percents inhibited (%) for tigecycline and comparators against 921 *Acinetobacter* spp. at each MIC (mcg/ml).



CONCLUSIONS

- Tigecycline inhibited 98.4% of *Acinetobacter* spp. tested in vitro at a MIC of 2 mcg/mL.
- Tigecycline's MIC_{90} of 1 mcg/mL against *Acinetobacter* spp. was the lowest among all broad spectrum antimicrobials tested.
- With the exception of imipenem, amikacin, and minocycline, all broad spectrum antimicrobials commonly prescribed evaluated in this study (cefepime, ceftazidime, levofloxacin and piperacillin/tazobactam) had limited activity against each *Acinetobacter* species.
- 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.