

In Vitro Activity of Tigecycline and 10 Common Therapeutic Agents Against Current Isolates of *Staphylococcus aureus* and *Enterococcus* Species Resistant to Other Drugs - Worldwide Data, 2006

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REVISED ABSTRACT

Background: Tigecycline (TIG), a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent activity against many gram-positive and -negative organisms. The T.E.S.T. program determined the in vitro activity of TIG against *S. aureus* and enterococci resistant to 10 commonly prescribed antimicrobials: amoxicillin-clavulanic acid (AUG), piperacillin-tazobactam (PT), levofloxacin (LVX), ceftriaxone (CAX), linezolid (LZD), minocycline (MIN), vancomycin (VAN), ampicillin (AMP), penicillin (P) and imipenem (IMP). Study strains were collected from 205 clinical laboratories worldwide between 2004-2006. **Methods:** A total of 8,104 clinical isolates (3,039 enterococci, 5,065 *S. aureus*) 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. TIG susceptible breakpoints were defined as ≤ 0.5 mcg/mL for *S. aureus* and ≤ 0.25 mcg/mL for enterococci. **Results:** 565/3039 (18.6%) enterococci and 557/5065 (11.0%) *S. aureus* were resistant to 3 or more CLSI drug classes. Among the MDR enterococci, resistance rates were LVX 99.6%, AMP 97.9%, VAN 96.6%, MIN 11.9%, LZD 0% and TIG 0%. Resistant rates for *S. aureus* (all the MDR staphylococci were MRSA) were PT 99.3%, AMP 100%, AUG 99.8%, LVX 100%, CAX 98.9%, IMP 100%, MIN 0.7%, LZD 0%, VAN 0% and TIG 0%. TIG inhibited 100% of the enterococci and *S. aureus* resistant to other drugs at MIC values of 0.25 and 0.5 mcg/mL, respectively. Modal TIG MICs ranged between 0.03 and 0.12 mcg/mL for all MDR strains. **Conclusion:** TIG retained potent activity against MDR *S. aureus* and enterococcal isolates, inhibiting 100% of all resistant strains tested at the defined susceptibility breakpoints. TIG should prove to be a useful drug for therapy of infections with these resistant gram-positive 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, 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]. Tigecycline has shown to be a highly effective 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 beta-lactamase (ESBL) and AmpC producing strains [10]. Tigecycline has demonstrated MIC₉₀ values of < 0.5 mcg/ml against methicillin-resistant *Staphylococcus aureus* (MRSA) and other gram-positive organisms [2, 4-6]. Tigecycline has shown potent activity against animal models infected with selected strains of multi-drug resistant *Enterococcus faecium* and *Enterococcus faecalis* [4, 5] with diverse genotypes van-A, -B and -C [6].

This study was designed to better define the in vitro activity of tigecycline in multi-drug resistant *Staphylococcus aureus* and *Enterococcus* clinical isolates collected from 205 study centers worldwide.

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. Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution.
- Clinical isolates (n=8,104) were collected tested between January 2004 - December 2006 from 205 study centers in 30 countries
- Custom broth microdilution panels were supplied by MicroScan (Dade MicroScan, 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 for all drugs except tigecycline followed published guidelines established by the CLSI where applicable [12]. MIC interpretive criteria for tigecycline followed criteria established by the Federal Drug Administration (FDA, United States, 2005) where applicable [13].
- Quality control of broth microdilution panels followed manufacture's and CLSI guidelines using the following ATCC strains: *Enterococcus faecalis* ATCC 29212; *Staphylococcus aureus* ATCC 29213.
- The collection and transportation 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, USA).

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. Macielago, 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 Herwood, 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 Clinical Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; 16th Informational Supplement. CLSI document M100-S16. Wayne, PA, 2006.
- 13 Tygacil[®], 2005. Tigecycline FDA package insert.

ACKNOWLEDGEMENTS

This study was supported by a grant from Wyeth Pharmaceuticals. We gratefully acknowledge contributions from the current 205 participants in the T.E.S.T. program who have helped make this program a success.

RESULTS

The results are listed in the following tables.

Table 1. In vitro activity of tigecycline and comparative agents against 1,122 multi-drug resistant clinical isolates of *Staphylococcus aureus* and *Enterococcus* species.*

Multi-drug Resistant [‡]	Drug	%Sus	MIC (mcg/mL)		
			MIC ₅₀	MIC ₉₀	Range
<i>Enterococcus</i> spp (all enterococci combined) (n=565)	Tigecycline	100	0.06	0.12	0.015 - 0.25
	Ampicillin	2.1	>16	>16	1 - >16
	Levofloxacin	0.4	>32	>32	2 - >32
	Linezolid	96.1	2	2	≤ 0.5 - 4
	Minocycline	69.9	≤ 0.25	>8	≤ 0.25 - >8
<i>Enterococcus faecium</i> (n=546)	Tigecycline	100	0.03	0.12	0.015 - 0.25
	Ampicillin	1.6	>16	>16	2 - >16
	Levofloxacin	0.4	>32	>32	2 - >32
	Linezolid	96.2	2	2	≤ 0.5 - 4
	Minocycline	71.2	≤ 0.25	>8	≤ 0.25 - >8
<i>Enterococcus faecalis</i> (n=3)	Tigecycline	**	**	**	0.12 - 0.12
	Ampicillin	**	**	**	1 - 2
	Levofloxacin	**	**	**	32 - >32
	Linezolid	**	**	**	39115
	Minocycline	**	**	**	>8 - >8
<i>Enterococcus avium</i> (n=1)	Tigecycline	**	**	**	0.06 - 0.06
	Ampicillin	**	**	**	>16 - >16
	Levofloxacin	**	**	**	32 - 32
	Linezolid	**	**	**	1 - 1
	Minocycline	**	**	**	8 - 8
<i>Enterococcus durans</i> (n=10)	Tigecycline	100	0.06	0.12	0.03 - 0.25
	Ampicillin	0	>16	>16	>16 - >16
	Levofloxacin	0	>32	>32	32 - >32
	Linezolid	90	2	2	1 - 4
	Minocycline	20	8	>8	4 - >8
<i>Enterococcus gallinarum</i> (n=1)	Tigecycline	**	**	**	0.03 - 0.03
	Ampicillin	**	**	**	>16 - >16
	Levofloxacin	**	**	**	16 - 16
	Linezolid	**	**	**	1 - 1
	Minocycline	**	**	**	≤ 0.25 - ≤ 0.25
<i>Enterococcus Group D</i> (n=1)	Tigecycline	**	**	**	0.03 - 0.03
	Ampicillin	**	**	**	>16 - >16
	Levofloxacin	**	**	**	>32 - >32
	Linezolid	**	**	**	2 - 2
	Minocycline	**	**	**	8 - 8
<i>Enterococcus hirae</i> (n=1)	Tigecycline	**	**	**	0.03 - 0.03
	Ampicillin	**	**	**	>16 - >16
	Levofloxacin	**	**	**	32 - 32
	Linezolid	**	**	**	2 - 2
	Minocycline	**	**	**	≤ 0.25 - ≤ 0.25
<i>Enterococcus raffinosus</i> (n=1)	Tigecycline	**	**	**	0.06 - 0.06
	Ampicillin	**	**	**	>16 - >16
	Levofloxacin	**	**	**	>32 - >32
	Linezolid	**	**	**	2 - 2
	Minocycline	**	**	**	4 - 4
<i>Enterococcus, non-specified</i> (n=1)	Tigecycline	**	**	**	0.06 - 0.06
	Ampicillin	**	**	**	>16 - >16
	Levofloxacin	**	**	**	32 - 32
	Linezolid	**	**	**	≤ 0.5 - ≤ 0.5
	Minocycline	**	**	**	2 - 2
<i>Staphylococcus aureus</i> , MRSA (n=557)	Tigecycline	100	0.12	0.5	0.03 - 0.5
	AmoxClav	0.2	>8	>8	4 - >8
	Ampicillin	0	>16	>16	1 - >16
	Ceftriaxone	0.2	>64	>64	4 - >64
	Imipenem	0	>16	>16	16 - >16
	Levofloxacin	0	16	>32	4 - >32
	Linezolid	100	2	2	≤ 0.5 - 4
	Minocycline	91.6	≤ 0.25	4	≤ 0.25 - >8
	Penicillin	0	>8	>8	8 - >8
	PipTazo	0.7	>16	>16	1 - >16
Vancomycin	100	1	1	0.25 - 2	

* Susceptibilities are defined in CLSI document M100-S16 (2006) where applicable. Tigecycline breakpoints are defined in FDA package insert (Tygacil[®], 2005) as susceptible less than or equal to 0.25 mcg/mL for vancomycin-susceptible *E. faecalis*. This breakpoint was expanded to include all enterococci for comparative purposes only.

[‡] Multi-drug resistance is defined as any organism resistant to 3 or more CLSI (M100-S16, 2006) drug classes. All multi-drug resistant *S. aureus* were also oxacillin-resistant.

** %Susceptible, MIC₅₀ and MIC₉₀ not calculated for species with n<10.

CONCLUSIONS

- Tigecycline inhibited 100% of all multi-drug resistant (MDR) *Staphylococcus aureus* at or below 0.5 mcg/mL and 100% of all multi-drug resistant enterococci at or below 0.25 mcg/mL. The in vitro activity of tigecycline was equivalent to linezolid and vancomycin against MDR *S. aureus* and equivalent to linezolid against all MDR enterococci.
- All of the multi-drug resistant *S. aureus* were resistant to oxacillin (methicillin-resistant phenotype) and 93% of all the multi-drug resistant enterococci were resistant to vancomycin.
- The in vitro activity of tigecycline in this study suggests that tigecycline should be seriously considered for the treatment of *S. aureus* and enterococci that are resistant to multiple drugs and multiple drug classes including methicillin-resistant and vancomycin-resistant phenotypes.