

Vancomycin Resistant Enterococci (VRE) in Central and South America: Antimicrobial Susceptibility

ER006

S. Hawser¹, M. Hackel¹, S. Bouchillon¹, B. Johnson¹, D. Hoban¹, M. Renteria¹, J. Johnson¹, R. Badal¹, 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: Tigecycline (TIG), a member of a new class of antimicrobials (glycylcyclines), has been shown to have 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 tigecycline compared to amoxicillin-clavulanic acid, piperacillin-tazobactam, levofloxacin, ceftriaxone, linezolid (LZD), minocycline (MIN), vancomycin (VAN), ampicillin (AM), penicillin (PEN), and imipenem against VRE collected from hospitals in Central and South America throughout 2004-2008. **Methods:** 94 VRE (17 *Enterococcus faecalis*, 77 *E. faecium*) clinical isolates 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 supplied broth microdilution panels and interpreted according to CLSI guidelines with tigecycline susceptible defined as ≤ 2 $\mu\text{g/ml}$. **Results:** %S of all VRE to TIG, LZD, and MIN were 100, 100, and 68.1, respectively. Vancomycin-resistant *E. faecalis* strains were 100% sensitive to TIG, LZD, and AM. For vancomycin-resistant *E. faecium*, the three most active drugs were TIG (100%), LZD (100%), and MIN (68.8%). **Conclusions:** Tigecycline exhibited activity against all VRE, inhibiting 100% of strains at MIC values of ≤ 0.25 $\mu\text{g/ml}$ ($\text{MIC}_{90} = 0.25$), surpassing LZD ($\text{MIC}_{90} = 2$) as the most active drug in this study. The broad spectrum of TIG, which includes many other multi-resistant Gram-positive and Gram-negative bacteria in addition to VRE, may make it a possible addition to hospital formularies.

Introduction

Tigecycline is a member of a new class of antimicrobial agents, the glycylcyclines. This synthetic analogue of the tetracyclines exhibits antibacterial activity that is both bacteriostatic and, in certain instances, bactericidal with killing activity as much as fourfold better than vancomycin and daptomycin [1, 2]. The development of tigecycline is important in that it and other glycylcyclines 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 restored 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 MIC_{90} s at or below 2 $\mu\text{g/ml}$, including difficult-to-treat methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* [4-7]. The relatively limited treatment options for infections due to VRE in particular have led to development of new compounds with activity against these problematic pathogens. This study was undertaken to document the in vitro activity of tigecycline against clinical isolates of VRE from Central and South America. This study is part of the larger ongoing global Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) project.

Materials & Methods

- All isolates were collected between 2004-2008 and 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. 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 [8]. 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 $\mu\text{g/ml}$): ampicillin (0.06-16); linezolid (0.5-8); levofloxacin (0.06-32); minocycline (0.25-8); tigecycline (0.008-16); penicillin (0.06-8); and vancomycin (0.12-32). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [9] and the recent US Food and Drug Administration package insert for tigecycline [10], where applicable.
- Quality controls (QC) were performed by each testing site on each day of testing using ATCC control strains *S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2007) guidelines [8].

References

- Hoellman, D.B., et al., Antipneumococcal activities of GAR-936 (a new glycylcycline) compared to those of nine other agents against penicillin-susceptible and -resistant pneumococci. *Antimicrob Agents Chemother*, 2000, 44(4): p. 1085-8.
- 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 glycylcycline 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 glycylcycline, 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 beta-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-A8. 2007: 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 19087-18.
- Tygaicil, 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

Results are shown in the following tables.

Table 1. Rates of Vancomycin resistance among *Enterococcus faecalis* and *Enterococcus faecium* isolates from Central and South America.

	% Vancomycin Resistant
<i>Enterococcus faecalis</i>	2.4% (17/715)
<i>Enterococcus faecium</i>	42.3% (77/182)

Table 2. In vitro activity of tigecycline and comparative antimicrobials against 94 vancomycin-resistant *Enterococcus* spp from Central and South America.

Organism	Drug	%Sus	%Int	%Res	MIC ($\mu\text{g/ml}$)	
					MIC_{50}	MIC_{90}
Vancomycin-Resistant <i>Enterococcus</i> spp (combined) (n=94)	Tigecycline	100	0	0	0.06	0.25
	Ampicillin	20.2	0	79.8	>16	>16
	Levofloxacin	0	0	100	>32	>32
	Linezolid	100	0	0	2	2
	Minocycline	68.1	10.6	21.3	0.5	>8
	Penicillin	18.1	0	81.9	>8	>8
<i>E. faecalis</i> , VRE (n=17)	Tigecycline	100	0	0	0.12	0.25
	Ampicillin	100	0	0	2	4
	Levofloxacin	0	0	100	32	>32
	Linezolid	100	0	0	1	2
	Minocycline	64.7	11.8	23.5	4	>8
	Penicillin	88.2	0	11.8	4	>8
<i>E. faecium</i> , VRE (n=77)	Tigecycline	100	0	0	0.06	0.25
	Ampicillin	2.6	0	97.4	>16	>16
	Levofloxacin	0	0	100	>32	>32
	Linezolid	100	0	0	2	2
	Minocycline	68.8	10.4	20.8	≤ 0.25	>8
	Penicillin	2.6	0	97.4	>8	>8
	Vancomycin	0	0	100	>32	>32

* Interpretive criteria as defined by CLSI, M100-S18 (2008), where applicable; Tigecycline FDA breakpoints for enterococci are approved for vancomycin susceptible *E. faecalis*, only; susceptibilities for all other enterococci are entered for comparison purposes only [10].

Table 3. In vitro activity of tigecycline and comparators against vancomycin resistant *Enterococcus* spp. from Central and South America (n=94) showing frequency distribution (n) and cumulative percent inhibited (%).

	MIC (mcg/mL)												
	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	≥ 64
Tigecycline	24	39	20	11									
Ampicillin						8	6	3	2	1	74		
						8.5	14.9	18.1	20.2	21.3	100		
Levofloxacin							1			8	12	73	
										1.1	9.6	22.3	100
Linezolid						27	66	1					
						28.7	98.9	100					
Minocycline			45	2	3	3	11	10	20				
			47.9	50.0	53.2	56.4	68.1	78.7	100				
Penicillin							2	8	7	77			
							2.1	10.6	18.1	100			
Vancomycin											6	88	
											6.4	100	

Conclusions

- Tigecycline exhibited in vitro activity against VRE in Central and South America, inhibiting 100% of strains at MICs ≤ 0.25 $\mu\text{g/mL}$.
- Tigecycline's MIC_{90} of 0.25 $\mu\text{g/mL}$ vs. VRE was 8 fold lower than that of linezolid, and >64 fold lower than that of any other comparator in this study.
- Tigecycline's potent activity against vancomycin-resistant *E. faecalis* and *E. faecium* should make it a useful addition to the list of antimicrobial agents against these resistant strains with limited therapeutic options.