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An In Vitro Evaluation of Tigecycline and Ten Comparators against Methicillin-Resistant *Staphylococcus Aureus* Collected From a Recent Global Population: TEST Program 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 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 amoxicillin-clavulanic acid, piperacillin-tazobactam, levofloxacin, ceftriaxone, linezolid (LZD), minocycline (MIN), vancomycin (VAN), ampicillin, penicillin and imipenem against methicillin-resistant *S. aureus* (MRSA) isolates collected globally throughout 2004-2005. **Methods:** A total of 2,180 clinical isolates of MRSA were identified to the species level at each participating site and confirmed by the central laboratory. Minimum Inhibitory Concentration (MICs) were determined by the local laboratory using supplied broth microdilution panels and interpreted according to CLSI guidelines, except for tigecycline, which used the susceptible breakpoint ≤ 0.5 mcg/mL for *S. aureus* (including MRSA) as defined in the FDA approved package insert. **Results:** The %S for the study drugs with MRSA activity--TIG, VAN, LZD, and MIN--was 99, 100, 100, and 98, respectively. There were no significant differences among geographic regions, except for lower activity of MIN in Asia (%S = 75%) compared to Europe (98%) and North America (99%), whereas TIG inhibited 99% or better of MRSA at 0.5 mcg/mL in all regions. There was little difference seen in the susceptibilities of isolates from hospital (n=1,636) vs. community acquired MRSA (n=408). **Conclusion:** TIG was as potent as VAN, LZD, and MIN in this study, inhibiting 2,160/2,180 (99%) of the MRSA isolates at their respective breakpoints. TIG's excellent expanded broad spectrum of activity against MRSA should make it a very useful drug in treatment of difficult staphylococcal infections.

INTRODUCTION

Resistant, *Staphylococcus aureus* and other resistant gram-positive bacteria, continue to be a therapeutic challenge for the clinician. Despite the introduction of new antimicrobials Glycylcyclines are showing the promise of significant activity against many gram-positive pathogens including methicillin-resistant *S. aureus*. Tigecycline, the first glycylcycline to enter clinical trials, has shown excellent activity against *Staphylococcus* spp.

While developed to provide activity against tetracycline- and multi-drug-resistant gram-positive pathogens, tigecycline has been demonstrated to possess significant broad-spectrum activity against aerobic and anaerobic gram-positive and gram-negative microorganisms [1,3-5]. Tigecycline MIC₉₀ value of ≤ 0.5 mcg/ml have been demonstrated against methicillin-resistant *S. aureus* (MRSA) [2, 4-6].

Tigecycline resistance is very infrequent and difficult to induce in the laboratory [7, 8] with a selection frequency observed at less than 10^{-9} [2, 3, 7]. Most tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline [1-4, 6, 9-11]. The pharmacokinetics of parenteral tigecycline is linear with an unusually long half-life of 36 hours and a maximum serum concentration (C_{MAX}) of a 300 mg dose infused over 1 hour of 2.8 mcg/ml [12].

This study was initiated to evaluate the in vitro activity of tigecycline as compared with those of 8 comparator agents (amoxicillin-clavulanic acid, imipenem, ceftriaxone, levofloxacin, minocycline, linezolid, piperacillin-tazobactam and vancomycin) against *S. aureus* including methicillin-resistant *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA) from the T.E.S.T. program evaluation 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.
- Clinical isolates were collected and tested during the time period from January 2004 to March 2006 at 205 study centers in 30 countries.
- Antimicrobial agents tested with concentrations (expressed in mcg/ml) were: amoxicillin/clavulanic acid (0.03-8); levofloxacin (0.06-32); ceftriaxone (0.03-64); linezolid (0.5-8); minocycline (0.25-8); vancomycin (0.12-32); tigecycline (0.008-16) and imipenem (0.12-16). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute (CLSI) where applicable [13]. Tigecycline tentative breakpoints (in units of mcg/mL) against *S. aureus* are defined as susceptible < 0.5 (Tygacil® 2005) [14].
- Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution. All MRSA and MSSA were confirmed by the central laboratory using oxacillin disk test (Oxoid).
- Quality control followed CLSI guidelines using quality control organism *S. aureus* ATCC 29213.
- The collection and transportation of organisms and the confirmation of identification, as well as, construction and management of a centralized database was coordinated by Laboratories International for Microbiology Studies (LIMS), a subsidiary of International Health Management Associates, Inc. (IHMA, Schaumburg, IL).

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RESULTS

Table 1: In vitro activity of Tigecycline and comparator agents against 2,180 isolates of methicillin-resistant *Staphylococcus aureus*.

Organism	Drug ^a	%Sens	%Int	%Res	MIC (mcg/ml)	
					MIC ₅₀	MIC ₉₀
<i>Staphylococcus aureus</i> , MRSA (n=617)	Tigecycline	99.1	0	0.9	0.12	0.25
	Amox/Clav	31.6	0	68.4	8	>8
	Ceftriaxone	11	45.8	43.2	32	>64
	Imipenem	76.8	3.4	19.8	0.5	>16
	Levofloxacin	19.2	3.3	77.6	8	>32
	Linezolid	100	0	0	2	2
	Minocycline	97.6	2.2	0.2	≤ 0.25	2
	Pip/Tazo	38.3	0	61.7	16	>16
	Vancomycin	100	0	0	1	1

^aBreakpoints as defined by CLSI (M100-S16), 2006. Tigecycline breakpoints defined as: susceptible ≤ 0.5 mcg/mL; no intermediate; resistant >0.5 mcg/mL (Tygacil®, 2005).

Table 2: Regional *In vitro* activity of tigecycline and comparator agents against 2,180 isolates of methicillin-resistant *Staphylococcus aureus*.

Region	Drug ^a	%Sens	%Int	%Res	MIC (mcg/mL)	
					MIC ₅₀	MIC ₉₀
Asia / Pacific Rim (n=86)	Tigecycline	100	0	0	0.12	0.5
	AmoxClav	34.9	0	65.1	>8	>8
	Ceftriaxone	17.4	17.4	65.1	>64	>64
	Imipenem	53.5	2.3	44.2	2	>16
	Levofloxacin	26.7	0	73.3	4	>32
	Linezolid	100	0	0	2	2
	Minocycline	75.6	22.1	2.3	2	8
	PipTazo	33.7	0	66.3	>16	>16
	Vancomycin	100	0	0	1	1
	Europe (n=269)	Tigecycline	98.9	0	1.1	0.12
AmoxClav		31.1	0	68.9	>8	>8
Ceftriaxone		10.1	27.7	62.2	>64	>64
Imipenem		59.8	2.3	38	2	>16
Levofloxacin		12	3.7	84.3	8	32
Linezolid		100	0	0	2	2
Minocycline		98.1	1.9	0	≤ 0.25	4
PipTazo		34.1	0	65.9	>16	>16
Vancomycin		100	0	0	1	2
Latin America (n=95)		Tigecycline	98.9	0	1.1	0.12
	AmoxClav	13.7	0	86.3	>8	>8
	Ceftriaxone	6.3	9.5	84.2	>64	>64
	Imipenem	23.2	4.2	72.6	>16	>16
	Levofloxacin	14.7	11.6	73.7	4	16
	Linezolid	100	0	0	2	2
	Minocycline	97.9	2.1	0	≤ 0.25	4
	PipTazo	13.7	0	86.3	>16	>16
	Vancomycin	100	0	0	1	1
	North America (n=1,701)	Tigecycline	99.2	0	0.8	0.12
AmoxClav		32.5	0	67.5	8	>8
Ceftriaxone		10.9	52.7	36.3	32	>64
Imipenem		84.4	3.6	11.9	0.5	16
Levofloxacin		20	2.9	77.1	16	>32
Linezolid		100	0	0	2	2
Minocycline		99.4	0.5	0.1	≤ 0.25	0.5
PipTazo		40.7	0	59.3	16	>16
Vancomycin		100	0	0	1	1

^aBreakpoints as defined by CLSI (M100-S16), 2006. Tigecycline breakpoints defined as: susceptible ≤ 0.5 mcg/mL; no intermediate; resistant >0.5 mcg/mL (Tygacil®, 2005). Regions with n's <20 are not shown.

Table 3: Comparison of Hospital vs. Community Acquired MRSA In vitro activity of tigecycline and comparator agents.

Demographics	Drug ^a	%Sens	%Int	%Res	MIC (mcg/mL)	
					MIC ₅₀	MIC ₉₀
Hospital Acquired MRSA (n=1,636)	Tigecycline	99	0	1	0.12	0.25
	AmoxClav	30.7	0	69.3	8	>8
	Ceftriaxone	10.6	44	45.4	32	>64
	Imipenem	75.2	3.9	21	0.5	>16
	Levofloxacin	16.9	3.1	80	8	>32
	Linezolid	100	0	0	2	2
Community Acquired MRSA (n=408)	Minocycline	97.5	2.4	0.1	≤ 0.25	2
	PipTazo	37.7	0	62.3	16	>16
	Vancomycin	100	0	0	1	1
	Tigecycline	99.8	0	0.2	0.12	0.25
	AmoxClav	32.8	0	67.2	8	>8
	Ceftriaxone	11	55.9	33.1	16	>64
Community Acquired MRSA (n=408)	Imipenem	85.5	1.7	12.7	0.5	16
	Levofloxacin	28.9	3.4	67.6	4	>32
	Linezolid	100	0	0	2	2
	Minocycline	99.5	0.5	0	≤ 0.25	0.5
	PipTazo	39.2	0	60.8	16	>16
	Vancomycin	100	0	0	1	1

^aBreakpoints as defined by CLSI (M100-S16), 2006. Tigecycline breakpoints defined as: susceptible ≤ 0.5 mcg/mL; no intermediate; resistant >0.5 mcg/mL (Tygacil®, 2005).

CONCLUSIONS

- Tigecycline inhibited the growth of >99% of a global population of methicillin-resistant *Staphylococcus aureus* at a MIC value of 0.5 mcg/ml.
- Tigecycline demonstrates greater in vitro activity against MRSA than levofloxacin, imipenem and the comparator beta-lactam antimicrobials.
- Tigecycline demonstrates in vitro activity comparable to commonly prescribed antimicrobial agents, linezolid and vancomycin, currently used for the treatment of serious staphylococcal nosocomial infections.
- Regional variations of tigecycline in vitro activity were insignificant with >98% of all MRSA inhibited at 0.5 mcg/mL.
- There were no discernable differences in tigecycline in vitro activity between hospital or community acquired MRSA.
- Tigecycline appears to be promising agent in the treatment of MRSA with in vitro activity equivalent to linezolid and vancomycin.