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Tigecycline, a Novel Glycylcycline with Promising Anti-Staphylococcal Activity

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REVISED ABSTRACT

Background: Resistance of gram-positive bacteria continues to be a therapeutic challenge for the clinician. The development of glycylcyclines, which are novel derivatives of tetracyclines, are showing promise of significant activity against many gram-positive pathogens. Tigecycline (GAR-936, Wyeth) is a new glycylcycline currently in development, that has shown potent activity against *Staphylococcus* spp. The activity of tigecycline was compared with other agents against methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA) from hospitals in Europe, the Middle East and South Africa. **Methods:** Clinical isolates were collected between January 2001 - September 2002. A total of 499 isolates were identified to genus and species at each site and confirmed by the central laboratory. MIC's were determined by the central laboratory using broth microdilution panels from Dade Microscan according to NCCLS guidelines and manufacturer's instructions. **Results:** The susceptibility results of the 499 isolates of *Staphylococcus aureus* are listed in Table 1.

Table 1. In Vitro activity of Tigecycline Against 499 Enterobacteriaceae

Antibiotic	MSSA (n=250)				MRSA (n=249)			
	Range Low	Range High	MIC ₅₀	MIC ₉₀	Range Low	Range High	MIC ₅₀	MIC ₉₀
Tigecycline	0.12	1	0.25	0.25	0.12	2	0.25	0.5
Amoxicillin/clav	0.25	64	1	1	0.25	64	32	64
Ampicillin/sulb	0.5	>32	1	4	0.5	>32	32	32
Imipenem	0.5	>64	0.5	0.5	0.5	>64	32	64
Cefepime	0.5	>64	8	8	0.5	>64	>64	>64
Ceftazidime	2	>64	8	8	0.5	>64	>64	>64
Ceftriaxone	0.5	>64	4	4	0.5	>64	>64	>64
Levofloxacin	0.25	16	0.25	0.25	0.25	32	8	16
Vancomycin	0.5	>64	1	1	0.25	>64	1	1
Quinupristin/dalfopristin	0.12	>32	0.25	0.25	0.12	>32	0.5	1
Linezolid	1	>32	2	4	0.5	>32	2	4

Conclusion: The in vitro activity of tigecycline against MSSA and MRSA was comparable in all isolates tested. Tigecycline activity against MRSA was superior to all antimicrobial tested including linezolid, imipenem and quinupristin/dalfopristin.

INTRODUCTION

Glycylcyclines are tetracyclines with a 9-glycylamido substituent and were developed to avoid the two most prevalent tetracycline resistance mechanisms, ribosomal protection and efflux. Tigecycline is a glycylcycline derivative of minocycline, a semi-synthetic tetracycline, with a 9-t-butylglycylamido substitution [1]. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit. Although its antibacterial activity is significant, it is considered to be bacteriostatic [2, 3]. While developed to provide activity against tetracycline- and multi-drug-resistant gram-positive pathogens, it has been demonstrated to

possess significant broad-spectrum activity against aerobic and anaerobic gram-positive and gram-negative microorganisms [2, 4-6]. Tigecycline MIC₉₀ values of ≤ 0.5 mcg/ml have been demonstrated against methicillin-resistant *Staphylococcus aureus* (MRSA) [3, 5-7].

Tigecycline resistance is very infrequent and difficult to induce in the laboratory [8, 9] with a selection frequency observed at less than 10^{-9} [3, 4, 8]. Most tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline [2-5, 7, 10-12]. 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 µg/mL [13, 14].

This study compared the activity of tigecycline with other agents against methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA) from hospitals in Europe, the Middle East and South Africa.

MATERIALS & METHODS

- All isolates were derived from blood, respiratory tract, urine (no more than 30% of all isolates), skin, wound, fluids and other defined sources. Only one isolate per patient was accepted.
- Clinical isolates were collected between January 2001 - September 2002 from 34 study centers in 16 countries.
- Isolates were identified to genus and species at each site and confirmed by the central laboratory (Laboratories International for Microbiology Studies, Schaumburg, IL, USA).
- Organism collection, transport, confirmation of organism identification, antimicrobial susceptibility testing, as well as, development and management of a centralized database was coordinated by Laboratories International for Microbiology Studies (LIMS).

Antimicrobial Susceptibility Testing

- MIC's were determined by the central laboratory using broth microdilution panels by Dade Microscan (Dade Behring Inc., Sacramento, CA, USA) according to NCCLS guidelines and manufacturer's instructions [15].
- Quality Control was performed using the following ATCC strains: *E. coli* ATCC 25922, *E. faecalis* ATCC 29212, and *S. aureus* ATCC 29213.

RESULTS

Results are presented in the following tables and graphs.

Table 2. In Vitro Activity of Tigecycline and Comparator Agents Against 499 Isolates of *Staphylococcus aureus*.

Organism/Phenotype	Drug	NCCLS BP*	MIC (mg/ml)		% Sus
			Range	MIC ₅₀ MIC ₉₀	
<i>S. aureus</i> , MSSA (250)	Tigecycline	2**	0.12 - 1	0.25 0.25	100.0
	Amox/Clav	4/2	0.25 - 64	1 1	95.6
	Amp/Sulb	8/4	0.5 - >32	1 4	95.6
	Cefepime	8	0.5 - >64	2 4	95.2
	Ceftazidime	8	2 - >64	8 8	93.6
	Ceftriaxone	8	0.5 - >64	4 4	94.4
	Imipenem	4	0.5 - >64	0.5 0.5	96.4
	Levofloxacin	2	0.25 - 16	0.25 0.25	94.0
	Linezolid	4	1 - >32	2 4	99.2
	Quinu/Dalfo	1	0.12 - >32	0.25 0.25	99.2
	Vancomycin	4	0.5 - >64	1 1	99.6
	<i>S. aureus</i> , MRSA (249)	Tigecycline	2**	0.12 - 2	0.25 0.5
Amox/Clav		4/2	0.25 - 64	32 64	17.3
Amp/Sulb		8/4	0.5 - >32	32 32	24.9
Cefepime		8	0.5 - >64	>64 >64	10.4
Ceftazidime		8	0.5 - >64	>64 >64	3.2
Ceftriaxone		8	0.5 - >64	>64 >64	6.0
Imipenem		4	0.5 - >64	32 64	24.9
Levofloxacin		2	0.25 - 32	8 16	13.7
Linezolid		4	0.5 - >32	2 4	99.2
Quinu/Dalfo		1	0.12 - >32	0.5 1	99.2
Vancomycin		4	0.25 - >64	1 1	99.6

* Breakpoints defined by the NCCLS 2002, document M100-S12 [16]
** Tigecycline tentative breakpoint defined as susceptible ≤ 2 mcg/ml.

MRSA: methicillin resistant *S. aureus*; MSSA: methicillin susceptible *S. aureus*.

Figure 1. In Vitro Activity of Tigecycline and Comparators Against 250 MSSA Showing Cumulative Percent Inhibited (%) at Each MIC (µg/mL)

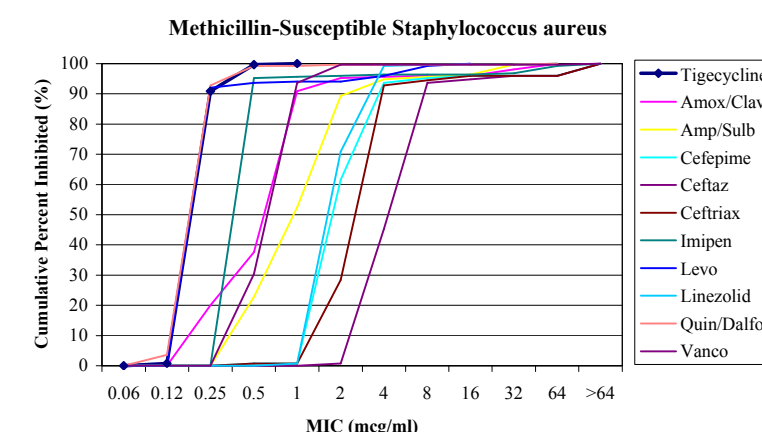
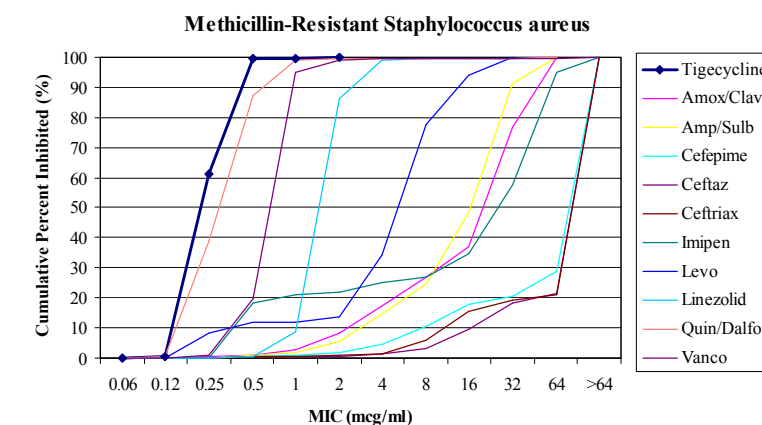


Figure 2. In Vitro Activity of Tigecycline and Comparators Against 249 MRSA Showing Cumulative Percent Inhibited (%) at Each MIC (µg/mL)



CONCLUSIONS

- Tigecycline inhibited the growth of all MSSA and MRSA at a MIC ≤ 2 µg/mL.
- Tigecycline demonstrates in vitro activity comparable to or better than both vancomycin and quinupristin/dalfopristin against all MSSA and MRSA.
- Tigecycline demonstrates greater in vitro activity against MSSA and MRSA than linezolid, levofloxacin, imipenem and the β -lactam antimicrobials.
- Tigecycline appears to be promising agent in the treatment of methicillin sensitive and methicillin resistant *Staphylococcus aureus*.

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