C2-2000

Activity of Tigecycline Tested Against 3,498 *Staphylococcus aureus*: An Assessment Versus Community-Acquired ORSA

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ICAAC 2004
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ABSTRACT

Background:

Tigecycline (TIG; formerly GAR-936) is the first glycylcycline to be developed as a parenteral agent targeting respiratory, skin and soft tissue and other pathogens. We evaluated in vitro activity of TIG and selected comparators against recent *S. aureus* (SA) isolates (3,498) recovered from nosocomial (NA) and community-acquired (CA) infections.

Methods:

The collection included non-duplicate SA strains originating from CA infections (oxacillin-susceptible [Oxa-S], 1,592 strains; oxacillin-resistant [Oxa-R] 652 strains) and from NA infections (Oxa-S, 706 strains; Oxa-R, 548 strains) submitted to the TIG surveillance program (2000-2003). MIC values for 21 antimicrobials were determined using reference NCCLS methods. A tentative TIG breakpoint of ≤1 µg/ml was used for comparison only.

Results:

Oxa-S SA originating from CA or NA infections were almost identical in their antibiograms with greater than 90% S to all tested compounds; only erythromycin (74.7 to 72.9%, respectively) and penicillin (17.7 to 17.4%) were less S. Compared to Oxa-S strains, Oxa-R strains from both groups demonstrated significant increases in R rates to erythromycin, clindamycin, chloramphenicol, gentamicin and fluoroquinolones, and was most notable among NA SA. Ciprofloxacin S among all Oxa-S strains varied from 89.7 to 91.3%, but dropped to 15.2 and 6.0%, respectively, among CA and NA Oxa-R strains. Greater than 90% of SA isolates remained S to tetracycline (90.8 to 97.2%) and doxycycline (96.1 to 99%) with the lowest S occurring among Oxa-R strains originating from CA infections. TIG, however, was uniformly active against SA (MIC_{50} and MIC_{90} at 0.25 and 0.5 µg/ml) and all strains were inhibited by 1 µg/ml or less. Multi-drug resistant mechanisms in Oxa-R SA did not affect TIG potency (MIC_{90}, 0.5 µg/ml).

Conclusions:

Given the limited choices available for treatment of serious NA or CA Oxa-R SA infections, TIG may offer an additional option because of its enhanced antibacterial spectrum and stability to tetracycline resistance mechanisms.

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (ORSA) is a cause of serious nosocomial infection worldwide and is notorious as an intractable resident of hospitals and long-term care-facilities. Recent recognition of serious and, in some cases fatal, MRSA infections being acquired by individuals while in the community (community-acquired ORSA), has been a worrisome development. The continued emergence of methicillin resistance in staphylococci, and cross-resistance to other agents, has necessitated the development of novel compounds.

Tigecycline (formerly GAR-936) is the sentinel representative of the glycylcycline class currently in clinical trails and is being developed as a parenteral agent targeting common pathogens responsible for community-acquired pneumonia and skin and soft tissue infections. The compound is a semisynthetic derivative of minocycline, whose action on bacterial ribosomes overlaps binding sites targeted by tetracyclines. The glycylcyclines have the distinct advantage of enhanced stability to the major tetracycline-resistance mechanisms, specifically an increased binding affinity to Tet M- and Tet O-protected tetracycline-resistant ribosomes and secondarily through the inhibition of tetracycline efflux determinants.

This report summarizes the in vitro activity of tigecycline and comparator agents tested against a large collection of recent *S. aureus* isolates recovered from invasive infections, and which could be categorized as being either community-acquired or nosocomial in origin.

MATERIALS AND METHODS

Specimen collection: The collection was constructed on the basis of whether the strains (non-duplicates) originated from community acquired infections (oxacillin-susceptible, 1,592 strains; oxacillin-resistant 652 strains) or from nosocomial infections (oxacillin-susceptible, 706 strains; oxacillin-resistant 548 strains). All isolates came from recent global surveillance programs (2000-2003) for which demographic data was available.

Laboratory Methods: All isolates were confirmed as being *S. aureus* by the monitoring facility (The JONES Group/JMI Laboratories, Iowa, USA) using colonial characteristics on standard media and standard biochemical tests (catalase, coagulase, latex agglutination kits). MIC values for antimicrobials including tetracycline, doxycycline and tigecycline were determined using validated, dry-form broth microdilution panels with cation-adjusted Mueller-Hinton medium (TREK Diagnostics Inc., Cleveland, OH). Testing, incubation and MIC interpretation were performed using the manufacturers recommendations and/or recommendations from the National Committee for Clinical Laboratory Standards (NCCLS) [NCCLS, 2003 and 2004]. Quality control was performed using American Type Culture Collection (ATCC) strain *S. aureus* ATCC 29213. A breakpoint of ≤1 µg/ml was used for comparative purposes for tigecycline whereas the breakpoint for tetracycline is ≤4 µg/ml [NCCLS, 2004].

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ACKNOWLEDGEMENT

The study was supported by a grant from Wyeth Pharmaceuticals.

RESULTS

- Oxacillin-susceptible *S. aureus* originating from community or hospital infections are essentially identical in their antibiograms with greater than 90% susceptibility to all tested compounds; only erythromycin (74.7 to 72.9%, respectively) and penicillin (17.7 to 17.4%) are less susceptible (Table 1).

Table 1. Antimicrobial activity of tigecycline tested against oxacillin-susceptible *S. aureus* isolates classified as community- or nosocomially-acquired (2,298 strains from the United States, 2000-2003).

Origin of infection/ oxacillin susceptibility (no. tested)	Antimicrobial agent	MIC (µg/ml) 50%	90%	Range	% susceptible
Community-acquired					
oxacillin-susceptible	Tigecycline	0.25	0.5	≤0.12-1	(100.0)[a]
(1,592)	Tetracycline	≤4	≤4	≤4->8	95.9
	Doxycycline	≤0.5	≤0.5	≤0.5->4	99.0
	Penicillin	4	32	≤0.016->32	17.7
	Amoxicillin/Clavulanate	≤2	≤2	≤2->16	99.4
	Ceftazidime	8	8	≤1->16	91.2
	Ceftriaxone	4	4	0.5->32	98.9
	Imipenem	≤0.5	≤0.5	≤0.5->8	99.9
	Erythromycin	0.25	>8	≤0.06->8	74.7
	Clindamycin	0.12	0.12	≤0.06->8	94.5
	Q/D[b]	0.25	0.5	≤0.25-2	99.9
	Chloramphenicol	8	8	≤2->16	96.5
	Ciprofloxacin	≤0.25	1	≤0.25->4	91.3
	Levofloxacin	0.12	0.5	≤0.03->4	93.4
	Gentamicin	≤2	≤2	≤2->8	98.7
	Rifampin	≤0.25	≤0.25	≤0.25->2	99.8
	T/S[b]	≤0.5	≤0.5	≤0.5->2	96.8
	Linezolid	2	2	0.12-4	100.0
	Teicoplanin	1	2	≤0.12-4	100.0
	Vancomycin	1	1	≤0.12-2	100.0
Nosocomial-acquired					
oxacillin-susceptible	Tigecycline	0.25	0.5	≤0.12-1	(100.0)[a]
(706)	Tetracycline	≤4	≤4	≤4->8	97.2
	Doxycycline	≤0.5	≤0.5	≤0.5->4	99.0
	Penicillin	4	32	≤0.016->32	17.4
	Amoxicillin/Clavulanate	≤2	≤2	≤2->16	99.2
	Ceftazidime	8	16	≤1->16	89.8
	Ceftriaxone	4	4	≤0.25->32	98.7
	Imipenem	≤0.5	≤0.5	≤0.5->8	99.7
	Erythromycin	0.25	>8	0.12->8	72.9
	Clindamycin	0.12	0.25	≤0.06->8	91.6
	Q/D[b]	0.25	0.5	≤0.25-1	100.0
	Chloramphenicol	8	8	≤2->16	95.7
	Ciprofloxacin	≤0.25	2	≤0.25->4	89.7
	Levofloxacin	0.12	0.5	≤0.03->4	91.5
	Gentamicin	≤2	≤2	≤2->8	97.9
	Rifampin	≤0.25	≤0.25	≤0.25->2	99.7
	T/S[b]	≤0.5	≤0.5	≤0.5->2	96.6
	Linezolid	2	2	0.12-4	100.0
	Teicoplanin	1	2	0.25-2	100.0
	Vancomycin	1	1	0.5-2	100.0

a. Interpretive criteria of the NCCLS [2004] were used, where available, and ≤1 µg/ml was applied to tigecycline for comparison purposes only.
b. Q/D = quinupristin/dalfopristin and T/S = trimethoprim/sulfamethoxazole.

- Compared to oxacillin-susceptible strains, oxacillin-resistant strains from both groups demonstrated significantly higher rates of resistance to erythromycin, clindamycin, chloramphenicol, gentamicin and fluoroquinolones, and was especially notable among nosocomially-acquired *S. aureus* (Table 2).

Table 2. Antimicrobial activity of tigecycline tested against oxacillin-resistant *S. aureus* isolates classified as community- or nosocomially-acquired (1,200 strains from the United States, 2000-2003).

Origin of infection/ oxacillin susceptibility (no. tested)	Antimicrobial agent	MIC (µg/ml) 50%	90%	Range	% susceptible
Community-acquired					
oxacillin-resistant	Tigecycline	0.25	0.5	≤0.12-1	(100.0)[a]
(652)	Tetracycline	≤4	≤4	≤4->8	90.8
	Doxycycline	≤0.5	2	≤0.5->4	96.1
	Penicillin	32	>32	≤0.016->32	0.5[c]
	Amoxicillin/Clavulanate	16	>16	≤2->16	12.1[c]
	Ceftazidime	>16	>16	4->16	2.0[c]
	Ceftriaxone	>32	>32	0.5->32	3.8[c]
	Imipenem	1	>8	≤0.5->8	74.0[c]
	Erythromycin	>8	>8	0.12->8	6.1
	Clindamycin	>8	>8	≤0.06->8	33.7
	Q/D[b]	0.5	1	≤0.25-1	100.0
	Chloramphenicol	8	16	≤2->16	83.3
	Ciprofloxacin	>4	>4	≤0.25->4	15.2
	Levofloxacin	>4	>4	0.06->4	17.6
	Gentamicin	≤2	>8	≤2->8	89.6
	Rifampin	≤0.25	≤0.25	≤0.25->2	93.1
	T/S[b]	≤0.5	≤0.5	≤0.5->2	92.2
	Linezolid	2	2	0.5-16	99.8[d]
	Teicoplanin	1	2	≤0.12-4	100.0
	Vancomycin	1	1	0.5-4	100.0
Nosocomial-acquired					
oxacillin-resistant	Tigecycline	0.25	0.5	≤0.12-1	(100.0)[a]
(548)	Tetracycline	≤4	≤4	≤4->8	94.7
	Doxycycline	≤0.5	1	≤0.5->4	96.8
	Penicillin	32	>32	0.12->32	0.2[c]
	Amoxicillin/Clavulanate	16	>16	≤2->16	3.5[c]
	Ceftazidime	>16	>16	8->16	0.5[c]
	Ceftriaxone	>32	>32	≤0.25->32	3.8[c]
	Imipenem	1	>8	≤0.5->8	66.4[c]
	Erythromycin	>8	>8	0.25->8	3.1
	Clindamycin	>8	>8	≤0.06->8	23.5
	Q/D[b]	0.5	1	≤0.25-1	100.0
	Chloramphenicol	8	16	4->16	79.6
	Ciprofloxacin	>4	>4	≤0.25->4	6.0
	Levofloxacin	>4	>4	0.06->4	6.9
	Gentamicin	≤2	>8	≤2->8	86.6
	Rifampin	≤0.25	≤0.25	≤0.25->2	93.1
	T/S[b]	≤0.5	≤0.5	≤0.5->2	92.7
	Linezolid	2	2	0.5-4	100.0
	Teicoplanin	0.5	2	≤0.12-8	100.0
	Vancomycin	1	2	0.25-2	100.0

a. Interpretive criteria of the NCCLS [2004] were used, where available, and ≤1 µg/ml was applied to tigecycline for comparison purposes only.
b. Q/D = quinupristin/dalfopristin and T/S = trimethoprim/sulfamethoxazole.
c. All oxacillin-resistant isolates should be considered resistant to -lactams regardless of in vitro testing results listed here [NCCLS, 2004].
d. Includes one tested strain with a G2576U ribosomal target mutation.

- Whereas ciprofloxacin susceptibility among all oxacillin-susceptible strains varied from 89.7 to 91.3%, this dropped to 15.2% and 6.0%, respectively, among community- and nosocomially-acquired oxacillin-resistant strains.
- Greater than 90% of *S. aureus* isolates remained susceptible to tetracycline (90.8 to 97.2%) and doxycycline (96.1 to 99%) with the lowest susceptibility rates occurring among oxacillin-resistant strains originating from infections in the community.
- Tigecycline remained uniformly active against *S. aureus* (MIC_{50} and MIC_{90} results at 0.25 and 0.5 µg/ml) and all strains were inhibited by 1 µg/m or less, including strains with increased MIC values (4 µg/ml) to vancomycin (100% susceptible; Table 3).
- Potency of tigecycline appeared unaffected by the multi-drug resistant mechanisms frequently associated with oxacillin resistance in staphylococci.
- Only vancomycin, quinupristin/dalfopristin and linezolid remained active against all staphylococci with slight differences in potency documented between these agents.

Table 3. Tigecycline MIC distributions for four groups of *S. aureus* indexed by oxacillin susceptibility and the clinical origin of the infection.

Clinical origin	Oxacillin-susceptibility (no. tested)	Occurrence (cum. %) at tigecycline MIC in µg/ml: ≤0.12	0.25	0.5	1
Community	Susceptible (1,592)	730(45.9)	540(79.8)	309(99.2)	13(100.0)
	Resistant (652)	246(37.7)	235(73.8)	154(97.4)	17(100.0)
Nosocomial	Susceptible (706)	333(47.2)	227(79.3)	144(99.7)	2(100.0)
	Resistant (548)	209(38.1)	214(77.2)	116(98.4)	9(100.0)

CONCLUSIONS

- Tigecycline is the first glycylcycline to undergo clinical trials and demonstrates potent activity against the most commonly-occurring pathogens responsible for community-acquired respiratory tract infections and for skin and soft tissue infections, including strains that prove refractory to other current therapies.
- Given the limited choices available for treatment of serious hospital- or community-acquired ORSA infections, tigecycline offers a promising option given its enhanced antibacterial spectrum and stability to the commonlyoccurring tetracycline resistance mechanisms.