Sustained Activity of Tigecycline Against Methicillin-Resistant *S. aureus* from United States Medical Centers (2004-2008)

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ABSTRACT

Background: Tigecycline (TIG) is a glycylcycline which has been approved by the USA-FDA for the treatment of complicated skin and skin structure infection (SSSI), intra-abdominal infections and community-acquired pneumonia, and has demonstrated non-inferiority against MRSA infections. We report the TIG activity versus MRSA collected from 32 USA hospitals in a 5-year period (2004-2008).

Methods: A total of 18,917 unique *S. aureus* stains were consecutively collected and tested for susceptibility (S) against TIG and various comparators by CLSI broth microdilution methods. TIG S breakpoint established by the USA-FDA for *S. aureus* (≤0.5 μg/ml) was applied.

Results: MRSA rates increased continuously from 49.6% in 2004 to 57.3% in 2008 (54.1% overall). MRSA isolates were mainly from bacteremia (33.4%), SSSI (13.4%) and pneumonia (10.7%). TIG sustained potent activity against MRSA during the study period with 99.95-100.00% S. Only 3 strains (0.03%) were non-S to TIG, with TIG MIC only one or two doubling dilution above the S breakpoint. Vancomycin ($MIC_{50/90}$, 1/1 μg/ml) and linezolid ($MIC_{50/90}$, 1/2 μg/ml) were also very active against MRSA (99.95% S and 5 non-S strains for both compounds), but 4- to 8-fold less potent than TIG ($MIC_{50/90}$, 0.12/0.25 μg/ml). Clindamycin (MIC_{90}, >2 μg/ml; 58.3% S) and levofloxacin (MIC_{90}, >4 μg/ml; 26.5% S) exhibited limited anti-MRSA activity, while trimethoprim/sulfamethoxazole remained potent (97.8% S) against current USA MRSA strains. TIG was also very active against methicillin-susceptible *S. aureus* (100.0% S; 99.5% inhibited at ≤0.25 μg/ml of TIG).

Year (no. of MRSA tested)	Cumulative % of MRSA inhibited at TIG MIC (μg/ml) of:					No. of TIG non-S strains
	≤0.06	0.12	0.25	0.5[a]	1	
2004 (1,210)	24.0	76.5	95.8	100.0	100.0	0
2005 (1,839)	22.7	67.8	98.7	99.95	100.0	1
2006 (2,438)	27.4	80.7	98.4	99.96	99.96	1
2007 (2,390)	21.2	79.9	98.9	100.0	-	0
2008 (2,365)	24.7	69.6	97.0	99.96	100.0	1
All (10,242)	24.1	74.4	98.0	99.97	100.0	3

a. USA-FDA breakpoint

Conclusions: TIG was very active against a large contemporary collection of MRSA (10,242) from USA hospitals. TIG potency and spectrum against MRSA has not changed since its approval by the USA-FDA and its anti-MRSA spectrum was similar to those of vancomycin and linezolid.

INTRODUCTION

Tigecycline is a glycylcycline antibiotic that exhibits a wide range of activity against Gram-positive and -negative organisms, including multidrug-resistant (MDR) strains. Tigecycline binds to the 30S ribosomal subunit which results in protein inhibition. Tigecycline has been approved by the United States Food and Drug Administration (USA-FDA) for the treatment of complicated skin and skin structure infections (cSSSI), intra-abdominal infections and community-acquired pneumonia, and has demonstrated non-inferiority against methicillin-resistant *S. aureus* (MRSA) infections.

Staphylococcus aureus is a leading cause of bacteremia, pneumonia and SSSI. MRSA are commonly recovered from hospital-acquired infections and the incidence of community-acquired MRSA has steadily increased over the past few years in some geographic areas, mainly in the USA. In addition, MRSA are typically resistant to multiple antimicrobial agents and present a challenge for successful treatment. The drug of choice for MRSA infections have been glycopeptides, typically vancomycin. However, the emergence of *S. aureus* strains with reduced susceptibilities to glycopeptides and the increasing number reports of unfavorable clinical outcomes of MRSA infections treated with vancomycin have stimulated the pharmaceutical industry to search for alternative therapies.

The objective of this study was to determine tigecycline potency and spectrum against a large collection of MRSA strains isolated from 32 USA hospitals from 2004 through 2008.

MATERIALS AND METHODS

Bacterial isolates: A total of 18,917 unique *S. aureus* strains were identified from the SENTRY Antimicrobial Surveillance Program, 2004 - 2008. Species identification was confirmed by standard biochemical tests and the Vitek Systems (bioMerieux, Hazelwood, Missouri, USA), when necessary.

Susceptibility testing: MIC values were determined for all isolates based on the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method (M07-A8) using fresh Mueller-Hinton media to test tigecycline. Quality control (QC) ranges and interpretive criteria for comparator compounds used the CLSI M100-S19 document; QC strains included *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, among others.

Antimicrobial agents: All antimicrobial agents used for this study, tigecycline, clindamycin, levofloxacin, linezolid, oxacillin, tetracycline, trimethoprim/sulfamethoxazole and vancomycin were obtained from the respective manufacturer or from Sigma-Aldrich (St. Louis, Missouri, USA).

Susceptibility categories: MRSA was defined as any *S. aureus* strain exhibiting an oxacillin MIC value >2 μg/ml. Tigecycline-susceptible *S. aureus* was defined, based on the USA-FDA criteria, as those strains with a tigecycline MIC value ≤0.5 μg/ml.

ACKNOWLEDGMENT

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SELECTED REFERENCES

1. Clinical and Laboratory Standards Institute (2009). *M07-A8. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - eighth edition.* Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute (2009). *M100-S19. Performance standards for antimicrobial susceptibility testing. 19th informational supplement* Wayne, PA: CLSI.
3. Corey GR (2009). *Staphylococcus aureus* bloodstream infections: definitions and treatment. *Clin Infect Dis* 48 Suppl 4: S254-S259.
4. French GL (2008). A review of tigecycline. *J Chemother* 20 Suppl 1: 3-11.
5. Livermore DM (2005). Tigecycline: what is it, and where should it be used? *J Antimicrob Chemother* 56: 611-614.
6. Nicolau DP (2009). Management of complicated infections in the era of antimicrobial resistance: the role of tigecycline. *Expert Opin Pharmacother* 10: 1213-1222.
7. Peterson LR (2008). A review of tigecycline--the first glycylcycline. *Int J Antimicrob Agents* 32 Suppl 4: S215-S222.
8. Stryjewski ME, Corey GR (2009). New treatments for methicillin-resistant *Staphylococcus aureus*. *Curr Opin Crit Care*

RESULTS

- MRSA rates increased continuously from 49.6% in 2004 to 57.3% in 2008 (54.1% overall; Figure 1). The isolates were recovered from patients exhibiting bacteremia (33.4%), cSSSI (13.4%) and pneumonia (10.7%).
- Tigecycline showed potent sustained activity against MRSA during the study period with percent susceptibility ranging from >99.9% to 100.0% (Table 1).
- Only three strains (0.03%) were non-susceptible to tigecycline, one each from 2005, 2006 and 2008. These three strains exhibited tigecylcine MIC values of 1 μg/ml (two isolates) or 2 μg/ml (one isolate), which are only one or two doubling dilution above the USA-FDA breakpoint of 0.5 μg/ml; Table 2).
- Vancomycin ($MIC_{50/90}$, 1/1 μg/ml) and linezolid ($MIC_{50/90}$, 1/2 μg/ml) were active against MRSA (>99.9% susceptible and five non-susceptible strains for both compounds), but four- to eight-fold less potent than tigecycline ($MIC_{50/90}$, 0.12/0.25 μg/ml; Table 2).
- Clindamycin (MIC_{90}, >2 μg/ml; 58.3% susceptible) and levofloxacin (MIC_{90}, >4 μg/ml; 26.5% susceptible) exhibited limited anti-MRSA activity, while trimethoprim/sulfamethoxazole (TMP/SMX) remained potent (97.8% susceptible) against current USA MRSA strains in the USA (Table 2).
- Susceptibility to TMP/SMX (96.8-98.6%) and tetracycline (93.1-95.2%) remained stable during the study period (2004-2008). In contrast, susceptibility to clindamycin and levofloxacin increased from 46.4 and 22.3% in 2004 to 64.7 and 29.4% in 2008, respectively (Table 2). These susceptibility changes may reflect the spread of the MRSA-USA300 clone in USA hospitals.
- Tigecycline was also very active against methicillin-susceptible *S. aureus* ($MIC_{50/90}$, 0.12/0.25 μg/ml; 100.0% susceptible; with 99.5% of strains being inhibited at ≤0.25 μg/ml of tigecycline; data not shown).

Table 1. Five year (2004-2008) MIC distributions for tigecycline tested against 10,242 MRSA strains, stratified by year.

Year	Number of isolates (cumulative %) inhibited at tigecycline MIC (μg/ml)[a]						
	≤0.03	0.06	0.12	0.25	0.5	1	2
2004 (1,210)	4 (0.3)	286 (24.0)	636 (76.5)[b]	233 (95.8)	51 (100.0)	-	-
2005 (1,839)	4 (0.2)	413 (22.7)	830 (67.8)[b]	568 (98.7)	24 (>99.9)	1 (100.0)	-
2006 (2,438)	13 (0.5)	654 (27.4)	1301 (80.7)[b]	432 (98.4)	37 (>99.9)	0 (>99.9)	1 (100.0)
2007 (2,390)	5 (0.2)	501 (21.2)	1331 (76.9)[b]	527 (98.9)	26 (100.0)	-	-
2008 (2,365)	1 (0.04)	583 (24.2)	1061 (69.6)[b]	650 (97.0)	69 (>99.9)	1 (100.0)	-
All Years (10,242)	27 (0.3)	2437 (24.1)	5159 (74.4)[b]	2410 (98.0)	204 (>99.9)	2 (>99.9)	1 (100.0)

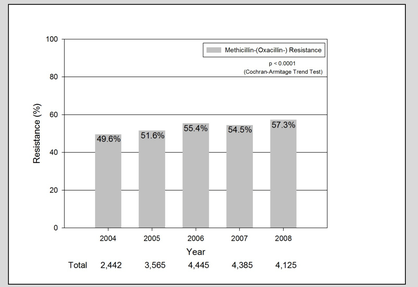
a. Cochran-Armitage Trend Test, MIC_{50} p = 0.2 (no statistically significant change in proportions across study years).
b. Underline values represent the MIC_{50} values.

Table 2. Antimicrobial activity of tigecycline and various comparator agents against *S. aureus*, stratified by year.

Antimicrobial	Percent Susceptible (%)					All Years			
	2004	2005	2006	2007	2008	MIC_{50}	MIC_{90}	% susceptible	% resistant
Tigecycline	99.8	99.9	>99.9	100.0	>99.9	0.12	0.25	>99.9	-
Clindamycin	46.4	53.7	57.9	61.7	64.7	≤0.25	>2	58.3	41.6
Levofloxacin	22.3	23.7	26.5	27.8	29.4	>4	>4	26.5	72.1
Tetracycline	94.2	93.1	93.5	94.2	95.2	≤2	≤2	94.1	5.6
Linezolid	100.0	100.0	>99.9	>99.9	99.9	1	2	>99.9	-
TMP/SMX[a]	97.9	97.7	96.8	98.2	98.6	≤0.5	≤0.5	97.8	2.2
Vancomycin	99.9	100.0	>99.9	99.9	100.0	1	1	>99.9	0.0

a. TMP/SMX = trimethoprim/sulfamethoxazole.

Figure 1. Annual prevalence of MRSA, 2004-2008, all sites in USA.



CONCLUSIONS

- Tigecycline was very active against a large contemporary collection of MRSA (10,242) isolated from USA hospitals.
- Potency and spectrum of tigecycline against MRSA has not changed since its approval by the USA-FDA and its anti-MRSA spectrum was similar to those of vancomycin and linezolid.
- Tigecycline has emerged as a valuable treatment option for MRSA infections.