In vitro Activity of Tigecycline, a New Glycylcycline, Tested Against 1,326 Clinical Bacterial Strains Isolated from Latin America

Ana C. Gales[1*], Ronald N. Jones[2], Soraya S. Andrade[1], Andrea S. Pereira[1] and Hélio S. Sader[2]

Federal University of São Paulo, Division of Infectious Diseases[1], Department of Medicine, São Paul1, Brazil; The JMI Laboratories[2], North Liberty, IA, USA.

The *in vitro* activity of tigecycline (former GAR-936), a new semisynthetic tetracycline, was evaluated in comparison with tetracycline and other antimicrobial agents. Material and Methods: A total of 1,326 contemporary clinical isolates collected from the Latin American region were collected in 2000-2002 period and tested with microdilution broth according to the CLSI guidelines. The bacterial pathogens evaluated included *Staphylococcus aureus* (505), *Streptococcus pneumoniae* (269), coagulase-negative *staphylococci* (CoNS; 227), *Haemophilus influenzae* (129), *Enterococcus* spp. (80), *Moraxella catarrhalis* (54), β-haemolytic *streptococci* (28), *viridans* group *streptococci* (26), and *Neisseria meningitidis* (8) Results: Tigecycline demonstrated excellent activity against all Gram-positive cocci, with 90% of penicillin-resistant *S. pneumoniae* strains being inhibited at 0.12 μg/mL, while the same isolates had an MIC_{90} of > 16 μg/mL for tetracycline. All *Enterococcus* spp. were inhibited at 0.25 μg/mL of tigecycline. Tigecycline (MIC_{50}, 0.25 μg/mL) was eight-fold more potent than minocycline (MIC_{50}, 2 μg/mL) against oxacillin-resistant *S. aureus* (ORSA); all ORSA were inhibited at ≤ 2 μg/mL of tigecycline. Tigecycline demonstrated excellent activity (MIC_{50}, 0.5 μg/mL) against CoNS with reduced susceptibility to teicoplanin (MIC, 16 μg/mL). Tigecycline also showed high potency against respiratory pathogens such as *M. catarrhalis* (MIC_{50}, 0.12 μg/mL) and *H. influenzae* (MIC_{50}, 0.5 μg/mL). No tigecycline resistant isolates were detected when the proposed susceptible breakpoints (≤ 4 μg/mL) was applied. Conclusions: This results indicate that tigecycline has potent *in vitro* activity against clinically important pathogenic bacteria, including Gram-positive isolates resistant to both tetracycline and minocycline.

Key Words: Antimicrobial susceptibility, tigecycline, Latin America and SENTRY.

The tetracyclines have been widely used during in last four decades, due to their broad-spectrum of antimicrobial activity against Gram-positive and Gram-negative aerobic bacteria, including many intracellular pathogens and anaerobic organisms [1,2]. However, indications for the use of tetracyclines have been limited to specific clinical indications, due to the emergence of resistant strains in frequently isolated species, such as *Staphylococcus aureus*, *Enterococcus* spp., *Streptococcus pneumoniae*, and *Neisseria gonorrhoeae* [1-4].

Tigecycline, former GAR-936, is the first representative of a new class of antimicrobial agents known as glycylcyclines. This compound is a semisynthetic 9-t-butylglycylamido derivative of the minocycline molecule [5]. Although tigecycline acts on the bacterial ribosome by binding sites similar to those of tetracycline, the radical added to position 9 of the

Received on 17 May 2005; revised 27 September 2005.
Address for correspondence: Dr. Ana Cristina Gales, MD, PhD. Laboratório Especial de Microbiologia Clínica, Division of Infectious Diseases, Universidade Federal de São Paulo. Rua Leandro Dupret, 188, Zip code: 04025-010 São Paulo - SP - Brazil. Email: galesac@aol.com. Fax: + 55 (11) 5571 5180. Phone: + 55 (11) 5081 2819. This study was presented in part at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois. September 14-17, 2003.

The Brazilian Journal of Infectious Diseases 2005;9(5):348-356

tigecycline molecule has provided additional steric hindrance features that result in a greater spectrum of activity [6]. Thus, tigecycline has documented activity against tetracycline-resistant (*tet*-R) Gram-positive and Gram-negative pathogens, refractory to both efflux and ribosomal protection mechanisms [7].

Our main objective was to evaluate the *in vitro* activity of tigecycline in comparison to tetracycline and other antimicrobial agents against clinical bacterial isolates recently collected from Latin American medical centers.

Material and Methods

Organisms

A total of 1,326 clinical bacterial isolates collected from the Latin American region in 2000-2002 period were evaluated. The distribution of species was as following as: *Staphylococcus aureus* (505 strains), *Streptococcus pneumoniae* (269 strains), coagulase negative staphylococci (227 strains), *Haemophilus influenzae* (129 strains), *Enterococcus* spp. (80 strains), β-haemolytic streptococci (28 strains), viridans group streptococci (26 strains), *Moraxella catarrhalis* (54 strains), and *Neisseria meningitides* (8 strains). Only a single isolate per patient was evaluated. The isolates were identified to the species level by the participating medical center, and sent to the coordinating laboratory for identification confirmation and reference susceptibility testing.

Medical centers

Clinical isolates of facultatively aerobic bacteria were collected in 11 Latin American laboratories distributed throughout 10 cities (six countries): São Paulo, Florianópolis, Porto Alegre and Brasília (only 2002), Brazil; Buenos Aires and San Isidro, Argentina; Santiago (two centers), Chile; Medellin, Colombia (only 2000); Caracas, Venezuela; and Mexico City, Mexico. The selection of participating centers was based on the principle that they should be sentinels in their respective geographic region. The participating medical centers were directed by a protocol to collect isolates from consecutive patients from specific sites of infections, including bloodstream infections, community-acquired respiratory infections, pneumonia in hospitalized patients, and skin and soft tissue infections.

Susceptibility testing

Antimicrobial susceptibility testing was performed using broth microdilution methods, as described by the Clinical Laboratory Standard Institute (CLSI, formerly NCCLS) [8]. Antimicrobial agents were obtained from their respective manufacturers as laboratory grade powder. Minimal inhibitory concentrations (MICs) results were interpreted according to NCCLS breakpoints [9]. A tigecycline susceptible breakpoint of $\leq$4 μg/mL for staphylococci and enterococci, and $\leq$ 2 μg/mL for other pathogens were used for comparative purposes only. Quality control measures were utilized by testing *S. pneumoniae* ATCC 49619, *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853.

Results

The largest number of isolates was collected from the Brazilian medical centers (573 isolates, 43.2%), followed by the Chilean (377 isolates, 28.4%) and Argentinean (264 isolates, 19.9%) medical centers. These three countries contributed with >90% of isolates (Table 1). Species tested in rank order of frequency were as follows: *S. aureus* (42.9% oxacillin-resistant); *S. pneumoniae* (27.1% penicillin-non-susceptible), CoNS (79.3% oxacillin-resistant), *H. influenzae* (17.8% β-lactamase-producers), *Enterococcus* spp. (10.3% vancomycin-resistant), *M. catarrhalis* (92.6% β-lactamase-producers), β-haemolytic streptococci (34.6% erythromycin-non-susceptible), *viridans* group *streptococci* (30.8% penicillin-non-susceptible), and *Neisseria meningitides*.

Table 1. Frequency of pathogens tested for tigecycline susceptibility according to the country of isolation (SENTRY Antimicrobial Surveillance Program, Latin America, 2000-2002)

	Country						
Organism	Argentina	Brazil	Chile	Colombia	Mexico	Venezuela	Total (%)
Staphylococcus aureus							
Oxacillin-susceptible	53	144	63	7	5	16	288 (21.7)
Oxacillin-resistant	37	108	68	1	1	2	217 (16.3)
CoNS[a]							
Oxacillin-susceptible	10	24	-	1	2	10	47 (3.5)
Oxacillin-resistant	33	108	8	4	16	11	180 (13.5)
Enterococcus spp.	15	41	10	1	1	12	80 (6.0)
Streptococcus pneumoniae	64	84	113	-	-	8	269 (20.2)
b-haemolytic *streptococci*	5	5	11	1	0	6	28 (2.1)
Viridans group *streptococci*	3	8	10	-	2	2	26 (1.8)
Haemophilus influenzae	34	41	54	-	-	-	129 (9.7)
Moraxella catarrhalis	9	10	33	-	-	2	54 (4.0)
Neisseria meningitidis	1	-	7	-	-	-	8 (0.6)
Total (%)	**264 (19.9)**	**573 (43.2)**	**377 (28.4)**	**15 (1.1)**	**26 (1.9)**	**69 (5.2)**	**1,326 (100.0)**

[a] CoNS: Coagulase-negative *staphylococci*.

The antimicrobial activity of tigecycline was compared to selected antimicrobial agents (Table 2). Tigecycline was highly active against both oxacillin-resistant and –susceptible *S. aureus* (MIC_{50}, 0.25 µg/mL and MIC_{90}, 0.5 µg/mL for both groups). More than 99% of the strains were inhibited at ≤0.5 µg/mL of tigecycline. Similarly to *S. aureus*, both oxacillin-resistant and -susceptible coagulase-negative staphylococci were very susceptible to tigeclycline (MIC_{50}, 0.25 µg/mL and MIC_{90}, 0.5 µg/mL for both). Vancomycin and linezolid were the only antimicrobial agents active against all staphylococcal strains at the susceptible breakpoint. Tigecycline (MIC_{50}, 0.25 µg/mL) was at least four-fold more potent than vancomycin (MIC_{50}, 1 µg/mL) or linezolid (MIC_{50}, 1-2 µg/mL) against oxacillin-resistant staphylococci. Tigecycline was also highly active against tetracycline-resistant staphylococci. Co-resistance among tetracycline, erythromycin, and fluoroquinolones was noticed within the subsets of oxacillin-resistant staphylococci and did not affect tigecycline *in vitro* activity against staphylococci.

Although tigecycline and linezolid inhibited 100% of the *Enterococcus* spp. strains tested, tigecycline (MIC_{50}, 0.25 µg/mL) was eight-fold more potent than linezolid (MIC_{50}, 2 µg/mL). The vast majority of *Enterococcus* spp. were susceptible to ampicillin (MIC_{50}, ≤ 1 µg/mL; 88.8% susceptible) and resistant to quinupristin/dalfopristin (MIC_{50}, 8 µg/mL; 13.8% susceptible), reflecting the preponderance of *E. faecalis* in the collection. Tigecycline showed excellent potency against both vancomycin- and tetracycline-resistant *Enterococcus* spp.

Table 2. Antimicrobial activity of tigecycline in comparison to selected antimicrobial agents against 1,326 pathogen isolates from Latin American medical centers (SENTRY Antimicrobial Surveillance Program, 2000-2002)

Organism/antimicrobial agent (no. tested)	MIC (μg/mL)[a]		% susceptible[b]
	MIC_{50}	MIC_{90}	
Staphylococcus aureus			
Oxacillin-susceptible (288)			
Tigecycline	0.25	0.5	100.0[c]
Tetracycline	≤4	>8	90.2
Erythromycin	0.25	>8	85.1
Ciprofloxacin	0.25	0.5	96.9
Quinupristin/Dalfopristin	0.25	0.5	100.0
Teicoplanin	0.5	1	99.7
Vancomycin	1	1	100.0
Linezolid	2	2	100.0
Oxacillin-resistant (217)			
Tigecycline	0.25	0.5	100.0[c]
Tetracycline	8	>8	49.8
Erythromycin	>8	>8	7.4
Ciprofloxacin	>2	>2	4.6
Quinupristin/Dalfopristin	0.5	1	100.0
Teicoplanin	1	2	99.1
Vancomycin	1	1	100.0
Linezolid	2	2	100.0
CoNS			
Oxacillin-susceptible (47)			
Tigecycline	0.25	0.5	100.0[c]
Tetracycline	4	>8	76.6
Erythromycin	0.25	>8	74.4
Ciprofloxacin	0.25	0.25	95.3
Quinupristin/Dalfopristin	0.25	0.25	100.0
Teicoplanin	1	2	100.0
Vancomycin	1	2	100.0
Linezolid	1	1	100.0
Oxacillin-resistant (180)			
Tigecycline	0.25	0.5	100.0[c]

Tetracycline	≤4	>8	78.3
Erythromycin	>8	>8	25.0
Ciprofloxacin	2	>2	47.8
Quinupristin/Dalfopristin	0.25	0.5	96.7
Teicoplanin	2	8	93.3
Vancomycin	1	2	100.0
Linezolid	1	2	100.0
Streptococcus pneumoniae (269)			
Tigecycline	0.12	0.12	100.0[c]
Tetracycline	≤4	>8	83.6[f]
Erythromycin	0.25	1	87.7
Penicillin	0.03	2	72.9
Ceftriaxone	0.25	1	98.5[e]
Gatifloxacin	0.25	0.25	100.0
Quinupristin/Dalfopristin	0.25	0.5	100.0
Teicoplanin	0.12	0.12	100.0
Vancomycin	0.25	0.5	100.0
Linezolid	1	1	100.0
β-haemolytic streptococci (28)			
Tigecycline	0.12	0.12	100.0[c]
Tetracycline	>8	>8	46.4
Erythromycin	0.06	1	89.3
Penicillin	0.03	0.06	96.4
Gatifloxacin	0.25	0.5	96.4
Quinupristin/Dalfopristin	0.25	0.5	100.0
Teicoplanin	0.12	0.12	100.0
Vancomycin	0.25	0.5	100.0
Linezolid	1	1	100.0
Viridans group streptococci (26)			
Tigecycline	0.12	0.25	100.0[c]
Tetracycline	≤4	>8	73.1
Erythromycin	0.06	2	65.4
Penicillin	0.12	2	69.2
Gatifloxacin	0.25	0.5	96.2
Quinupristin/Dalfopristin	0.5	1	92.3
Teicoplanin	0.12	0.12	100.0
Vancomycin	0.5	1	100.0
Linezolid	1	1	100.0
Enterococcus spp. (80)			
Tigecycline	0.25	0.5	100.0[c]
Tetracycline	>8	>8	27.5
Ampicillin	≤1	16	88.8

Ciprofloxacin	1	>2	55.0
Quinupristin/Dalfopristin	8	8	13.8
Teicoplanin	0.25	1	92.5
Vancomycin	2	8	89.7
Linezolid	2	2	100.0
Haemophilus influenzae (129)			
Tigecycline	0.25	0.25	100.0[c]
Tetracycline	≤4	≤4	96.1[f]
Azithromycin	0.5	1	100.0
Clarithromycin	8	8	93.0
Ampicillin	0.5	1	82.2
Amoxicillin/Clavulanate	0.5	1	100.0
Ceftriaxone	0.008	0.016	100.0
Ciprofloxacin	≤0.03	≤0.03	100.0
Chloramphenicol	≤2	≤2	94.6
Moraxella catarrhalis (54)[g]			
Tigecycline	0.12	0.5	100.0[c]
Tetracycline	≤4	≤4	100.0
Azithromycin	≤0.12	≤0.12	100.0
Clarithromycin	≤0.25	≤0.25	100.0
Ampicillin	≤0.5	2	7.4
Amoxicillin/Clavulanate	0.12	0.25	100.0
Ceftriaxone	0.12	0.5	100.0
Ciprofloxacin	≤0.03	0.06	100.0
Chloramphenicol	≤2	≤2	100.0

[a]Minimal inhibitory concentration determined by the broth microdilution technique [8]. [b]Percentage of susceptibility calculated using the NCCLS breakpoints [9].[c]A susceptible breakpoint of ≤ 4 μg/mL was used for comparative purposes only.[d]No breakpoint has been established by the NCCLS.[e]Breakpoints for non-meningitis were applied.[f]Includes susceptible and intermediate. [g]Breakpoints for *H. influenzae* were used.

Against *S. pneumoniae*, tigecycline, gatifloxacin, quinupristin/dalfopristin, vancomycin, teicoplanin, and linezolid showed a susceptibility rate of 100.0%. Four *S. pneumoniae* isolates were not susceptible to ceftriaxone when non-meningitis breakpoints were applied. Tigecycline (MIC_{50}, 0.12 μg/mL) was as potent as teicoplanin (MIC_{50}, 0.12 μg/mL) and two-fold more potent than ceftriaxone (MIC_{50}, 0.25 μg/mL), gatifloxacin (MIC_{50}, 0.25 μg/mL), and vancomycin (MIC_{50}, 0.25 μg/mL) against *S. pneumoniae*. Tigecycline was also highly active against *S. pneumoniae*, including isolates resistant to penicillin and/or tetracycline and/or erythromycin.

Tigecycline demonstrated excellent activity against viridans group streptococci ($MIC_{50/90}$, ≤ 0.12/0.25 μg/mL) and β-haemolytic streptococci ($MIC_{50/90}$, ≤ 0.12 μg/mL), whereas the corresponding MIC_{90} values for tetracycline were > 8 μg/mL. Tigecycline, vancomycin, teicoplanin, and linezolid (100.0% susceptible) exhibited excellent coverage against these pathogens. No cross-resistance between tigecycline and any of the antimicrobial agents tested was observed among streptococcal isolates.

Table 3. Tigecycline MIC distribution among 1,326 pathogens from the SENTRY Antimicrobial Surveillance Program (Latin America, 2000-2002)

Organism (n tested)	No. of isolates (cumulative %) inhibited at MIC (μg/mL)				
	≤ 0.12	0.25	0.5	1	2
Staphylococcus aureus					
Oxacillin-susceptible (288)	111 (38.5)	94 (71.2)	81 (99.3)	2 (100.0)	-
Oxacillin-resistant (217)	63 (29.1)	100 (75.1)	51 (98.6)	2 (99.5)	1 (100.0)
CoNS[a]					
Oxacillin-susceptible (47)	15 (31.9)	15 (63.8)	14 (93.6)	3 (100.0)	-
Oxacillin-resistant (180)	41 (22.8)	55 (53.3)	70 (92.2)	13 (99.4)	1 (100.0)
Streptococcus pneumoniae *(269)*	*268 (99.6)*	*1 (100.0)*	-	-	-
Haemophilus influenzae (129)	8 (6.2)	28 (27.9)	72 (83.7)	17 (96.9)	4 (100.0)
Enterococcus spp. (80)	37 (43.3)	23 (75.0)	20 (100.0)	-	-
Moraxella catarrhalis (54)	31 (57.4)	17 (88.9)	6 (100.0)	-	-
β-haemolytic streptococci (28)	28 (100.0)	-	-	-	-
Viridans group streptococci (26)	23 (88.5)	1 (92.3)	2 (100.0)	-	-
Neisseria meningitidis (8)	8 (100)	-	-	-	-

a.CoNS: Coagulase-negative staphylococci.

Nearly 18.0% and 93.0% of the *H. influenzae* and *M. catarrhalis* strains produced β-lactamase, respectively. *Haemophilus influenzae* ($MIC_{50/90}$, 0.25 μg/mL) and *M. catarrhalis* ($MIC_{50/90}$, ≤ 0.12/ 0.5 μg/mL) isolates were very susceptible to tigecycline (100.0% susceptible), including β-lactamase producing isolates. Only eight *N. meningitidis* isolates were tested. Seven of them were collected from a Chilean medical center. All of the *N. meningitidis* showed tigecycline MIC at concentrations ≤ 0.12 μg/mL. The tigecycline MIC distribution among 1,326 pathogens tested is shown in Table 3. The tigecycline MICs distributions were not influenced by co-phenotypes of resistance, such as oxacillin-resistance among staphylococci, penicillin-resistance among *S. pneumoniae* or glycopeptide resistance among *Enterococcus* spp. The vast majority of isolates tested (1320 of 1326 or 99.5%) were inhibited at a concentration of ≤ 1 μg/mL of tigecycline.

Discussion

Tigecycline, a novel glycylcycline antibiotic, exhibits strong activity against Gram-positive, Gram-negative, aerobic, anaerobic, and atypical bacterial species, including many resistant pathogens, i.e., vancomycin-resistant enterococci, methicillin-resistant *S. aureus* and penicillin-resistant *S. pneumoniae* [10-13]. In addition, tigecycline has shown excellent activity against most Gram-negative pathogens, including *Enterobacteriaceae*, *Acinetobacter* spp., *Stenotrophomonas maltophilia* [10,11], *Haemophilus influenzae*, and *Neisseria* spp. [14]. Tigecycline's expanded broad-spectrum activity is further evidenced by its activity against *Legionella pneumophila* [15], *Chlamydia* [16], rapidly growing nontuberculosis mycobacteria [17] and anaerobes [18]. On the other hand, tigecycline has demonstrated limited activity against *P. aeruginosa* and *Proteae* isolates [5,10,11].

The results of two randomized trials assessing the clinical efficacy of tigecycline were recently released [19]. The studies evaluated tigecycline versus vancomycin plus aztreonam to treat complicated skin and skin structure infections (cSSSI), and tigecycline versus imipenem plus cilastatin to treat complicated intrabdominal infections (cIAI). In the first trial, 274 patients received tigecycline and 269 received vancomycin plus aztreonam. The clinical cure rate of cSSSI between the two groups was not statistically different (84.3% *versus* 86.9%, respectively). The cIAI trial comprised 404 and 413 patients treated with tigecycline and imipenem plus cilastatin, respectively. Clinical cure was again not statistically distinct (86.6% of the tigecycline group and in 84.4% of those on combination therapy). In both trials, the most frequently reported adverse events for patients on tigecycline were nausea and vomiting [19].

Our results agree with previous *in vitro* studies [5,10-14] and emphasize that tigecycline has excellent activity and spectrum against Gram-positive bacteria, including multi-drug resistant strains, and bacterial pathogens causing community-acquired respiratory tract infections isolated from patients hospitalized in Latin American medical centers. These results, associated with the tigecycline clinical efficacy data already published, suggest that tigecycline may have an important role in the treatment of severely ill patients, especially in an environment with high antimicrobial resistance levels such as the Latin American region.

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