E-1537

In Vitro Activity of Tigecycline, a New Glycylcycline, Tested Against 1,326 Clinical Bacterial Strains Isolated from the Latin American Region

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ICCAC 2003

ABSTRACT

Background: The in vitro activity of tigecycline (TIG; former GAR-936), a new semisynthetic tetracycline, was evaluated in comparison with tetracycline and other antimicrobial agents.
Material & Methods: A total of 1,326 recent clinical isolates collected from the Latin American region were tested by microdilution broth according to the NCCLS recommendations. The following species were tested *Staphylococcus aureus* (SA; 505), *Streptococcus pneumoniae* (SPN; 269), coagulase-negative staphylococci (CoNS; 227), *Haemophilus influenzae* (HI; 129), *Enterococcus* spp. (80), *Moraxella catarrhalis* (MCAT; 54), beta-haemolytic streptococci (28), viridans group streptococci (26), and *Neisseria meningitidis* (NM; 8)
Results: TIG demonstrated excellent activity against all Gram-positive cocci with 90% of penicillin-resistant SPN strains 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 TIG. TIG (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 < 0.5 μg/mL of TIG. TIG demonstrated excellent activity (MIC_{50}, 0.5 μg/mL) against CoNS with reduced susceptibility to teicoplanin (MIC, 16 μg/mL). TIG also showed high potency against respiratory pathogens such as MCAT (MIC_{50}, 0.12 μg/mL) and HI (MIC_{50}, 0.5 μg/mL). No TIG resistant isolates would be detected if the proposed breakpoint of susceptibility (≤ 4 μg/mL) was applied.
Conclusions: These results indicate that TIG has potent in vitro activity against clinically important pathogenic bacteria, including Gram-positive isolates resistant to both tetracycline and minocycline.

INTRODUCTION

Tetracyclines have been widely used in the 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. However, indications for the use of tetracyclines have been limited to specific clinical indications due to the emergence of resistant strains among frequently isolated species, such as *S. aureus*, *Enterococcus* spp., *S. pneumoniae*, and *Neisseria gonorrhoeae*.

Tigecycline, formely GAR-936, is a semisynthetic glycylcycline derived from the minocycline molecule. Tigecycline has documented activity against tetracycline-resistant (tet-R) Gram-positive and Gram-negative pathogens refractory by both efflux and ribosomal protection mechanisms. The present study was conducted to evaluate the in vitro activity of tigecycline in comparison to tetracycline and other antimicrobial agents against clinical bacterial isolates collected in Latin American medical centers.

MATERIALS & METHODS

Organisms: Clinical isolates of facultatively aerobic bacteria were collected in 11 Latin American laboratories distributed throughout 10 cities (six countries): Sao Paulo, Florianopolis, Porto Alegre and Brasilia (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 participant centers was based on the principle that they should be sentinel in their respective geographic region. The participant medical centers were directed by a protocol to collect isolates from consecutive patients from specific sites of infections. A total of 1,326 clinical bacterial isolates collected from the Latin American region in the years 2000 and 2002 were evaluated.

Susceptibility testing: Antimicrobial susceptibility testing was performed using broth microdilution methods as described by the National Committee for Clinical Laboratory Standards (NCCLS). Antimicrobial agents were obtained from their respective manufacturers as laboratory grade powder. MIC results were interpreted according to NCCLS breakpoints. A tigecycline susceptible breakpoints of ≤4 μg/mL for staphylococci and enterococci, and ≤ 2 μg/mL for other pathogens were used for comparative purposes only. Quality control measures were utilized by testing *Streptococcus pneumoniae* ATCC 49619, *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853.

COMMENTS

- Brazil provided the largest number of isolates (573, 43.2%), followed by Chile (377, 28.4%) and Argentina (264, 19.9%). These three countries contributed with >90% of isolates (Table 1).
- Tigecycline was highly active against both oxacillin-resistant and –succeptible *S. aureus* (MIC_{50}, 0.25 μg/mL and MIC_{90}, 0.5 μg/mL for both groups). More than 99% of strains were inhibited at ≤0.5 μg/mL of tigecycline (Tables 2 and 3).
- 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; Tables 2 and 3).
- Resistance to either oxacillin or tetracycline did not affect tigecycline in vitro activity against staphylococci (Table 2).

COMMENTS (continued)

- Only tigecycline (MIC_{50}, 0.25 μg/mL and MIC_{90}, 0.5 μg/mL) and linezolid (MIC_{50} and MIC_{90} of 2 μg/mL) were active against 100% of *Enterococcus* spp. strains. Around 10% of strains showed resistance to vancomycin (MIC_{90}, 8 μg/mL) and the vast majority were resistant to quinupristin/dalfopristin (MIC_{50} and MIC_{90} of 8 μg/mL), reflecting the preponderance of *E. faecalis* in the collection.
- All streptococcal species tested were highly susceptible to tigecycline. The vast majority of strains (98.8%) were inhibited at ≤0.12 μg/mL of tigecycline.
- Tigecycline was highly active against *S. pneumoniae* (MIC_{50} and MIC_{90} of ≤0.12 μg/mL), including isolates resistant to penicillin and/or tetracycline and/or erythromycin.
- All *H. influenzae* and *M. catarrhalis* isolates were very susceptible to tigecycline (MIC_{90}, 0.25 and 0.5 μg/mL, respectively). Almost 20% of *H. influenzae* and the vast majority of *M. catarrhalis* (92.6%) were resistant to ampicillin due to the production of ß-lactamase.

RESULTS

Table 1. Frequency of pathogens tested for tigecycline susceptibility according to the country of isolation.

Organism	Country						Total (%)
	Argentina	Brazil	Chile	Colombia	Mexico	Venezuela	
S. 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)
Viridans group streptococci	3	8	10	-	2	2	26 (1.8)
ß-haemolytic streptococci	5	5	11	1	0	6	28 (2.1)
Streptococcus pneumoniae	64	84	113	-	-	8	269 (20.2)
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.

Table 2. Tigecycline MIC distribution among 1,326 pathogens from the Latin America region.

Organism (n tested)	No. of isolates (cumulative %) inhibited at MIC (μg/mL)				
	≤0.12	0.25	0.5	1	2
S. 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)
Enterococcus spp. (80)	37(43.3)	23(75.0)	20(100.0)	-	-
Viridans group streptococci (26)	23(88.5)	1(92.3)	2(100.0)	-	-
ß-haemolytic streptococci (28)	28(100.0)	-	-	-	-
S. 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)
Moraxella catarrhalis (54)	31(57.4)	17(88.9)	6(100.0)	-	-
Neisseria meningitidis (8)	8(100)	-	-	-	-

a. CoNS: Coagulase-negative staphylococci.

RESULTS

Table 3. Antimicrobial activity of tigecycline in comparison to selected antimicrobial agents against Gram-positive pathogens isolated in Latin American medical centers (2000 and 2002).

Organism/antimicrobial agent (no. tested)	MIC (μg/mL)		% susceptible
	50%	90%	
S. aureus			
Oxacillin-susceptible (288)			
Tigecycline	0.25	0.5	100.0[a]
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[a]
Tetracycline	8	>8	49.8
Erythromycin	>8	>8	7.4
Ciprofloxacin	>4	>4	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[a]
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[a]
Tetracycline	4	>8	78.3
Erythromycin	>8	>8	25.0
Ciprofloxacin	2	>4	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
Enterococcus spp. (80)			
Tigecycline	0.25	0.5	100.0[a]
Tetracycline	>8	>8	27.5
Ampicillin	≤1	16	88.8
Ciprofloxacin	1	>4	55.0
Quinupristin/Dalfopristin	8	8	13.8
Teicoplanin	0.25	1	92.5
Vancomycin	2	8	89.7
Linezolid	2	2	100.0
ß-haemolytic streptococci (28)			
Tigecycline	0.12	0.12	100.0[a]
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 (25)			
Tigecycline	0.12	0.25	100.0[a]
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

Table 3. Continued.

Organism/antimicrobial agent (no. tested)	MIC (μg/mL)		% susceptible
	50%	90%	
S. pneumoniae (269)			
Tigecycline	0.12	0.12	100.0[a]
Tetracycline	≤4	>8	83.6[c]
Erythromycin	0.25	1	87.7
Penicillin	0.03	2	72.9
Ceftriaxone	0.25	1	98.5[b]
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
H. influenzae (129)			
Tigecycline	0.5	1	100.0[a]
Tetracycline	≤2	≤2	96.1[c]
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
M. catarrhalis (54)[d]			
Tigecycline	0.12	0.5	100.0[a]
Tetracycline	≤2	≤2	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. A susceptible breakpoint of ≤ 4 μg/mL was used for comparative purposes only.
b. Breakpoints for non-meningitis were applied.
c. Includes susceptible and intermediate.
d. Breakpoints for *H. influenzae* were used.

CONCLUSIONS

- Tigecycline showed excellent activity and spectrum against Gram-positive bacteria, including multi-drug resistant strains, causing infection in patients hospitalized in selected Latin American medical centers.
- Tigecycline was also highly active against bacterial pathogens causing community-acquired respiratory tract infections (*S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*) in the Latin American region evaluated.
- The results of the present study indicate that tigecycline may have an important role in the treatment of both hospital- and community-acquired infections in the Latin American region.

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