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Activity of Tigecycline Tested against Clinical Isolates of *Haemophilus influenzae*, *Moraxella catarrhalis* and *Neisseria meningitidis*, a Worldwide Perspective

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ABSTRACT

Background:

Tigecycline (TIG, formerly GAR-936), is a novel glycylcycline which is currently in phase 3 clinical trials. The in vitro activity of the TIG was evaluated in comparison with tetracycline (TET) and other antimicrobial agents against recent (2000-2002) clinical isolates collected worldwide from patients with respiratory infections and meningitis.

Methods:

A total of 1,727 isolates were tested against TIG and more than 20 comparator agents by broth microdilution according to the NCCLS reference methods and interpretative criteria. The collection included, *H. influenzae* (HI; 1,215 strains, 20% beta-lactamase-producing), *M. catarrhalis* (MCAT; 495 strains, 96% beta-lactamase-producing), and *N. meningitidis* (NM; 17 strains).

Results:

TIG demonstrated excellent activity against these organisms with all isolates being inhibited at ≤4 mg/L (TET susceptibility breakpoint). TIG was highly active against HI (MIC_{90}, 1 mg/L) and MCAT (MIC_{90}, 0.25 mg/L), and its potency against these pathogens was not affected by ß-lactamase production. TIG was 4-fold more potent than TET against HI and TET-resistant isolates showed low (≤1 mg/L) TIG MICs. NM isolates were highly susceptible to TIG (MIC_{90}, ≤0.12 mg/L) and to the vast majority of antimicrobial agents evaluated.

Conclusions:

These results indicate that tigecycline has potent in vitro activity against clinically important Gram-negative bacteria that cause community-acquired respiratory infections and meningitis, including TET-R isolates. Further evaluations of TIG activity, as well as, clinical studies are necessary to assess the role of this compound in the treatment of both community- and hospital-acquired infections.

INTRODUCTION

Increasing resistance among commonly occurring respiratory tract and skin and soft tissue pathogens has complicated the treatment of these infections, necessitating the development of therapeutic alternatives. Tigecycline, formerly GAR-936, a semisynthetic derivative of the minocycline molecule, is the first member of the glycylcycline class to undergo clinical development.

Prior studies have demonstrated a broad-spectrum of activity for tigecycline against aerobic and anaerobic Gram-positive and -negative microorganisms. The glycylcyclines, like the tetracyclines, inhibit protein synthesis by preventing the attachment of aminoacyl-tRNA to the ribosomal A-site. Tigecycline, however, has documented activity against tetracycline-resistant (tet-R) Gram-positive and -negative pathogens by virtue of efflux and ribosomal protection mechanisms.

In this study we evaluated the in vitro activity of tigecycline against a total of 1,727 Gram-negative bacterial isolates recovered from patients with community-acquired respiratory tract infections and meningitis.

MATERIALS AND METHODS

Specimen Collection. The isolates were collected from 93 medical centers representing 29 countries distributed in North and South America, Europe, Asia and Australia. The isolates were collected consecutively from clinical infections and only one isolate per patient was included in the study. The collection included: *Haemophilus influenzae* (1,215 strains, 20% ß-lactamase producing), *M. catarrhalis* (495 strains, 96% ß-lactamase producing) and *Neisseria meningitidis* (17 strains). Isolates were initially identified by the submitting laboratory and subsequently shipped to the monitoring laboratory (The JONES Group/JMI Laboratories, Iowa, USA) where identifications were confirmed using standard methods and antimicrobial susceptibility testing was performed.

Susceptibility Testing. MIC values for tigecycline and comparator agents were tested using validated dry-form broth microdilution panels (TREK Diagnostics, Cleveland, OH) with Haemophilus Test Medium for *H. influenzae*, cation-adjusted Mueller-Hinton broth for *M. catarrhalis* and cation-adjusted Mueller-Hinton broth with supplemental 2-5% lysed horse blood for testing of *N. meningitidis*. Testing, incubation and MIC interpretation were performed using the manufacturers recommendations and the published procedures of the NCCLS. ß-lactamase production was detected by the chromogenic cephalosporin method. Quality control strains utilized included *H. influenzae ATCC 49247, Streptococcus pneumoniae* ATCC 49619 and *Escherichia coli* ATCC 25922.

SELECTED REFERENCES

1. Bergeron J, Ammirati M, Danley D, James L, Norcia M, Retsema J, Strick CA, Su W-G, Sutliffe J, Wondrack L. (1996). Glycylcyclines bind to the high-affinity tetracycline ribosomal binding site and evade Tet(M)-and Tet(O)-mediated ribosomal protection. *Antimicrobial Agents and Chemotherapy* 40:2226-2228.
2. Deshpande LM, Gales AC, Jones RN. (2001). GAR-936 (9-t-butylglycylamido-minocycline) susceptibility test development for streptococci, *Haemophilus influenzae* and *Neisseria gonorrhoeae*: Preliminary guidelines and interpretive criteria. *International Journal of Antimicrobial Agents* 18:29-35.
3. Gales AC, Jones RN. (2000). Antimicrobial activity and spectrum of the new glycylcycline, GAR-936, tested against 1,203 recent clinical bacterial isolates. *Diagnostic Microbiology and Infectious Disease* 36:19-36.
4. Goldstein EJ, Citron DM, Merriam CV, Warren Y, Terrel K. (2000). Comparative in vitro activities of GAR-936 against aerobic and anaerobic animal and human wound pathogens. *Antimicrobial Agents and Chemotherapy* 44:2747-2751.
5. National Committee for Clinical Laboratory Standards. (2003). *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard-sixth edition*. Approved document M7-A6. Wayne, PA:NCCLS.
6. National Committee for Clinical Laboratory Standards. (2004). *Performance standards for antimicrobial susceptibility testing,* 14th informational supplement, M100-S14. Wayne, PA:NCCLS.
7. Petersen PJ, Jacobus NV, Weiss WJ, Sum PE, Testa RT. (1999). In vitro and in vivo antibacterial activities of a new glycylcycline, the 9-t-butyglycylamido derivative of minocycline (GAR-936). *Antimicrobial Agents and Chemotherapy* 43:738-744.

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RESULTS

Table 1. Antimicrobial activity of tigecycline and nine selected agents tested by reference NCCLS [2003] method against *H. influenzae* (1,215 strains), *M. catarrhalis* (495 strains) and *N. meningitidis* (17 strains).

Organism (no. tested)/Antimicrobial agent	MIC (mg/L) 50%	MIC (mg/L) 90%	% by category Susceptible	% by category Resistant
H. influenzae				
ß-lactamase-positive (249)				
Tigecycline	0.5	1	(100.0)[a]	-[b]
Tetracycline	≤2	4	89.6	8.0
Amoxicillin/Clavulanate	1	2	99.6	0.4
Piperacillin/Tazobactam	≤1	≤1	99.2	0.8
Ceftriaxone	≤0.008	≤0.008	100.0	-[b]
Azithromycin	1	1	100.0	-[b]
Clarithromycin	8	16	85.9	0.8
Ciprofloxacin	≤0.03	≤0.03	100.0	-
Chloramphenicol	≤2	≤2	93.6	5.6
Trimethoprim/Sulfamethoxazole	≤0.5	>4	72.7	22.9
ß-lactamase-negative (966)				
Tigecycline	0.5	1	(100.0)[a]	-[b]
Tetracycline	≤2	≤2	99.6	0.3
Amoxicillin/Clavulanate	0.5	1	100.0	0.0
Piperacillin/Tazobactam	≤1	≤1	99.2	0.8
Ceftriaxone	≤0.008	≤0.008	100.0	-[b]
Azithromycin	1	1	99.8	-[b]
Clarithromycin	8	8	90.4	1.1
Ciprofloxacin	≤0.03	≤0.03	100.0	-[b]
Chloramphenicol	≤2	≤2	99.7	0.0
Trimethoprim/Sulfamethoxazole	≤0.5	>4	81.8	15.2
M. catarrhalis[a]				
ß-lactamase-positive (474)				
Tigecycline	≤0.12	0.25	(100.0)[a]	-[b]
Tetracycline	≤2	≤2	99.4	0.6
Amoxicillin/Clavulanate	0.12	0.25	100.0	0.0
Piperacillin/Tazobactam	≤1	≤1	99.8	0.2
Ceftriaxone	0.25	0.5	100.0	-[b]
Azithromycin	≤0.12	≤0.12	100.0	-[b]
Clarithromycin	≤0.25	≤0.25	100.0	0.0
Ciprofloxacin	≤0.03	≤0.03	100.0	-[b]
Chloramphenicol	≤2	≤2	100.0	0.0
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	98.3	0.0
ß-lactamase-negative (21)				
Tigecycline	≤0.12	0.25	(100.0)[a]	-[b]
Tetracycline	≤2	≤2	100.0	0.0
Amoxicillin/Clavulanate	≤0.06	≤0.06	100.0	0.0
Piperacillin/Tazobactam	≤1	≤1	100.0	0.0
Ceftriaxone	≤0.008	0.016	100.0	-[b]
Azithromycin	≤0.12	≤0.12	100.0	-[b]
Clarithromycin	≤0.25	≤0.25	100.0	0.0
Ciprofloxacin	≤0.03	0.06	100.0	-[b]
Chloramphenicol	≤2	≤2	100.0	0.0
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	100.0	0.0
N. meningitidis (17)				
Tigecycline	≤0.12	≤0.12	(100.0)[a]	-[b]
Tetracycline	≤4	≤4	-[b]	-[b]
Doxycycline	≤0.5	≤0.5	-[b]	-[b]
Penicillin	≤0.016	0.25	-[b]	-[b]
Ceftriaxone	≤0.25	≤0.25	-[b]	-[b]
Meropenem	≤0.06	≤0.06	-[b]	-[b]
Erythromycin	≤0.06	0.12	-[b]	-[b]
Clindamycin	2	2	-[b]	-[b]
Ciprofloxacin	≤0.25	≤0.25	-[b]	-[b]
Trimethoprim/Sulfamethoxazole	≤0.5	>1	-[b]	-[b]

a. NCCLS breakpoints for *H. influenzae* were categorically applied to *M. catarrhalis*.
b. No breakpoint has been established by the NCCLS [2004].

- Twenty percent of tested *H. influenzae* and 96% of *M. catarrhalis* strains produced a ß-lactamase.
- *H. influenzae* (MIC_{50} and MIC_{90} of 0.5 and 1 mg/L, respectively) and *M. catarrhalis* (MIC_{50} and MIC_{90} of ≤0.12 and 0.25 mg/L, respectively) were uniformly susceptible to tigecycline, including ß-lactamase-positive strains (Table 1).
- Tigecycline was 4-fold more active than tetracycline against *H. influenzae*. When using the NCCLS tetracycline susceptibility breakpoint of ≤4 mg/L, 100% of strains would be considered susceptible to tigecycline, whereas only 89.6% would be categorized as susceptible to tetracycline.
- All *H. influenzae* and *M. catarrhalis* strains were inhibited by tigecycline at ≤2 mg/L and ≤0.5 mg/L, respectively.
- Tigecycline was also very active, along with most comparator agents, against isolates of *N. meningitidis*. The tigecycline MIC_{50} and MIC_{90} results were at ≤0.12 mg/L versus these meningococci.

CONCLUSIONS

- *H. influenzae* and *M. catarrhalis* were uniformly susceptible to tigecycline, regardless of ß-lactamase production.
- Tigecycline, a novel glycylcycline, appears to be a promising agent against the most commonly occurring Gram-negative pathogens responsible for community-acquired respiratory tract infections, including strains resistant to tetracycline and/or other antimicrobial agents (ß-lactams, macrolides, fluoroquinolones, etc.).
- By retaining the broad-spectrum of the tetracycline class with enhanced potency and incorporating stability to the commonly occurring tetracycline resistance mechanisms, tigecycline has become a promising new class (glycylcyclines) representative warranting continued clinical development.