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Activity of Tigecycline Tested Against Non-Fermentative Gram-negative (NFB) Bacilli Other Than *P. aeruginosa*

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AMENDED ABSTRACT

Background:
Tigecycline (TIG; GAR-936) is the sentinel representative of a new antimicrobial class, glycylcyclines, that displays an enhanced spectrum to both Gram-positive and -negative organisms and appears stable to resistance (R) mechanisms among commonly occurring pathogens. This report summarizes the susceptibility (S) of TIG against selected NFBs, a group that pose special therapeutic challenges.

Methods:
The collection included 381 strains (155 *Acinetobacter* spp.; 44 *Aeromonas* spp.; 9 *Alcaligenes xylosoxidans*, 20 *B. cepacia* [BC], 5 *Chryseobacterium* spp. [CHR], 18 *Pseudomonas* spp. [PSP], 130 *S. maltophilia* [XM]) acquired internationally from various surveillance collections. MIC results were determined by NCCLS methods.

Results: TIG activity against NFB other than PSA.

	TIG MIC (µg/ml)			
Organism (n)	50%	90%	Range	% S[a]
Acinetobacter spp. (155)	0.5	2	0.06-8	98.7
Aeromonas spp. (44)	0.25	0.5	0.12-1	100.0
A. xylosoxidans (9)	0.5	-	0.06-2	100.0
BC (20)	1	8	0.03-16	85.0
CHR (5)	8	-	4-8	40.0
PSP (non-*aeruginosa*; 18)	8	16	0.12-32	44.4
XM (130)	1	2	0.12-8	99.2

a. Tentative breakpoint of ≤ 4 µg/ml, as applied to tetracyclines [NCCLS, 2004].

TIG was very active against all tested species (MIC_{50}, ≤ 1 µg/ml, except CHR and PSP (MIC_{50}, 8 µg/ml). Also the TIG MIC_{90} (8 µg/ml) for BC complex was modestly elevated; highest MIC = 16 µg/ml. Potency of TIG appeared unaffected by R mechanisms frequently associated with these organisms.

Conclusions:
Infections produced by NFB often occur in the setting of severe patient debilitation. Given the limited choices available for treatment of these serious infections produced by them, TIG offers promising activity and an enhanced spectrum worthy of continued development.

INTRODUCTION

Non-fermentative Gram-negative bacilli and others such as *Aeromonas* spp. are bacteria that can be found in moist environments and are ubiquitous around people, animals, plants and water. These bacterial species are often recovered as nosocomial pathogens from patients with severe underlying conditions and contaminate hospital environments and therapeutic equipment. Nosocomial infections produced by these Gram-negative microorganisms are associated with significant morbidity and mortality due to the multidrug resistance to a broad range of antimicrobial agents. The treatment of these infections has become more difficult in recent years due to the increased prevalence of such infections and to the rising incidence of resistance to many of the therapeutic agents commonly used.

Tigecycline is a novel 9-t-butylglycylamido derivative of minocycline currently in clinical trials and has demonstrated potent activity against a variety of pathogens including Gram-positives, Enterobacteriaceae, anaerobes, *Haemophilus influenzae, Neisseria gonorrhoeae,* chlamydiae, and mycoplasmas. This compound acts on bacterial ribosomes by overlapping binding sites targeted by tetracyclines, but remains stable to the major tetracycline-resistance mechanisms; Tet M, Tet O protected ribosomes and efflux determinants. This broad spectrum of activity and a lack of cross resistance to other classes of antimicrobial agents makes tigecycline an attractive therapeutic option for the treatment of serious hospital or community-acquired infections.

This report summarizes the activity of tigecycline and comparator compounds when tested against a collection of non-fermentative Gram-negative bacilli (other than *Pseudomonas aeruginosa*) and *Aeromonas* spp., a group of known pathogens with recognized resistance profiles to commonly utilized antimicrobial agents.

RESULTS

- Susceptibility profiles for tigecycline and 13 comparators against 155 *Acinetobacter* spp. isolates are summarized in Table 1. Only tigecycline and imipenem demonstrated ≥ 90% susceptibility when applying a tentative breakpoint of ≤ 4 µg/ml for tigecycline; all other agents were less active with ≤ 72.3% susceptibility.
- The MIC susceptibility results for *Aeromonas* and *Achromobacter* strains are summarized in Tables 2 and 3. Tigecycline was active (≤ 2 µg/ml) against all strains including those classified as tetracycline resistant; other agents were variably active against both groups.
- Results of MIC testing of *Burkholderia cepacia* isolates are summarized in Table 4. High rates of resistance (≥70%) were observed for tetracycline, ticarcillin/clavulanate, and aminoglycosides. The antimicrobial agents with the greatest susceptibilities were ceftazidime = trimethoprim/sulfamethoxazole (90%) and cefepime = tigecycline (85%).
- Tables 5 and 6 show the susceptibility testing results of tigecycline and comparator agents against *Chryseobacterium* and *Pseudomonas* spp. isolates. Tigecycline was least active against these organism groups with ≤ 44.4% susceptibility ; imipenem and the aminoglycosides had no activity against *Chryseobacterium*, but retained modest activity against the *Pseudomonas* spp.
- Only tigecycline (99.2% susceptible), trimethoprim/sulfamethoxazole (97.7% susceptible) and levofloxacin (87.7% susceptible) demonstrated activity against *S. maltophilia* isolates with all other agents being < 54% susceptible.

MATERIALS AND METHODS

A total of 337 consecutive, non-duplicate non-fermentative Gram-negative bacillus and 44 *Aeromonas* spp. isolates originating from clinical infections were collected from participant sites in North America, Europe, and Latin America as part of the 2003 tigecycline surveillance survey. Isolate identifications were confirmed by the central monitoring facility (JMI Laboratories, North Liberty, Iowa, USA) using colony morphology on standard media, routine biochemical tests and Vitek (bioMerieux, Hazelwood, MO) identification when necessary.

All isolates were tested for susceptibility by National Committee for Clinical Laboratory Standards (NCCLS, 2003) methods using commercially prepared and validated, dry-form broth microdilution panels (TREK Diagnostics Inc., Cleveland, OH,) with cation-adjusted Mueller-Hinton broth. Sixteen antimicrobial agents were tested including tigecycline, tetracycline, and representatives from other classes of antimicrobial agents used in the treatment of non-fermentative Gram-negative bacilliary infections. MIC results were interpreted using NCCLS breakpoint criteria (M100-S14; 2004) where available. A tentative breakpoint for susceptibility to tigecycline of ≤ 4 µg/ml (as applied to tetracycline) was used for comparative purposes.

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- The cumulative percentages of tigecycline susceptibility at each MIC result (range 0.03 – 32 µg/ml) indexed by organism group are displayed in Table 8. 95% of all isolates tested had MIC values of ≤ 4 µg/ml; those with higher MIC results were primarily pseudomonads and chryseobacteria.

Table 1. In vitro activity of tigecycline in comparison to selected antimicrobial agents tested against 155 isolates of *Acinetobacter* spp.[a]

	MIC (µg/ml)			Category:	
Antimicrobial agent	50%	90%	Range	% susceptible	% resistant
Tigecycline	0.5	2	0.06-8	98.7[b]	-[b]
Tetracycline	≤2	>8	≤2->8	61.3	27.1
Ampicillin/Sulbactam	4	>32	≤0.25->32	65.2	24.5
Piperacillin/Tazobactam	32	>64	≤0.12->64	49.7	43.9
Ceftazidime	8	>16	≤1->16	52.3	38.7
Cefepime	8	>16	≤0.12->16	57.4	29.0
Aztreonam	>16	>16	≤0.12->16	9.0	74.2
Imipenem	≤0.5	2	≤0.5->8	92.3	7.1
Amikacin	4	>32	≤0.25->32	72.3	23.9
Gentamicin	≤2	>8	≤2->8	58.1	38.7
Tobramycin	1	>16	≤0.12->16	67.7	26.5
Ciprofloxacin	0.5	>4	≤0.03->4	50.3	49.0
Levofloxacin	0.5	>4	≤0.03->4	57.4	38.1
Polymyxin B	≤1	≤1	≤1->8	-[c]	-[c]

a. Includes *A. anitratus* (nine strains), *A. calcoaceticus* (nine strains), *A. baumannii* (107 strains), *A. junii* (one strain), *A. lwoffii* (16 strains), *Acinetobacter* spp. (13 strains).
b. No breakpoints have been established by NCCLS [2004], tentative breakpoint of ≤ 4 µg/ml was applied for comparison purposes.
c. No breakpoints have been established by NCCLS [2004].

Table 2. In vitro activity of tigecycline in comparison to selected antimicrobial agents tested against 44 isolates of *Aeromonas* spp.[a]

	MIC (µg/ml)			Category:	
Antimicrobial agent	50%	90%	Range	% susceptible	% resistant
Tigecycline	0.25	0.5	0.12-1	100.0[b]	-[b]
Tetracycline	≤2	>8	≤2->8	75.0	18.2
Piperacillin/Tazobactam	8	>64	1->64	62.8	18.6
Ticarcillin/Clavulanate	64	>128	≤16->128	6.8	38.6
Ceftazidime	≤1	≤1	≤1->16	97.7	2.3
Cefepime	≤0.12	0.25	≤0.12-4	100.0	0.0
Aztreonam	≤0.12	0.25	≤0.12-2	100.0	0.0
Imipenem	≤0.5	2	≤0.5->8	93.2	2.3
Amikacin	2	8	1-16	100.0	0.0
Gentamicin	≤2	≤2	≤2->8	97.7	2.3
Tobramycin	1	4	0.25->16	93.2	6.8
Ciprofloxacin	≤0.03	0.25	≤0.03->4	97.7	2.3
Levofloxacin	≤0.03	0.25	≤0.03->4	97.7	2.3
Trimethoprim/Sulfamethoxazole	≤0.5	>2	≤0.5->2	88.6	11.4
Polymyxin B	≤1	2	≤1->8	-[c]	-[c]

a. Includes *A. caviae* (12 strains), *A. hydrophila* (25 strains), *A. sobria* (two strains) and *Aeromonas* spp. (five strains).
b. No breakpoints have been established by NCCLS [2004], tentative breakpoint of ≤ 4 µg/ml was applied for comparison purposes.
c. No breakpoints have been established by NCCLS [2004].

Table 3. In vitro activity of tigecycline in comparison to selected antimicrobial agents tested against nine isolates of *Achromobacter xylosoxidans*.

	MIC (µg/ml)			Category:	
Antimicrobial agent	50%	90%	Range	% susceptible	% resistant
Tigecycline	0.5	-	0.06-2	100.0[a]	-[a]
Tetracycline	>8	-	≤2->8	33.3	66.7
Piperacillin/Tazobactam	1	-	0.5->256	88.9	11.1
Ticarcillin/Clavulanate	≤16	-	≤16-128	88.9	11.1
Ceftazidime	4	-	2->16	88.9	11.1
Cefepime	>16	-	>16	11.1	55.6
Aztreonam	>16	-	>16	0.0	100.0
Imipenem	1	-	≤0.5-4	100.0	0.0
Amikacin	>32	-	4->32	44.4	55.6
Gentamicin	>8	-	≤2->8	33.3	55.6
Tobramycin	16	-	2->16	44.4	55.6
Ciprofloxacin	2	-	1->4	11.1	44.4
Levofloxacin	2	-	1->4	66.7	11.1
Trimethoprim/Sulfamethoxazole	≤0.5	-	≤0.5->2	77.8	22.2
Polymyxin B	2	-	≤1->8	-[b]	-[b]

a. No breakpoints have been established by NCCLS [2004], tentative breakpoint of ≤ 4 µg/ml was applied for comparison purposes.
b. No breakpoints have been established by NCCLS [2004].

Table 4. In vitro activity of tigecycline in comparison to selected antimicrobial agents tested against 20 isolates of *Burkholderia cepacia*.

	MIC (µg/ml)			Category:	
Antimicrobial agent	50%	90%	Range	% susceptible	% resistant
Tigecycline	1	8	0.03-16	85.0[a]	-[a]
Tetracycline	>8	>8	≤2->8	5.3	94.7
Piperacillin/Tazobactam	4	256	0.5->256	80.0	15.0
Ticarcillin/Clavulanate	>128	>128	≤16->128	10.0	75.0
Ceftazidime	4	4	≤1->16	90.0	10.0
Cefepime	8	16	≤0.12->16	85.0	10.0
Aztreonam	16	>16	≤0.12->16	40.0	20.0
Imipenem	4	8	≤0.5->8	65.0	10.0
Amikacin	>32	>32	0.5->32	20.0	70.0
Gentamicin	>8	>8	≤2->8	15.0	80.0
Tobramycin	>16	>16	≤0.12->16	15.0	75.0
Ciprofloxacin	1	4	0.06->4	75.0	20.0
Levofloxacin	1	4	≤0.03->4	80.0	10.0
Trimethoprim/Sulfamethoxazole	≤0.5	2	≤0.5->2	90.0	10.0
Polymyxin B	>8	>8	≤1->8	-[b]	-[b]

a. No breakpoints have been established by NCCLS [2004], tentative breakpoint of ≤ 4 µg/ml was applied for comparison purposes.
b. No breakpoints have been established by NCCLS [2004].

Table 5. In vitro activity of tigecycline in comparison to selected antimicrobial agents tested against five isolates of *Chryseobacterium* spp.[a]

	MIC (µg/ml)			Category:	
Antimicrobial agent	50%	90%	Range	% susceptible	% resistant
Tigecycline	8	-	4-8	40.0[b]	-[b]
Tetracycline	>8	-	>8	0.0	100.0
Piperacillin/Tazobactam	2	-	2-4	100.0	0.0
Ticarcillin/Clavulanate	>128	-	64->128	0.0	60.0
Ceftazidime	>16	-	4->16	40.0	60.0
Cefepime	8	-	0.5-16	80.0	0.0
Aztreonam	>16	-	>16	0.0	100.0
Imipenem	>8	-	8->8	0.0	80.0
Amikacin	32	-	32->32	0.0	40.0
Gentamicin	>8	-	>8	0.0	100.0
Tobramycin	>16	-	>16	0.0	100.0
Ciprofloxacin	1	-	0.5->4	60.0	40.0
Levofloxacin	0.5	-	0.5->4	60.0	40.0
Trimethoprim/Sulfamethoxazole	2	-	1-2	100.0	0.0
Polymyxin B	>8	-	>8	-[c]	-[c]

a. Includes *C. indologenes* (two strains), *C. meningosepticum* (two strains) and *Chryseobacterium* spp. (one strain).
b. No breakpoints have been established by NCCLS [2004], tentative breakpoint of ≤ 4 µg/ml was applied for comparison purposes.
c. No breakpoints have been established by NCCLS [2004].

Table 6. In vitro activity of tigecycline in comparison to selected antimicrobial agents tested against 18 isolates of *Pseudomonas* spp. (not PSA).[a]

	MIC (µg/ml)			Category:	
Antimicrobial agent	50%	90%	Range	% susceptible	% resistant
Tigecycline	8	16	0.12-32	44.4[b]	-[b]
Tetracycline	>8	>8	≤2->8	38.9	55.6
Piperacillin/Tazobactam	8	128	1-256	83.3	11.1
Ticarcillin/Clavulanate	32	>128	≤16->128	27.8	38.9
Ceftazidime	2	>16	≤1->16	83.3	11.1
Cefepime	4	16	0.25->16	83.3	5.6
Aztreonam	8	>16	0.25->16	61.1	22.2
Imipenem	1	>8	≤0.5->8	88.9	11.1
Amikacin	2	32	0.5-32	88.9	0.0
Gentamicin	≤2	>8	≤2->8	83.3	11.1
Tobramycin	0.5	>16	0.25->16	88.9	11.1
Ciprofloxacin	0.12	4	0.03->4	61.1	33.3
Levofloxacin	0.5	>4	0.06->4	61.1	27.8
Trimethoprim/Sulfamethoxazole	>2	>2	≤0.5->2	22.2	77.8
Polymyxin B	≤1	8	≤1->8	-[c]	-[c]

a. Includes *P. fluorescens* (three strains), *P. fluorescens/putida* (one strain), *P. mendocina* (two strains), *P. stutzeri* (one strain) and *Pseudomonas* spp. (11 strains).
b. No breakpoints have been established by NCCLS [2004], tentative breakpoint of ≤ 4 µg/ml was applied for comparison purposes.
c. No breakpoints have been established by NCCLS [2004].

Table 7. In vitro activity of tigecycline in comparison to selected antimicrobial agents tested against 130 isolates of *Stenotrophomonas maltophilia*.

	MIC (µg/ml)			Category:	
Antimicrobial agent	50%	90%	Range	% susceptible	% resistant
Tigecycline	1	2	0.12-8	99.2[a]	-[a]
Tetracycline	>8	>8	≤2->8	3.1	69.2
Piperacillin/Tazobactam	256	>256	8->256	5.5	72.4
Ticarcillin/Clavulanate	≤16	128	≤16->128	50.0	22.3
Ceftazidime	8	>16	≤1->16	53.1	36.2
Cefepime	16	>16	1->16	19.2	46.9
Aztreonam	>16	>16	4->16	3.8	93.1
Imipenem	>8	>8	2->8	2.3	97.7
Amikacin	>32	>32	0.5->32	11.5	82.3
Gentamicin	>8	>8	≤2->8	11.5	85.4
Tobramycin	>16	>16	1->16	10.0	86.2
Ciprofloxacin	2	>4	0.12->4	29.2	34.6
Levofloxacin	1	4	0.12->4	87.7	4.6
Trimethoprim/Sulfamethoxazole	≤0.5	1	≤0.5->2	97.7	2.3
Polymyxin B	≤1	4	≤1->8	-[b]	-[b]

a. No breakpoints have been established by NCCLS [2004], tentative breakpoint of ≤ 4 µg/ml was applied for comparison purposes.
b. No breakpoints have been established by NCCLS [2004].

Table 8. Frequency of occurrence and cumulative percentage of tigecycline MIC results against 381 non-fermentative Gram-negative bacilli and *Aeromonas* spp.

	MIC (µg/ml)										
Organism (no. tested)	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32
Acinetobacter spp. (155)	-	5	21	41	27	40	18	1	2	-	-
	-	3.2	16.8	43.2	60.6	86.5	98.1	98.7	100.0	-	-
Aeromonas spp. (44)	-	-	13	21	8	2		-	-	-	-
	-	-	29.5	77.3	95.5	100.0		-	-	-	-
Achromobacter xylosoxidans (9)	-	1	1	-	3	3	1	-	-	-	-
	-	11.1	22.2	22.2	55.6	88.9	100.0	-	-	-	-
Burkholderia cepacia (20)	1	-	-	-	4	6	4	2	2	1	-
	5.0	5.0	5.0	5.0	25.0	55.0	75.0	85.0	95.0	100.0	-
Chryseobacterium spp. (5)	-	-	-	-	-	-	-	2	3	-	-
	-	-	-	-	-	-	-	40.0	100.0	-	-
Pseudomonas spp. (18)	-	-	2	2	-	1	2	1	6	3	1
	-	-	11.1	22.2	22.2	27.8	38.9	44.4	77.8	94.4	100.0
Stenotrophomonas maltophilia (130)	-	-	2	9	40	49	20	9	1	-	-
	-	-	1.5	8.5	39.2	76.9	92.3	99.2	100.0	-	-

CONCLUSIONS

- Tigecycline has demonstrated antimicrobial activity against non-fermentative Gram-negative bacilli and *Aeromonas* spp. with 95% susceptibility when applying a tentative breakpoint of ≤ 4 µg/ml. Compared to tetracycline, activity was markedly enhanced, stressing the stability of tigecycline to tetracycline resistance mechanisms.
- *Pseudomonas* spp. isolates $MIC_{50/90}$ results of 8/16 µg/ml for tigecycline were comparable to previously reported values when testing *P. aeruginosa* isolates.
- In addition to its documented potent activity against Gram-positives, Enterobacteriaceae, *H. influenzae* and other pathogens, tigecycline appears to be a promising alternative therapeutic for certain non-fermentative bacilli and aeromonads.