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Tigecycline In Vitro Antibacterial Activity Against Isolates of Non-Enterobacteriaceae

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REVISED ABSTRACT

Background: Tigecycline (GAR-936) is a new glycylcycline, which has been shown to have potent activity against organisms with either ribosomal protection or active efflux. Tigecycline has shown activity against most members of non-*Enterobacteriaceae*. The activity of tigecycline was compared with those of other agents against *Acinetobacter* spp and *Pseudomonas aeruginosa* from hospitals throughout Europe, the Middle East and South Africa.

Methods: A total of 776 clinical isolates were identified to the species level at each participating site and confirmed by the central laboratory. Isolates were collected between January 2001 – September 2002. MIC's were determined by the central laboratory using broth microdilution panels from Dade Microscan according to NCCLS guidelines and manufacturer's instructions.

Results: MIC_{50}s and MIC_{90}s for *Acinetobacter* spp and *P. aeruginosa* are shown in Table 1.

Table 1. In Vitro Activity (mcg/mL) of Tigecycline and Comparators Against Non-*Enterobacteriaceae*

	Acinetobacter spp (n=470)			*P. aeruginosa* (n=306)		
	MIC (µg/ml)			MIC (µg/ml)		
Antibiotic	**Range**	**MIC50**	**MIC90**	**Range**	**MIC50**	**MIC90**
Tigecycline (GAR-936)	0.12-4	0.5	2	1->16	>16	>16
Amoxicillin/clavulanic acid	0.25->64	16	>64	32->64	>64	>64
Ampicillin/sulbactam	0.5->32	4	>32	16->32	>32	>32
Imipenem	0.5->64	0.5	32	0.5->64	1	16
Cefepime	0.5->64	8	>64	0.5->64	4	16
Ceftazidime	0.5->64	8	>64	0.5->64	2	16
Ceftriaxone	0.5->64	16	>64	4->64	32	>64
Levofloxacin	0.25->64	0.5	16	0.25->64	0.5	16

Conclusion: Tigecycline's in vitro activity against *Acinetobacter* is better than all other compounds tested and equal to or slightly less than other agents tested against *P. aeruginosa*. These results suggest that tigecycline is a promising new antimicrobial agent with excellent activity against this non-*Enterobacteriaceae* population.

BACKGROUND

Tigecycline is a novel antimicrobial with an expanded broad-spectrum of activity from a new class of compounds, glycylcyclines. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit. Although it's antibacterial activity is significant, it is perceived to be bacteriostatic [1,2]. Tigecycline was developed to provide activity against tetracycline- and multi-drug-resistant gram-positive pathogens and has demonstrated significant broad-spectrum activity against aerobic and anaerobic gram-positive and gram-negative microorganisms [2, 3].

Tigecycline resistance is very infrequent and is also difficult to induce in the laboratory [6, 7] with a selection frequency observed at less than 10-9 [3, 6, 8]. With the exception of *P. aeruginosa*, tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline [2-4, 8-12]. The MIC_{90} values for pseudomonal isolates are generally elevated, in the range of 8-16 mcg/ml [11, 13]. The pharmacokinetics of parenteral tigecycline is linear with a mean half-life of 36 hours and a maximum serum concentration (C_{MAX}) of a 300mg dose infused over 1 hour of 2.8 mcg/ml [14,15].

Since tigecycline has been shown to have activity against most members of non-*Enterobacteriaceae*, this study compared the activity of tigecycline with other agents against *Acinetobacter* spp and *Pseudomonas aeruginosa* from hospitals throughout Europe.

METHODS

- All isolates were derived from blood, respiratory tract, urine (no more than 30% of all isolates), skin, wound, fluids and few other defined sources. Only one isolate per patient was accepted.
- Clinical isolates were collected between January 2001 – September 2002 from 36 study centers in 16 countries.
- Antimicrobial agents tested with concentrations (expressed in mcg/ml) were: Ampicillin-sulbactam (0.5 – 32); cefepime (0.5 – 64); ceftazidime (0.5 – 64); ceftriaxone (0.5 – 64); imipenem (0.5 – 64); levofloxacin (0.25 – 64); tigecycline (0.008 – 16). MIC interpretive criteria followed published guidelines established by the NCCLS where applicable [16]. Tigecycline tentative breakpoints (in units of mcg/mL) are defined as susceptible $\leq$ 2; intermediate = 4; and resistant $\geq$ 8.
- Isolates were identified to genus and species at each site and confirmed by the central laboratory (Laboratories International for Microbiology Studies, Schaumburg, IL, USA).
- Organism collection, transport, confirmation of organism identification, antimicrobial susceptibility testing, as well as, construction and management of a centralized database was coordinated by Laboratories International for Microbiology Studies (LIMS).

Antimicrobial Susceptibility Testing

- MIC's were determined by the central laboratory using broth microdilution panels manufactured by Dade Microscan (Dade Behring Inc., Sacramento, CA. USA) according to NCCLS guidelines and manufacturers instructions.
- Quality Control was performed using the following ATCC strains: *E. coli* ATCC 35218, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853.

RESULTS

Results are shown in the following tables.

Table 2. In Vitro Activity (mcg/ml) of Tigecycline and Comparative Agents Against 776 Isolates of *Acinetobacter* spp and *Pseudomonas aeruginosa*.

Organism / Phenotype	Drug	% Sus	%Int	%Res	MIC_{90}
		MIC (mcg/ml)			
Acinetobacter spp (470)	Tigecycline	99.1	0.9	0.0	2
	Doxycycline	82.6	1.9	15.5	>32
	Amp/Sulb	71.1	7.2	21.7	>32
	Cefepime	55.1	13.2	31.7	>64
	Ceftazidime	54.9	8.5	36.6	>64
	Ceftriaxone	32.8	24.3	43.0	>64
	Imipenem	83.8	4.3	11.9	32
	Levofloxacin	56.8	4.9	38.3	16
P. aeruginosa (306)	Tigecycline	1.3	4.6	94.1	>16
	Doxycycline	1.3	8.8	89.9	>32
	Amp/Sulb	0.0	0.3	99.7	>32
	Cefepime	85.0	8.8	6.2	16
	Ceftazidime	84.0	6.9	9.2	16
	Ceftriaxone	15.0	46.1	38.9	>64
	Imipenem	84.0	3.6	12.4	16
	Levofloxacin	74.8	7.5	17.6	16

* Breakpoints defined by the NCCLS 2002, document M100-S12; Tigecycline tentative breakpoints (mcg/mL) defined as susceptible $\leq$ 2; intermediate = 4; resistant $\geq$ 8

Table 3. In Vitro MICs (mcg/ml) and Cumulative Percent Inhibited (%) of Tigecycline and Comparative Agents Against 470 Isolates of *Acinetobacter* spp

Antimicrobial (n/Cum%)	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
	MIC (mcg/ml)											
Tigecycline		15	142	127	126	56	4					
		3.2	33.4	60.4	87.2	99.1	100.0					
Doxycycline	65	131	53	44	60	24	11	9	18	51	4	
	13.8	41.7	53.0	62.3	75.1	80.2	82.6	84.5	88.3	99.1	100.0	
Amox/Clav			8	5	14	14	28	89	77	72	56	107
			1.7	2.8	5.7	8.7	14.7	33.6	50.0	65.3	77.2	100.0
Amp/Sulb				19	46	124	74	71	34	36	66	
				4.0	13.8	40.2	56.0	71.1	78.3	86.0	100.0	
Cefepime				35	37	85	61	41	62	54	46	49
				7.4	15.3	33.4	46.4	55.1	68.3	79.8	89.6	100.0
Ceftazidime				16	22	91	79	50	40	31	15	126
				3.4	8.1	27.4	44.3	54.9	63.4	70.0	73.2	100.0
Ceftriaxone				8	9	13	37	87	86	28	10	192
				1.7	3.6	6.4	14.3	32.8	51.1	57.0	59.1	100.0
Imipenem				300	40	34	20	20	8	2	4	42
				63.8	72.3	79.6	83.8	88.1	89.8	90.2	91.1	100.0
Levofloxacin			234	12	9	12	23	120	50	4	1	5
			49.8	52.3	54.3	56.8	61.7	87.2	97.9	98.7	98.9	100.0

Dividing lines represent MIC_{90} demarcation.

Table 4. In Vitro MICs (mcg/ml) and Cumulative Percent Inhibited (%) of Tigecycline and Comparative Agents Against 307 Isolates of *Pseudomonas aeruginosa*

Antimicrobial (n/Cum%)	0.5	1	2	4	8	16	>16	32	>32	64	>64
	MIC (mcg/ml										
Tigecycline		4		14	88	142	59				
		1.3		5.9	34.5	80.8	100.0				
Doxycycline	1			3	28	111		71	93		
	0.3			1.3	10.4	46.6		69.7	100.0		
Amox/Clav								2		8	297
								0.7		3.3	100.0
Amp/Sulb						1		4	302		
						0.3		1.6	100.0		
Cefepime	4	33	104	70	50	27		9		8	2
	1.3	12.1	45.9	68.7	85.0	93.8		96.7		99.3	100.0
Ceftazidime	5	106	103	27	17	21		11		11	6
	1.6	36.2	69.7	78.5	84.0	90.9		94.5		98.0	100.0
Ceftriaxone				12	34	79		63		42	77
				3.9	15.0	40.7		61.2		74.9	100.0
Imipenem	86	130	30	12	11	28		6		1	3
	28.0	70.4	80.1	84.0	87.6	96.7		98.7		99.0	100.0
Levofloxacin		26	140	36	28	23	17	9		11	
		8.5	54.1	65.8	74.9	82.4	87.9	90.9		94.5	

Dividing lines represent MIC_{90} demarcation.

CONCLUSIONS

- Tigecycline inhibited 99% of *Acinetobacter* spp at a MIC of 2 mcg/ml which was the lowest MIC_{90} of all comparator study drugs.
- Tigecycline was less active against *Pseudomonas aeruginosa* with a MIC_{90} of $\geq$16 mcg/ml.
- The in vitro activity of tigecycline in this Gram-negative non-*Enterobacteriaceae* population warrants further investigation.
- Tigecycline appears to be a promising agent against non-enterobacteriaceae.
- Additional studies into the mechanism of resistance of *Pseudomonas aeruginosa* against tigecycline would be of interest.

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