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Antimicrobial Activity of Tigecycline (GAR-936) Tested Against Enterobacteriaceae, and Selected Non-Fermentative Gram-Negative Bacilli, A Worldwide Sample

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ECCMID 2004
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ABSTRACT

Background:
As resistances (R) among Gram-negative bacilli (GNBs) expand, few antimicrobial agents have been developed to address this clinical problem. Tigecycline (TIG), a novel glycylcycline, has an expanded spectrum of activity and potency. TIG covers many routine Gram-negative antimicrobial-resistant strains and additionally possesses activity versus some uncommonly isolated non-fermentative GNBs. This study compares TIG with contemporary broad-spectrum agents using recent clinical isolates from Europe and other continents.

Methods:
All strains (2,420) were centrally processed by reference, broth microdilution methods against more than 20 antimicrobials. All concurrent QC results were within NCCLS published ranges, with identifications performed by traditional methods and/or the Vitek System. Over 2,400 isolates were tested from the Enterobacteriaceae (ENT) and non-fermentative GNBs categories. Susceptibility (S) for TIG was defined as ≤4 mg/L, that breakpoint used for all tetracyclines by the NCCLS.

Results:
The ENT were divided into 3 groups for analysis: ESBL-producing isolates (154 strains), Proteae group (131 strains; includes *P. mirabilis* and indole-positive species) and all enteric bacilli. TIG was very active against all ESBL-producing isolates (MIC_{90}, 0.25-2 mg/L; highest among TC-R subsets), and all ENT (MIC50/90, 0.25/1 mg/L). *Proteae* had a MIC_{90} at 4 mg/L and all but one of TIG-R or intermediate strains (MICs, 8 and 16 mg/L) were *M. morganii* or *P. mirabilis*. *P. aeruginosa* was marginally inhibited by TIG (MIC_{90}, 32 mg/L). In contrast, *Acinetobacter* spp. (MIC_{90}, 2 mg/L; 96.1% S) and *S. maltophilia* (MIC_{90}, 2 mg/L; 100.0% S) were readily inhibited by TIG. Among all ENT studied, 31.0% were TC-R, but only one strain (*P. mirabilis*) was TIG-R (MIC at 16 mg/L).

Conclusions:
Remarkable potency and breadth of spectrum was observed for TIG against ENT (99.4% at ≤4 mg/L versus 66.8% for TC), *S. maltophilia* and *Acinetobacter* spp. Limited activity was noted versus *P. aeruginosa* (16.0% at ≤4 mg/L) and some Proteae (MIC_{90}, 4 mg/L). TIG should be of value for the treatment of infections caused by several commonly R GNB groups.

INTRODUCTION

The 9-t-butylglycylamido derivative of minocycline, tigecycline (formerly GAR-936), has become the sentinal representative of a new class known as the glycylcyclines. This compound offers important advantages to existing antimicrobials including enhanced spectrum of activity and stability against tetracycline resistance mechanisms (Tet A or B efflux determinants and Tet M or O ribosomal protection factors). Its mode of action on bacterial ribosomes shows identical and overlapping binding sites when compared to tetracycline, but the position 9 substitution of tigecycline provides additional steric hindrance features and resulting greater spectra of activity.

Tigecycline is currently undergoing extensive clinical evaluation as a parenteral agent because of its potent activity against a broad range of commonly occurring species, including many resistant organisms such as penicillin-resistant *Streptococcus pneumoniae* (PRSP), oxacillin-resistant staphylococci (ORSA), vancomycin-resistant enterococci (VRE), and extended-spectrum ß-lactamase (ESBL) producing strains of Enterobacteriaceae. Tigecycline is also

INTRODUCTION (Continued)

active against *Haemophilus influenzae*, *Moraxella catarrhalis,* pathogenic *Neisserias* and many other Gram-negative species.

In this study we evaluated the in vitro activity of tigecycline against a total of over 2,000 recent Gram-negative bacterial isolates (Enterobacteriaceae and non-fermentative gram-negative bacilli) recovered predominantly from patients with bloodstream, respiratory tract, skin and soft tissue and urinary tract infections.

MATERIALS AND METHODS

Specimen Collection. The collection initially consisted of 2,240 consecutively acquired, non-duplicate, patient isolates submitted from nearly 100 participating medical centers representing over 25 countries on the five continents (Asia, Australia, Europe, North America, South America). Isolates were identified by the submitting laboratory and subsequently shipped to the monitor (The JONES Group/JMI Laboratories, Iowa, USA) where identifications were confirmed using traditional methods and/or the Vitek system (bioMerieux Vitek, Hazelwood, MO, USA).

Susceptibility Testing. MIC values for tigecycline and 20 or more comparator agents were tested using validated dry-form broth microdilution panels (TREK Diagnostics, Cleveland, OH) with cation-adjusted Mueller-Hinton broth medium. Testing, incubation and MIC interpretation were performed using the manufacturers recommendations and suggested technical details of the NCCLS (2003 and 2004). Susceptibility for tigecycline was defined as ≤4 mg/L, that breakpoint used for all tetracyclines by the NCCLS. Quality control strains utilized included *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 35218, *Staphylococcus aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212.

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ACKNOWLEDGEMENT

The study was supported by a grant from Wyeth Pharmaceuticals.

RESULTS

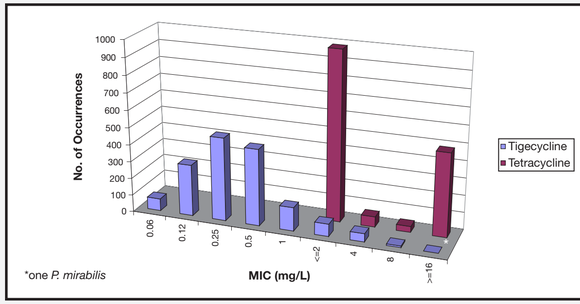
- Among all Enterobacteriaceae, tigecycline was highly active ($MIC_{50/90}$, 0.25 and 1 mg/L; 99.4% susceptible at ≤4 mg/L).
- Nearly one-third (31%) of Enterobacteriaceae were tetracycline-resistant, but only one strain (*Proteus mirabilis*) was tigecycline-resistant (MIC, 16 mg/L).
- Tigecycline was also very active against ESBL-producing isolates (MIC_{90}, 0.25 -2 mg/L) with the highest MIC values seen among tetracycline-resistant subsets (Table 1).
- Activity was more limited against *P. mirabilis* and indole-positive *Proteus* species as a group with a MIC_{90} of 4 mg/L. All but one of the tigecycline-resistant or -intermediate strains (MICs, 8 and 16 mg/L) were either *Morganella morganii* or *P. mirabilis* (Table 2).
- While *P. aeruginosa* was marginally inhibited by tigecycline (MIC_{90}, 32 mg/L; 16.0% susceptible), the compound was active against *Acinetobacter* spp. (MIC_{90}, 2 mg/L; 96.1% susceptible) and *Stenotrophomonas maltophilia* (MIC_{90}, 2 mg/L; 100.0% susceptible; see Table 2).

Table 1. Activity of tigecycline and tetracycline tested against ESBL-producing *E. coli* (67 strains) and *Klebsiella* spp. (87 strains).

Organism/tetracycline susceptibility group (no. tested)	Tigecycline MIC (g/ml) 50%	90%	Range	% at MIC ≤2 mg/L	≤4 mg/L
E. coli					
Susceptible (23)	0.12	0.25	0.06-0.5	100.0	100.0
Resistant (44)	0.25	0.5	0.06-4	97.7	100.0
Klebsiella spp.[a]					
Susceptible (49)	0.25	0.5	0.06-2	100.0	100.0
Resistant (38)[b]	0.5	2	0.25-4	92.1	100.0

a. Includes *K. oxytoca* (eight strains), *K. pneumoniae* (78 strains) and *Klebsiella* spp. NOS (one strain).
b. Includes intermediately susceptible strains (three *K. pneumoniae* isolates).

Figure 1: Activity of tigecycline against 1,573 Enterobacteriaceae (2003).



*one *P. mirabilis*

Table 2. Tigecycline activity against selected strains of Enterobacteriaceae and non-fermentative Gram-negative bacilli (species with ≥10 isolates).

Organism (no. tested)	Tigecycline MIC (µg/ml) 50%	90%	Range	% at ≤4 mg/L[a]
Citrobacter spp. (47)	0.25	1	0.12-2	100.0
Enterobacter spp. (136)	0.5	1	0.06-8	99.3
E. coli (716)	0.25	0.5	0.06-4	100.0
Klebsiella spp. (233)	0.5	1	0.06-4	100.0
Proteae				
P. mirabilis (95)	2	4	0.25-16	91.6
Indole-positive (36)	1	2	0.06-8	97.2
Salmonella spp. (213)	0.5	0.5	0.12-1	100.0
Serratia spp. (53)	1	2	0.12-4	100.0
Shigella spp. (24)	0.25	0.5	0.06-0.5	100.0
Acinetobacter spp. (51)	0.25	2	0.06-32	96.1
B. cepacia (10)	1	4	0.5-8	90.0
P. aeruginosa (369)	8	16	0.12-32	16.0
S. maltophilia (44)	1	2	0.12-4	100.0

a. Susceptible breakpoint applied to tetracyclines [NCCLS, 2004].

CONCLUSIONS

- These findings confirm that tigecycline displays remarkable potency and breadth of spectrum against Enterobacteriaceae (99.4% of isolates are ≤4 mg/L versus 66.8% for tetracycline), including ESBL-producing isolates.
- Among non-fermentative Gram-negative bacilli, tigecycline was among the most active against *Acinetobacter* spp (96.1% susceptible) and *S. maltophilia* (100.0% susceptible), but generally inactive against *P. aeruginosa*.
- Tigecycline should be of value for the treatment of infections caused by several of the commonly occurring resistant Gram-negative bacilli.
- Stability of tigecycline to the commonly occurring tetracycline resistance mechanisms coupled with its enhanced potency and spectrum, are recognized attributes making this glycylcycline an attractive candidate for continued clinical development.