Tigecycline Activity Tested Against Gram-positive Cocci and Enterobacteriaceae Collected in Europe, North America and Latin America

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AMENDED ABSTRACT

Background:
Tigecycline is a novel glycylcycline compound recently approved by the United States (US) Food and Drug Administration (FDA) for the treatment of complicated skin and skin structure and complicated intra-abdominal infections. The activity of tigecycline and >20 comparator agents was assessed against recent clinical bacterial isolates collected through a global surveillance program.

Methods: A total of 69,157 unique patient strains were tested by the reference broth microdilution methods according to CLSI (formerly NCCLS) guidelines and interpretative criteria. Susceptibility (S) breakpoints approved by US-FDA were used for tigecycline. The S patterns of the following organisms were analyzed (no. tested): *S. aureus* (20,835), coagulase-negative staphylococci (CoNS; 5,675), enterococci (6,766), *S. pneumoniae* (6,234), ß-haemolytic streptococci (ßST; 1,903), and Enterobacteriaceae (ENT; 15,978). The isolates were consecutively collected during the 2000-2005 period from patients with documented infections.

Results: Tigecycline activity against the main Gram-positive cocci (GP) and ENT pathogens are summarized in the table:

Organism (no. tested)	MIC (mg/L) 50%	MIC (mg/L) 90%	% inhibited at MIC of (mg/L): ≤0.25	0.5	1	2	4	% S
S. aureus (20,835)	≤0.12	0.25	91.6	99.6	100.0	100.0	100.0	99.6
E. coli (7,428)	0.12	0.25	92.9	99.3	99.8	>99.9	>99.9	>99.9
S. pneumoniae (6,234)	≤0.12	≤0.12	98.8	99.6	100.0	100.0	100.0	98.8
CoNS (5,675)	≤0.12	0.5	84.0	98.3	100.0	100.0	100.0	98.3
E. faecalis (4,941)	≤0.12	0.25	94.6	99.9	100.0	100.0	100.0	94.6
Klebsiella spp. (3,289)	0.5	1	43.3	84.3	94.3	98.4	99.9	98.4
Enterobacter spp. (1,930)	0.5	1	36.1	81.1	91.6	96.7	99.8	96.7
ßST (1,903)	≤0.12	≤0.12	99.8	100.0	100.0	100.0	100.0	99.8
E. faecium (EFM; 1,825)	≤0.12	0.25	97.7	99.7	100.0	100.0	100.0	97.7
All ENT (15,978)	0.5	1	61.5	83.5	91.6	96.4	99.4	96.4

In general, 50.7% of EFM were S to vancomycin (VAN), 62.9% of *S. aureus* were S to oxacillin, and 85.9, 89.4 and 89.8% of ENT were S to ciprofloxacin (CIP), gentamicin (GEN) and ceftriaxone (CTX) respectively. Tigecycline was consistently active against tetracycline-resistant (R) strains. R to oxacillin in staphylococci, to penicillin in streptococci or to VAN in enterococci did not adversely influence tigecycline in vitro activity.

Conclusions: Tigecycline exhibited a wide spectrum of antimicrobial potency versus clinical bacterial isolates collected worldwide. Tigecycline showed broader spectrum than VAN against GP and than CIP, GEN or CTX against indicated ENT. This agent represents a valuable alternative for treatment of serious infections in nosocomial environments, especially those caused by multi-drug-R pathogens.

INTRODUCTION

Tigecycline is a novel semisynthetic glycylcycline derived from the minocycline molecule that was recently approved by the United States Food and Drug Administration (US-FDA) and by the European Medicines Agency (EMEA) for the treatment of complicated skin and skin structure and complicated intra-abdominal infections.

This novel compound has documented activity against tetracycline-resistant (tet-R) Gram-positive and Gram-negative pathogens refractory by both efflux and ribosomal protection mechanisms. Tigecycline has also shown in vitro activity against multidrug-resistant organisms such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci and carbapenem-resistant Enterobacteriaceae and *Acinetobacter* spp.

The present study was conducted to evaluate the in vitro activity of tigecycline tested against recent clinical bacterial isolates collected through a global surveillance program.

MATERIALS AND METHODS

The organisms were consecutively collected isolates processed in a central laboratory system (JMI Laboratories, North Liberty, Iowa, USA) using common reference test reagents. Isolates were derived from a wide variety of clinical sources (Program Objectives) such as: bloodstream, community-acquired or nosocomial respiratory tract sites, skin and soft tissue infections, urinary tract infections and selected patient populations. In this investigation, the isolates were obtained at medical centers located in North America (≥ 25 sites in the USA and Canada), Latin America (10 nations) and Europe (≥ 25 sites).

All isolates were identified by the participant laboratories and confirmed by the monitoring facility. Each strain was tested by a reference broth microdilution method against more than 30 antimicrobial agents; only selected agents with the widest potential clinical utility and in vitro activity are reported here. Interpretation of quantitative MIC results was in accordance with Clinical and Laboratory Standards Institute (CLSI) methods and criteria. Tigecycline susceptible (S) breakpoints were defined as ≤ 2 mg/L for Enterobacteriaceae, ≤ 0.5 mg/L for staphylococci and ≤ 0.25 mg/L for streptococci and enterococci, as approved by the United States Food and Drug Administration (US-FDA). Current quality control (QC) testing was performed using the following organisms: *Streptococcus pneumoniae* ATCC 49619, *Staphylococcus aureus* ATCC 29213 and *Escherichia coli* ATCC 25923.

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RESULTS

- Tigecycline was very potent against staphylococci (MIC_{50}, 0.12 mg/L) and showed antimicrobial spectrum similar to that of linezolid and vancomycin (>99% susceptibility) against *S. aureus* and coagulase-negative staphylococci.
- Tigecycline (MIC_{90}, ≤0.12 mg/L; 98.8% susceptible), levofloxacin (MIC_{90}, 1 mg/L; 99.0% susceptible) and ceftriaxone (MIC_{90}, 1 mg/L; 97.7% susceptible) were the most active compounds tested against *S. pneumoniae* among the antimicrobials evaluated in the study.

Table 1. Antimicrobial activity of tigecycline and comparators tested against a large collection of Gram-positive cocci and Enterobacteriaceae collected worldwide (2000-2005).

Organism (no. tested)/ antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/ resistant
S. aureus (20,835)				
Tigecycline	0.12	0.25	≤0.015-1	99.6 / -[a]
Oxacillin	0.5	8	≤0.06->8	62.9 / 37.1
Levofloxacin	≤0.5	4	≤0.5->4	64.4 / 34.4
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	95.8 / 4.2
Linezolid	2	2	≤0.06->8	>99.9 / -
Vancomycin	1	1	≤0.12-4	>99.9/ 0.0
E. coli (7,428)				
Tigecycline	0.12	0.25	≤0.03->4	>99.9 / <0.1
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	95.0 / 4.1
Ceftazidime	≤1	≤1	≤1->16	95.9 / 2.5
Imipenem	≤0.5	≤0.5	≤0.5->8	>99.9 / <0.1
Levofloxacin	≤0.03	>4	≤0.03->4	83.3 / 14.6
Gentamicin	≤2	≤2	≤2->8	91.6 / 7.7
S. pneumoniae (6,234)				
Tigecycline	≤0.12	≤0.12	≤0.12->4	98.8 / -
Penicillin	≤0.03	2	≤0.03-8	68.9 / 15.4
Ceftriaxone	≤0.25	1	≤0.25-8	97.7 / 0.7
Erythromycin	≤0.25	>8	≤0.25->8	72.0 / 27.1
Clindamycin	≤0.25	>2	≤0.25->2	85.9 / 13.5
Levofloxacin	1	1	≤0.03->4	99.0 / 1.0
Trimethoprim/sulfamethoxazole	≤0.5	4	≤0.5->4	66.8 / 23.0
Coagulase-negative staphylococci (5,675)				
Tigecycline	0.12	0.5	≤0.015-2	98.3 / -
Oxacillin	>2	>2	≤0.06->2	23.2 / 76.8
Levofloxacin	2	>4	≤0.03->4	48.2 / 45.3
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	62.8 / 37.2
Linezolid	1	1	≤0.06->8	>99.9 / -
Vancomycin	1	2	≤0.12-4	>99.9 / 0.0
E. faecalis (4,941)				
Tigecycline	0.12	0.25	≤0.015-1	94.6 / -
Ampicillin	≤2	≤2	≤2->16	99.1 / 0.9
Gentamicin HL	≤500	≤1000	≤500->1000	67.6 / 32.4
Linezolid	1	2	≤0.25->8	99.8 / 0.1
Teicoplanin	≤2	≤2	≤2->16	97.6 / 2.3
Vancomycin	1	2	0.25->16	95.8 / 3.7

Organism (no. tested)/ antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/ resistant
Klebsiella spp. (3,289)				
Tigecycline	0.5	1	0.06->4	98.4 / 0.1
Ceftriaxone	≤0.25	>32	≤0.25->32	82.0 / 12.6
Ceftazidime	≤1	>16	≤1->16	84.4 / 12.8
Imipenem	≤0.5	≤0.5	≤0.5->8	99.2 / 0.5
Levofloxacin	0.06	4	≤0.03->4	88.7 / 9.3
Gentamicin	≤2	>8	≤2->8	83.6 / 14.4
Enterobacter spp. (1,930)				
Tigecycline	0.5	1	0.06->4	96.7 / 0.2
Ceftriaxone	≤0.25	>32	≤0.25->32	76.2 / 14.9
Ceftazidime	≤1	>16	≤1->16	73.8 / 22.0
Imipenem	≤0.5	1	≤0.5->8	99.1 / 0.3
Levofloxacin	0.06	4	≤0.03->4	89.3 / 8.9
Gentamicin	≤2	>8	≤2->8	87.7 / 10.4
ß-haemolytic streptococci (1,903)				
Tigecycline	≤0.12	≤0.12	≤0.12-0.5	99.8 / -
Penicillin	≤0.015	0.06	≤0.015-0.25	>99.9 / -
Erythromycin	≤0.06	>2	≤0.06->2	81.5 / 18.2
Clindamycin	≤0.25	≤0.25	≤0.25->8	93.7 / 5.9
Levofloxacin	0.5	1	≤0.5->4	99.1 / 0.7
E. faecium (1,825)				
Tigecycline	0.06	0.25	≤0.015-1	97.7 / -
Ampicillin	>16	>16	≤0.12->16	11.1 / 88.9
Gentamicin HL	≤500	≤1000	≤500->1000	66.7 / 33.3
Linezolid	1	2	≤0.06->16	99.3 / 0.4
Teicoplanin	≤2	>16	≤2->16	55.7 / 37.0
Vancomycin	2	>16	≤0.12->16	50.7 / 48.2
All Enterobacteriaceae (15,978)				
Tigecycline	0.25	1	≤0.03->4	96.4 / 0.6
Ceftriaxone	≤0.25	16	≤0.25->32	89.8 / 7.0
Ceftazidime	≤1	8	≤1->16	90.9 / 7.1
Imipenem	≤0.5	1	≤0.5->8	99.6 / 0.2
Levofloxacin	0.06	>4	≤0.03->4	87.0 / 10.9
Gentamicin	≤2	8	≤2->8	89.4 / 9.3

a. - = no breakpoint has been established by CLSI or US-FDA.

- Imipenem (MIC_{90}, 1 mg/L; 99.6% susceptible) and tigecycline (MIC_{90}, 1 mg/L; 96.4% susceptible) were the most active compounds tested against Enterobacteriaceae.
- *E. faecalis* showed high rates of susceptibility to many antimicrobials, including linezolid (99.8%), ampicillin (99.1%), teicoplanin (97.6%), vancomycin (95.8%) and tigecycline (94.6%; MIC_{90}, 0.25 mg/L). On the other hand, *E. faecium* showed high rates of resistance to most antimicrobials tested (48.2% resistance to vancomycin), with the most active compounds being tigecycline (MIC_{90}, 0.25 mg/L; 97.7% susceptible) and linezolid (MIC_{90}, 2 mg/L; 99.3% susceptible).

CONCLUSIONS

- Tigecycline was highly active against the most clinically important Gram-positive and Enterobacteriaceae species.
- Tigecycline may play an important role in the empiric treatment of infections in hospitalized patients.
- Continued surveillance through longitudinal programs remains necessary to monitor the in vitro activity of this important novel compound after its introduction into clinical practice.

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