Antimicrobial Activity of Tigecycline Tested Against Contemporary Bacterial Isolates Collected in European Hospitals

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ABSTRACT

Background:

Tigecycline (TGC) was approved in the US and Europe for treatment of complicated skin and skin structure infections (cSSSI) and intra-abdominal sepsis. We evaluated the activity of TGC against recent (2006) bacterial isolates from across Europe.

Methods:

Non-duplicate strains were consecutively collected in 24 medical centers (11 countries) from patients with bacteremia (51%), pneumonia (13%), community-acquired respiratory infections (13%) and cSSSI (6%). Isolates were susceptibility (S) tested by CLSI broth microdilution methods. TGC S breakpoints (US-FDA/EUCAST) were defined as ≤2/≤1 mg/L for Enterobacteriaceae; ≤0.5/≤0.5 mg/L for staphylococci, and ≤0.25/≤0.25 mg/L for streptococci and enterococci.

Results:

7,212 strains were evaluated (Table). TGC was highly active against the top 10 pathogens, except *P. aeruginosa* (PSA). Among the top 5 pathogens (5,245 strains; 72.7% of the total), TGC inhibited all strains at US-FDA S breakpoints. Important R phenotypes observed were: MRSA (28.6%), VRE (4.5%), ciprofloxacin-R *E. coli* (21.0%) and ESBL+ *Klebsiella* spp. (23.5%) and *E. coli* (6.7%); TGC showed excellent activity against these R pathogens.

	Cumulative % inhibited at TGC MIC (mg/L):						% S
Organism (no. tested)	≤0.12	0.25	0.5	1	2	4	(US-FDA/EUCAST)
S. aureus (2,071)	80.3	99.6	100.0				100.0/100.0
E. coli (935)	76.3	97.9	99.8	99.9	100.0		100.0/99.9
Enterococcus spp. (852)	82.0	100.0					100.0/100.0
S. pneumoniae (775)	100.0						100.0/100.0
CoNS (612)	64.9	97.4	100.0				100.0/100.0
Klebsiella spp. (298)	14.8	73.2	92.6	98.3	100.0		100.0/98.3
ß streptococci (295)	99.7	99.7	100.0				99.7/99.7
Enterobacter spp. (191)	3.7	57.6	83.2	93.7	99.0	100.0	99.0/93.7

Conclusions:

TGC was very active and potent against the vast majority of isolates except PSA. R to other antimicrobial classes did not adversely influence TGC activity.

INTRODUCTION

Tigecycline (formerly GAR-936) is the first clinically used agent in a new class of antimicrobials known as the glycylcyclines. The compound is a semisynthetic 9-t-butylglycylamido derivative of minocycline, whose action on bacterial ribosomes shows identical and overlapping binding sites when compared to tetracyclines. The position 9 substitution of tigecycline, however, provides additional steric hindrance features that result in a greater spectrum of activity.

Although contemporary tetracycline derivatives such as doxycycline and minocycline display an increased spectrum of activity and favorable pharmacokinetics compared with tetracycline, cross-resistance within the class persists. The glycylcyclines have the distinct advantage of enhanced stability to the major tetracycline resistance mechanisms, specifically an increased binding affinity to Tet (M)- and Tet (O)-protected tetracycline-resistant ribosomes and secondarily through the inhibition of tetracycline efflux determinants, and have been major advancements.

Tigecycline was approved in the United States (US) and Europe for treatment of complicated skin and skin structure infections (cSSSI) and intra-abdominal sepsis. The present study was conducted to evaluate the activity of tigecycline against recent (2006) bacterial isolates from across Europe.

MATERIALS AND METHODS

Bacterial isolates

The strains were collected in 24 medical centers located in nine European countries, Turkey and Israel during 2006. The isolates were consecutively collected and only one strain per patient was included in the study. The sites of infection included the bloodstream (51%), respiratory tract (mainly in hospitalized patients; 13%), and skin and soft tissue (6%).

Susceptibility testing

MIC values for tigecycline and other comparators were determined using validated broth microdilution panels with cation-adjusted Mueller-Hinton medium (TREK Diagnostics Inc., Cleveland, OH). Testing, incubation and MIC interpretation were performed using the manufacturer's recommendations and/or Clinical and Laboratory Standards Institute guidelines. Tigecycline breakpoints approved by the US Food and Drug Administration (US-FDA) were used as follows (susceptible/resistant): ≤2/≥8 mg/L for Enterobacteriaceae; ≤0.5/- mg/L for staphylococci, and ≤0.25/- mg/L for streptococci and enterococci. No tigecycline resistant breakpoints have been established for gram-positive organisms. Quality control was performed using American Type Culture Collection (ATCC) strains including *Escherichia coli* ATCC 25922 and 35218, *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Streptococcus pneumoniae* ATCC 49619 and *Pseudomonas aeruginosa* ATCC 27853.

RESULTS

- Tigecycline was highly potent against *S. aureus* and coagulase-negative staphylococci (CoNS; MIC_{50}, 0.12 mg/L and MIC_{90}, 0.25 mg/L for both organisms). All staphylococcal strains were inhibited at the tigecycline susceptible breakpoint of 0.5 mg/L (100.0% susceptible). Vancomycin was also active against all strains at the susceptible breakpoint while one CoNS strain was non-susceptible to linezolid (MIC of 8 mg/L; Table 1).
- Tigecycline was the most active compound tested against enterococci (MIC_{50}, 0.12 mg/L and MIC_{90}, 0.25 mg/L), and only tigecycline and linezolid were active against all strains at the susceptible breakpoint (100.0% susceptible; Table 1).
- Tigecycline was the only antimicrobial active against all *S. pneumoniae* strains tested (MIC_{90}, ≤0.03 mg/L; 100.0% susceptible). Ceftriaxone (MIC_{90}, 1 mg/L; 98.7% susceptible) and levofloxacin (MIC_{50} and MIC_{90} at 1 mg/L; 97.5% susceptible) were also very active against this Gram-positive pathogen.
- Tigecycline and imipenem were the most active agents tested against Enterobacteriaceae. All *E. coli* and *K. pneumoniae* strains were susceptible to tigecycline, and only two *Enterobacter* spp. strains exhibited elevated tigecycline MIC values, both in the intermediate category (4 mg/L; Table 2). In contrast, tigecycline showed limited activity against *P. aeruginosa* (MIC_{50}, 4 mg/L; data not shown).
- Imipenem non-susceptible strains were observed among *K. pneumoniae* (three strains; 1.0%) and *Enterobacter* spp. (five strains; 2.6%). Among these strains, the production of the metallo-ß-lactamase VIM-1 was identified on one *E. cloacae* strain from Germany and three *K. pneumoniae* strains from Spain (one) and Italy (two).
- *Acinetobacter* spp. exhibited high rates of resistance to all antimicrobials tested except tigecycline (MIC_{50}, 0.5 mg/L and MIC_{90}, 1 mg/L; 99.1% susceptible) and the polymyxins (colistin and polymyxin B). Only 52.3% of strains were susceptible to imipenem while all strains were inhibited at tigecycline MIC values of ≤4 mg/L.
- Tigecycline was also highly active (100.0% susceptible) against subsets of resistant organisms, including methicillin (oxacillin)-resistant staphylococci, vancomycin-resistant enterococci, ESBL-producing Enterobacteriaceae and imipenem-resistant *Acinetobacter* spp. (Table 3).

Table 1. Antimicrobial activity of tigecycline and comparators tested against Gram-positive isolates collected in European medical centers in 2006.

	MIC (mg/L):			
Organism (no. tested)/ antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/resistant
S. aureus (2,071)				
Tigecycline	0.12	0.25	≤0.03-0.5	100.0/-[a]
Oxacillin	0.5	>2	≤0.25->2	71.4/28.6
Levofloxacin	≤0.5	>4	≤0.5->4	68.7/30.5
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	98.7/1.3
Linezolid	2	2	0.12-2	100.0/0.0
Vancomycin	1	1	≤0.12-2	100.0/0.0
Coagulase-negative staphylococci (612)				
Tigecycline	0.12	0.25	≤0.03-0.5	100.0/-
Oxacillin	>2	>2	≤0.25->2	26.3/73.7
Levofloxacin	2	>4	≤0.5-4	45.6/44.9
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	61.8/38.2
Linezolid	1	1	≤0.06-8	99.8/-
Vancomycin	1	2	≤0.12-2	100.0/0.0
Enterococcus spp. (852)				
Tigecycline	0.12	0.25	≤0.03-0.25	100.0/-
Ampicillin	≤1	>16	≤1->16	73.6/26.4
Gentamicin (HL)[b]	≤500	>1000	≤500->1000	68.1/31.9
Linezolid	1	2	0.25-2	100.0/0.0
Teicoplanin	≤2	≤2	≤2->16	96.8/2.7
Vancomycin	1	2	0.25->16	95.5/4.1
S. pneumoniae (775)				
Tigecycline	≤0.03	≤0.03	≤0.03-0.12	100.0/-
Penicillin	≤0.03	2	≤0.03->4	67.9/17.0
Ceftriaxone	≤0.25	1	≤0.25-8	98.7/0.3
Erythromycin	≤0.25	>2	≤0.25->2	68.3/31.2
Clindamycin	≤0.25	>2	≤0.25->2	77.8/21.8
Levofloxacin	1	1	≤0.5->4	97.5/2.3
Trimethoprim/sulfamethoxazole	≤0.5	4	≤0.5->4	63.6/25.3
ß-haemolytic streptococci (295)				
Tigecycline	≤0.03	≤0.03	≤0.03-0.5	99.7/-
Penicillin	≤0.015	0.06	≤0.015-0.25	100.0/-
Erythromycin	≤0.25	>2	≤0.25->2	83.1/16.6
Clindamycin	≤0.25	≤0.25	≤0.25->2	91.2/8.8
Levofloxacin	≤0.5	1	≤0.5->4	100.0/0.0

a. - = no breakpoint has been established by the CLSI or US-FDA.
b. HL = high-level resistance.

Table 2. Antimicrobial activity of tigecycline and comparators tested against Enterobacteriaceae and *Acinetobacter* spp. collected in European medical centers in 2006.

	MIC (mg/L):			
Organism (no. tested)/ antimicrobial agent	50%	90%	Range	% susceptible/resistant
E. coli (935)				
Tigecycline	≤0.03	0.25	≤0.03-2	100.0/0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	94.4/5.2 (6.3)[a]
Ceftazidime	≤1	≤1	≤1->16	95.5/2.5 (6.7)[a]
Imipenem	0.25	0.25	≤0.12-1	100.0/0.0
Ciprofloxacin	≤0.03	>4	≤0.03->4	79.0/21.0
Gentamicin	≤2	≤2	≤2->8	94.2/5.2
Klebsiella spp. (298)				
Tigecycline	0.25	0.5	0.06->2	100.0/0.0
Ceftriaxone	≤0.25	>32	≤0.25->32	80.2/13.1 (23.5)[a]
Ceftazidime	≤1	>16	≤1->16	84.6/12.8 (21.8)[a]
Imipenem	0.25	0.5	≤0.12->8	99.0/0.3
Ciprofloxacin	≤0.03	4	≤0.03->4	84.2/13.4
Gentamicin	≤2	>8	≤2->8	88.9/10.4
Enterobacter spp. (191)				
Tigecycline	0.25	1	0.12-4	99.0/0.0
Ceftriaxone	≤0.25	>32	≤0.25->32	67.0/22.0
Ceftazidime	≤1	>16	≤1->16	64.4/21.4
Imipenem	0.5	2	≤0.12->4	97.4/1.6
Ciprofloxacin	≤0.03	4	≤0.03->4	78.0/21.5
Gentamicin	≤2	>8	≤2->8	85.3/13.1
Acinetobacter spp. (107)				
Tigecycline	0.5	1	≤0.03-4	99.1/0.0[b]
Ceftriaxone	>32	>32	≤0.25->32	15.0/72.0
Ceftazidime	>16	>16	≤1->16	29.0/66.4
Imipenem	2	>8	≤0.12->8	52.3/47.7
Ciprofloxacin	>4	>4	≤0.03->4	21.5/78.5
Amikacin	>32	>32	≤4->32	31.8/62.6
Colistin	≤0.5	≤0.5	≤0.5->4	99.1/0.9

a. Percentage of isolates with ESBL phenotypes.
b. Rates were calculated by applying breakpoints approved by the US-FDA for Enterobacteriaceae.

Table 3. Antimicrobial activity of tigecycline against resistant organisms collected in European medical centers in 2006.

	MIC (mg/L):			
Organism (no. tested)	50%	90%	Range	% susceptible/resistant
Oxacillin-resistant *S. aureus* (592)	0.12	0.25	≤0.03-0.5	100.0/-[a]
Vancomycin-resistant Enterococcus spp.(38)	0.06	0.12	≤0.03-0.12	100.0/-
ESBL-producing *E. coli* (59)[b]	0.12	0.5	0.06-0.5	100.0/0.0
ESBL-producing *Klebsiella* spp. (70)[b]	0.5	1	0.06-1	100.0/0.0
Imipenem-resistant *Acinetobacter* spp. (51)	0.5	1	0.12-2	100.0/0.0[c]

a. - = No breakpoint has been established.
b. Isolates with ESBL phenotype.
c. Rates were calculated by applying breakpoints approved by the US-FDA for Enterobacteriaceae.

CONCLUSIONS

- Tigecycline was highly active against the most frequently isolated pathogens causing serious bacterial infections in European medical centers, except for *P. aeruginosa*.
- Given its broad spectrum, tigecycline can play an important role in the treatment of infections among hospitalized patients in Europe.
- Continued surveillance through longitudinal programs remains necessary to monitor the in vitro activity of this important novel compound following its introduction into clinical practice.

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