

Tigecycline In Vitro Activity Against Often Difficult to Treat European Pathogens

P 1684

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REVISED ABSTRACT

Background: Enhanced activity agents such as tigecycline (TIG) may offer antibacterial coverage of common pathogens including multi-drug resistant gram-negatives/positives. The T.E.S.T. program monitored the in vitro activity of TIG and comparators against current European pathogens. **Methods:** For this study, 77 hospital sites in 21 European countries collected over 14,113 significant isolates from community/hospital infection sites. MICs were determined to TIG and comparators using broth microdilution panels (EUCAST specified and interpreted). **Results:** Selected European pathogens tested against tigecycline are shown below:

Organism (n)	Tigecycline		Cumul. % inhibited at MIC				%S*
	MIC ₅₀	MIC ₉₀	≤0.5	1	2	4	
<i>A. baumannii</i> (832)	0.25	1	60	96	99	100	na
<i>E. faecalis</i> (806)	0.12	0.25	100				100
EC, KO, KP ^a (3751)	0.25	1	90	96	98	99	95.5
ESBLb (314)	0.5	2	76	86	93	97	86.2
<i>Enterobacter</i> spp. (1794)	0.5	2	76	89	95	99	89.1
<i>P. aeruginosa</i> (1491)	8	>16	1	3	7	24	na
<i>S. aureus</i> (MR) (407)	0.12	0.25	100				100

* EC - *E. coli*, KO - *K. oxytoca*, KP - *K. pneumoniae*
^a ESBP producing EC, KO and KP
^b Interpretive criteria as defined by EUCAST, where available; CLSI breakpoints, where available, were used where no EUCAST breakpoints exist; na = not available.

Conclusion: Potentially difficult-to-treat European isolates of both gram-positive/negative community/hospital pathogens demonstrated generally excellent TIG MIC₉₀s and % susceptible (excluding *Pseudomonas*). For most organisms/phenotypes, TIG MIC₉₀s were ≤1 mcg/ml and % susceptible >90%. TIG activity was reduced against European ESBL-producing *Enterobacteriaceae* isolates (MIC₉₀ = 2; %S = 86.2). TIG promises expanded broad spectrum activity against multiply resistant European pathogens.

INTRODUCTION

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycylicyclines. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit. Although it is perceived to be bacteriostatic, its anti-bacterial activity is significant and has shown some bactericidal activity against key targeted pathogens [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 [2-4].

Tigecycline resistance is very infrequent and is also difficult to induce in the laboratory [5, 6] with a selection frequency observed at less than 10⁻⁹ [3, 5, 7]. With the exception of *P. aeruginosa*, tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline [2-4, 7-11]. Tigecycline has shown to be highly effective against multi-resistant *Acinetobacter* spp., particularly *A. baumannii* that are commonly associated with serious nosocomial infections. Similar activity has been observed against *Enterobacteriaceae*, even extended-spectrum beta-lactamase (ESBL) and AmpC producing strains [10]. Tigecycline has demonstrated MIC₉₀ values of ≤0.5 mcg/ml against methicillin-resistant *Staphylococcus aureus* (MRSA) and other gram-positive organisms [2, 4-6]. Tigecycline has shown potent activity in animal models infected with selected strains of multi-drug resistant *Enterococcus faecium* and *Enterococcus faecalis* [4,5] with diverse genotypes of vanA, vanB and vanC [6].

The T.E.S.T. program determined the in vitro activity of tigecycline compared to most commonly prescribed broad spectrum antimicrobials against gram-negative and gram-positive species collected from 320 hospitals globally from 2004 to 2006. This study was designed to evaluate the in vitro activity of tigecycline against potentially difficult-to-treat organisms collected in Europe.

MATERIALS & METHODS

For the T.E.S.T. program all isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, fluids, and other defined sources. Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution. Only one isolate per patient was accepted. For this study 14,113 clinical isolates were collected from 2004 to 2006 from 77 sites in 21 European countries (Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Norway, Poland, Portugal, Slovenia, Spain, Sweden, Switzerland, The Netherlands, and the United Kingdom). Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [12]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturer, MicroScan (Dade Behring Inc., Sacramento, CA, USA). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in mcg/ml): amikacin (0.5-64); amoxicillin/clavulanic acid (0.12/0.06-32/16); ampicillin (0.5-32, gram-negative panel, and 0.06-16, gram-positive panel); cefepime (0.5-32); ceftazidime (0.06-64); imipenem (0.06-16); linezolid (0.5-8); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16); penicillin (0.06-8); piperacillin/tazobactam (0.06/4-128/4) and vancomycin (0.12-32).

MIC interpretive criteria followed published breakpoints established by EUCAST where applicable [13]; if no EUCAST guidelines were available for a given antimicrobial, CLSI breakpoints [14] were used. *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftazidime were >1 mcg/ml using broth microdilution panels. ESBL activity was confirmed using the CLSI (2006) phenotypic confirmatory disk test (Oxoid, Ogdensburg, NY, USA) on Mueller-Hinton agar (Remel Inc., Lenexa, KS, USA) according to CLSI (2006) guidelines. ESBL presence was confirmed by testing the following antibiotic disks: cefotaxime (30-mcg), cefotaxime/clavulanic acid (30/10-mcg), ceftazidime (30-mcg), and ceftazidime/clavulanic acid (30/10-mcg). Antimicrobial disks were manufactured by Oxoid, Inc. (Ogdensburg, NY, USA). Mueller-Hinton agar used in testing was manufactured by Remel, Inc. (Lenexa, KS, USA). An organism was interpreted as containing an ESBL if there was an increase of >5 mm in the inhibition zone of the combination disk when compared to that of the cephalosporin alone.

Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains where applicable: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922; *Escherichia coli* ATCC 35218; *Klebsiella pneumoniae* ATCC 700603 (as positive ESBL control); *Haemophilus influenzae* ATCC 49247; *Haemophilus influenzae* ATCC 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; and *Pseudomonas aeruginosa* ATCC 27853. The collection and transportation of organisms, confirmation of identification, and construction and management of a centralized database were conducted and coordinated by Laboratories International for Microbiology Studies (LIMS), a subsidiary of International Health Management Associates, Inc. (IHMA, Schaumburg, IL, USA).

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RESULTS

Table 1. In vitro activity of tigecycline and comparative agents against selected gram-negative organisms.

Organism (n)		MIC (mcg/ml)		Cumulative % inhibited at MIC				%S*
		MIC ₅₀	MIC ₉₀	≤0.5	1	2	4	
<i>E. coli</i> ^a (1,925)	Tigecycline	0.12	0.25	99	99.7	100		99.7
	Amikacin	2	4	1.5	19.6	71.7	91.3	97.3
	AmoxClav	8	32	0.5	3.2	26.4	48	71.4
	Ampicillin	>32	>32	0.7	6.3	30.5	40.3	41.4
	Cefepime	≤0.5	4	85.6	88	89.5	91.6	88
	Ceftriaxone	≤0.06	16	86.9	87.6	88.4	89	87.6
	Imipenem	0.25	0.5	99.1	99.5	99.8	99.9	99.8
	Levofloxacin	0.03	>8	75.5	76	77.1	80.9	76
	Minocycline	1	8	36.8	60.5	73.8	83.1	83.1
PipTazo	1	8	27.8	68.6	83.4	87.7	93.5	
<i>Klebsiella</i> spp. ^b (1,857)	Tigecycline	0.5	1	79.6	90.8	95.4	99.1	90.8
	Amikacin	2	4	3.3	48.8	84.7	91.3	95.2
	AmoxClav	4	32	0.6	9.3	49.4	76.5	75.9
	Ampicillin	>32	>32	0	0	0	0	0
	Cefepime	≤0.5	4	80.1	84	87.3	90.1	84
	Ceftriaxone	≤0.06	32	79.3	79.9	81.4	83.7	79.9
	Imipenem	0.25	0.5	94.8	98.3	99.3	99.8	99.3
	Levofloxacin	0.06	4	83.5	87	89.4	92.9	87
	Minocycline	2	16	9	46.7	71.7	82.2	82.2
	PipTazo	2	128	17.9	48.4	70.6	78.7	85.8
	ESBL-producers ^c (314)	Tigecycline	0.5	2	75.8	86	93	97
Amikacin		4	32	1	14.6	36	53.5	74.8
AmoxClav		16	>32	0.3	0.3	1	4.5	28.7
Ampicillin		>32	>32	0	0	0.3	0.6	0.6
Cefepime		16	>32	4.5	11.5	21.7	35	11.5
Ceftriaxone		64	>64	2.2	2.9	4.8	10.2	2.9
Imipenem		0.25	0.5	95.2	97.4	98.7	99.7	98.7
Levofloxacin		4	>8	34.4	38.9	41.7	52.5	38.9
Minocycline		4	>16	6.7	22.6	43.9	62.1	62.1
PipTazo		8	>128	2.9	14	33.8	43	66.9
<i>Enterobacter</i> spp. (1,794)		Tigecycline	0.5	2	76.1	89.1	95.1	99.3
	Amikacin	2	4	1.4	42	83.7	91.4	96
	AmoxClav	>32	>32	0	0.2	0.4	0.6	1.8
	Ampicillin	>32	>32	0	0	0	0	0
	Cefepime	≤0.5	8	65.9	74	81.2	88.1	74
	Ceftriaxone	0.5	64	54.8	58.4	61.4	65	58.4
	Imipenem	0.5	1	75	94.6	98.5	99.6	98.5
	Levofloxacin	0.06	8	79.4	81.9	84.6	87.4	81.9
	Minocycline	2	8	2.6	15.3	57.9	82.9	82.9
PipTazo	2	128	7.6	30.9	51.7	58.7	72.1	
<i>A. baumannii</i> (832)	Tigecycline	0.25	1	80.2	95.9	98.8	100	na
	Amikacin	4	>64	2	14.2	45.1	64.4	70.4
	Cefepime	8	32	3.2	9.9	25.8	40.6	56.6
	Ceftriaxone	16	>64	1.2	1.9	4.4	13.2	35.5
	Imipenem	0.5	16	56.3	74.2	81.8	85.9	82.4
	Levofloxacin	1	>8	47.8	51.4	56.5	68.5	55.9
	Minocycline	≤0.5	4	67.7	82	87.4	92.5	92.5
	PipTazo	8	>128	33.8	38.7	42.7	46.3	62.4
	<i>P. aeruginosa</i> (1,491)	Tigecycline	8	>16	0.5	2.8	7	24.3
Amikacin		4	16	1.1	6.7	39.9	76.1	90.3
Cefepime		4	32	1.5	11.1	37.7	57.8	76.5
Ceftriaxone		64	>64	0.5	1.3	2.7	7.6	17.9
Imipenem		1	8	6.7	25.5	64.2	76.1	83.1
Levofloxacin		1	>8	44.9	57.9	67.5	74.1	56.1
Minocycline		>16	>16	0.3	0.8	1.9	6.2	6.2
PipTazo		4	128	3.4	6.6	29.6	62.4	89.8

* Includes 142 ESBL-producing *E. coli* strains.
^b Includes 1,315 *K. pneumoniae*; 511 *K. oxytoca*; 2 *K. ornithinolytica*; 2 *K. ozonae*; 4 *K. planticola*; 18 *K. pneumoxytoca*; 5 *Klebsiella*, non-specified of which 155 *K. pneumoniae* and 17 *K. oxytoca* were ESBL producing strains;
^c ESBL producing *E. coli*, *K. pneumoniae* and *K. oxytoca* only.
^d Interpretive criteria as defined by EUCAST, where available and CLSI breakpoints, where available, if no EUCAST breakpoints exist; na = not available.

Table 2. In vitro activity of tigecycline and comparative agents against selected gram-positive organisms.

Organism (n)		MIC (mcg/ml)		Cumulative % inhibited at MIC				%S*
		MIC ₅₀	MIC ₉₀	≤0.5	1	2	4	
<i>S. aureus</i> (MS) (1,257)	Tigecycline	0.12	12	100				100
	AmoxClav	0.5	2	50.9	89.4	99.2	100	100
	Ampicillin	4	>16	27.3	36	46.5	58.7	22.3
	Ceftriaxone	2	4	0.7	7.6	65.8	98	0.2
	Imipenem	≤0.12	0.25	99.4	99.8	99.9	100	99.4
	Levofloxacin	0.12	0.25	97	98.2	99.3	99.6	98.2
	Linezolid	2	4	1.9	24.8	88.7	100	100
	Minocycline	≤0.25	≤0.25	98.2	99.1	99.1	99.5	99.5
	Penicillin	8	>8	25.9	32.4	39.6	49.4	0
	PipTazo	0.5	1	56.3	94.8	98.7	99.8	100
	Vancomycin	0.5	1	54.6	96.7	100		100
<i>S. aureus</i> (MR) (407)	Tigecycline	0.12	0.25	100				100
	AmoxClav	>8	>8	3.2	8.1	16.5	31.4	0 ^a
	Ampicillin	>16	>16	1.2	3.7	8.4	10.3	0 ^a
	Ceftriaxone	>64	>64	0	0.5	3.9	8.4	0 ^a
	Imipenem	2	>16	40.7	47.7	53.9	58.2	0 ^a
	Levofloxacin	8	32	12.3	13.3	17.9	42.8	13.3
	Linezolid	2	2	2.7	28.7	92.4	100	100
	Minocycline	≤0.25	4	79.4	81.1	85.5	97.8	97.8
	Penicillin	>8	>8	2.2	3.4	6.6	9.3	0
	PipTazo	>16	>16	4.2	8.4	15.2	28	0
	Vancomycin	1	1	37.6	92.1	100		100
<i>E. faecalis</i> ^b (806)	Tigecycline	0.12	0.25	100				100
	Ampicillin	1	2	24.3	86	98.6	99.8	100
	Levofloxacin	1	32	21.8				