In vitro antimicrobial activity of tigecycline against Gram negative and Gram positive pathogens collected in Northen Italy (T.E.S.T. program 2010)

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SUMMARY

Background. In this study (part of the global T.E.S.T. program) was evaluated the *in vitro* activity of tigecycline, member of a new class of antimicrobial agents, the glycylcyclines, against clinical isolates collected in Italy.

Methods. A total of 194 clinical isolates were collected and identified in our Institution during 2010. Minimum inhibitory concentrations (MICs) of the antimicrobial agents were determined by the CLSI (2010) recommended broth microdilution method.

Results. Globally 129 Gram negative and 65 Gram positive pathogens were evaluated. Tigecycline demonstrated excellent inhibitory activity against *Escherichia coli, Haemophylus influenzae, Enterococcus* spp., *Staphylococcus aureus* MetS, *Streptococcus pneumoniae* and *Streptococcus agalactiae* with $MIC_{90} \leq 1$ mg/l.

Conclusion. Tigecycline exhibited potent *in vitro* antibacterial activity (comparable to or greater than most commonly employed antimicrobials) against both Gram positive and negative clinical pathogens. These data suggest that tigecycline, with an expanded broad-spectrum antimicrobial activity, may be an effective empiric therapeutic option for the treatment of serious infections caused by clinically relevant pathogens.

INTRODUCTION

Tigecycline is a first-in-class of expanded broad-spectrum glycylcycline. It inhibits bacterial protein synthesis by binding to the 30s ribosomial subunit, but with five times highter affinity than tetracyclines (2). This new drugs was approved for use in Europe in 2006 for complicated skin and soft-tissue and intra-abdominal infections (http://www.emea.europa.eu/humandocs/Humans/EPAR/tygacil/tygacil.htm).

In vitro studies demonstrate that it has good activity against many commonly encountered respiratory bacteria, including multiple resistant Gram positive, Gram negative, anaerobic, as well as multidrug-resistant (MDR) pathogens such methicillin-resistant *S. aureus* (MRSA) and *S. epidermidis* (MRSE), vancomycin-resistant *Enterococcus* spp. (VRE), penicillin-resistant *S. pneumoniae* (PRSP) and β-lactamase producing *H. influenzae* (3).

Tygeciclyne inhibits bacterial protein biosynthesis blocking the attachment of amino-acyl tRNA to the A site of the ribosome and preventing the elongation of peptide chains (6).

The drug mantaines its activity even in presence of efflux pumps (encoded by *tet*A-*tet*D and *tet*K genes) and ribosomal protection (*tet*M) mechanisms that otherwise confer tetracycline resistance. Tigecycline appears to overcame these mechanisms of resistance because of steric hindrance due to the addition of a large substituent on the D ring at the 9th position of the tetracycline molecule (7, 13).

This study is part of the larger global Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program and was undertaken to document the *in vitro* activity of tigecycline against clinical isolates collected in Northen Italy from in-patient and out-patient populations.

MATERIALS AND METHODS

A total of 194 clinical isolates were collected and identified to the species level in our Institution during 2010. Isolates were collected from both inpatients and outpatients with a documented infections in which the isolate collected was identified as the probable causative organism according to institutional criteria. Only one isolate per patient was accepted into the study.

Minimum inhibitory concentrations (MICs) of the antimicrobial agents were determined by the Clinical and Laboratory Standards Institute(CLSI) (11) recommended broth microdilution testing method. Overnight cultures of bacteria were diluted to give a final concentration of approximately $5x10^5$ cells/ml. Samples were then added to equivalent volumes of the various concentration of antibiotics distributed on a microplate and prepared from serial twofold dilutions. After 18-24

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hours of incubation at 37°C, the concentrations of drugs that prevented visible growth were recorded as the MICs. 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 panel of agents tested against Gram positive organisms was: tigecycline (0.008-16), amoxicillin/clavulanic acid (0.03-8), ampicillin (0.06-16), ceftriaxone (0.03-64), meropenem (0.12-16), linezolid (0.5-8), levofloxacin (0.06-32), minocycline (0.25-8), penicillin (0.06-8), piperacillin/tazobactam (0.25-16) and vancomycin (0.12-32). The panel of antimicrobial agents tested against Gram negative organisms was: tigecycline (0.008-16), amikacin (0.5-64), amoxicillin/clavulanic acid (0.12-32), ampicillin (0.5-32), cefepime (0.5-32), ceftazidime (8-32), ceftriaxone (0.06-64), levofloxacin (0.06-32) meropenem (0.12-16), minocycline (0.25-8) piperacillin/tazobactam (0.06-128).

MIC interpretive criteria established by CLSI (11) and recent US Food and Drug Administration guidelines for tigecycline (Tygacil, Product Insert. Wyeth Pharmaceuticals, Inc., Philadelphia, PA, USA, 2005) were followed. As no interpretative criterion for tigecycline with *Acinetobacter baumannii* has been established, Clinical and laboratory Standards Institute interpretative criteria for *Enterobacteriaceae* were used for *A. baumannii*, as had been reported in previous literature (1, 17). Quality controls (QC) were performed using the following strains: *Escherichia coli* ATCC 25922; *E. coli* ATCC 35218; *H. influenzae* ATCC 49766; *H. influenzae* ATCC 49247; *S. aureus* ATCC 29213; *P. aeruginosa* ATCC 27853; *Enterococcus faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2010).

RESULTS

The largest number of isolates was collected from in-patients population (medicine, surgery, ICU, nursing home\rehabilitation, renal, infectious diseases, paediatrics and obstetrics), only 35% of strains derived from community acquired infections (Table 1).

Globally 129 Gram negative and 65 Gram positive pathogens were evaluated. The first group of bacteria included 25 *E. coli*, 25 *Klebsiella* spp., 25 *Enterobacter* spp., 10 *Serratia marcescens*, 20 *P. aeruginosa*, 15 *A. baumannii*, (80% multi-drug resistant to cephalosporins aminoglycosides and quinolones simultaneously), 9 *H. influenzae* (11.1% β-lactamase-producers). Gram positive strains included 15 *Enterococcus* spp. (6.6% vancomycin-resistant), 25 *S. aureus* (68% methicillin-resistant), 15 *S. pneumoniae* (33.3% penicillin-non-susceptible), 10 *S. agalactiae*.

Bacterial isolates were obtained from blood (65, 33.5%), urine (17, 8.8%), respiratory tract (53, 27.3%), skin (20, 10.3%), wound (13, 6.7%), vagina swabs (13, 6.7%) and other site (8, 4.2%).

Table 1. *Distribution of the strains collected in this study according to different clinical settings.*

Microorganism	Tot	Community acquired	Hospital acquired									
			Med	Sur	ICU	Nursing home\ rehab	Ren	ID	Ped	Obs	Unk	Other
Gram negative												
E. coli	25	6	6	3	4	2		1				3
Klebsiella spp. (1)	25	17	1	6		1						
Enterobacter spp. (2)	25	4	5	6	4	1		1				4
S. marcescens	10	1			5						1	3
P. aeruginosa	20	10	1		5	1					1	2
A. baumannii	15	5	3		3	1						3
H. influenzae	9	2						2	3		1	1
Gram positive												
S. agalactiae	10	6				1				3		
Enterococcus spp. (3)	15	4		1	4	1	1		3			1
S. aureus	25	9	4	1	2	3	1				1	4
S. pneumoniae	15	4			2				8		1	

Med: medicine, Sur: surgery, ICU: Intensive Care Unit, NH\REH: Nursing home\ rehabilitation, Ren: renal, ID: Infectious Desease, Ped: pediatrics, Obs: obstetrics, Unk: non-specified unit.
(1) K. pneumoniae 16, *K. oxytoca* 7; *(2) E. cloacae* 21, *E. aerogenes* 4; *(3) E. faecalis* 10, *E. faecium* 5.

(Table 2).

Tigecycline demonstrate an excellent inhibitory activity against *Enterobacteriaceae* (Table 3), indeed tigecycline's MIC_{90} was minor or equal to 4 mg\l. Against *E. coli* and *Klebsiella* spp. only meropenem behaves better than tigecycline (MIC_{90} 0.12mg\l and 0.25 mg\l respectively).

This new agent, as the other tetracyclines, showed limited *in vitro* activity against *P. aeruginosa* with MIC_{90} values equal to 16mg\l (Table 4).

Tigecycline demonstrated a good inhibitory activity against *A. baumannii* (MIC_{50} 1mg\l and MIC_{90} 2mg\l) even on multi-drug resistant strain, with the exception of a single isolate which showed a MIC value corresponding to 8mg\l. Such result is consistent with recent reports of emergence of tigecycline-resistant *A. baumannii* after tigecycline therapy (1, 14) (Table 4). *In vitro* tigecycline's activity on *A. baumannii* was superior to beta-lactams, beta-lactams/beta-lactamase inhibitor combinations, cephalosporins, aminoglycosides and levofloxacin.

Tigecycline demonstrate excellent inhibitory activity against *H. influenzae* (MIC_{50} and MIC_{90} 0.25mg\l), included β-lactamase-producers strains (Table 4).

Against Gram positive isolates (Table 5), tigecycline shown an excellent activity against *Enterococcus* spp. The drug presented MIC_{90} of 0.25 mg\l, regardless of susceptibility to vancomycin. This value was the lowest of all comparative agents, in particular was several folds lower than linezolid, minocycline and levofloxacin.

The drug has shown a potent inhibitory activity against *S. aureus* regardless of methicillin-resistant phenotype. Tigecycline, with MIC_{50} and MIC_{90} values of 0.25 and 0.5 mg/l, respectively, demonstrated *in vitro* activity comparable to vancomycin and greater than linezolid and levofloxacin against MRSA. In MSSA the MIC_{50} and MIC_{90} value was 0.25 mg/l and 0.5 mg/l respectively.

Tigecycline demonstrated potent inhibitory activity against *S. agalactiae* and *S. pneumoniae* (Table 6), even in penicillin-resistant strains, with MIC_{90} values $\leq$1mg\l.

Table 2. *Distribution of the strains collecte din this study according to the type of clinical samples.*

Microorganisms	Blood	Urine	Respiratory tract	Skin	Wound	Vaginal swabs	Other
Gram negative							
E. coli	11	3	7			3	1
Klebsiella spp. (1)	9	3	9			4	
Enterobacter spp. (2)	12	2		5	6		
S. marcescens	7		3				
P. aeruginosa	4	1	8	4	2		1
A. baumannii		4	4	3	1		3
H. influenzae			9				
Gram positive							
S. agalactiae		1		2		7	
Enterococcus spp. (3)	12	2		1			
S. aureus	7	1	4	5	4	1	3
S. pneumoniae	3		12				
Total	65	17	56	20	13	15	8

DISCUSSION

Resistance to currently available antibiotics and incidence of infection due to multidrug-resistant bacteria has dramatically increased worldwide during the last twenty years. In presence of a serious infection, appropriate empirical antibiotic therapy can be life-saving and the choice of an antimicrobial to which the pathogens are susceptible may be critical. For these reasons, the development of new antimicrobial agents with expanded antibacterial spectrum (increased activity against Gram negative as well as Gram positive microrganisms) is more urgent than ever (5, 18).

Tigecycline's *in vitro* activity was comparable to or greater than most commonly prescribed antimicrobial against important clinical pathogens.

Tigecycline, for example, demonstrated on methicillin-resistant *S. aureus* (MRSA) *in vitro* activity comparable to vancomycin, the antimicrobial agents currently used for the treatment of serious staphylococcal infections and exhibits greater activity to linezolid against vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* (VRE). This promising compound may be usefull even in the treatment of serious infections caused by resistant Gram negative strains with limited therapeutic options. Tigecycline has shown to be highly effective agains *E. coli* and *Klebsiella* spp. *A. baumannii* is a problematic pathogen, particularly in ICUs. The results from TEST reveal that no antimicrobial agents tested was active against *A. baumanni*. Tigecycline was the only agent that shown a good inhibitory activity against *A. baumannii* that are commonly associated with serious nosocomial infections. Resistance of *Acinetobacter* to cephalosporins, aminoglycosides and quinolones is widespread with an

increasing of multi-drug resistance (9, 8). Tigecycline is a potent antimicrobial agent even against the infections due to this important pathogen.

The drug demonstrated a limited activity, similar to other tetracyclines, only against *P. aeruginosa*.

The *in vitro* activity of tigecycline observed in this study suggests that this drug is a suitable antimicrobial agent for empiric treatment of serious infections sustained by some of the commonly encountered pathogens.

Tigecycline is available as parenteral agent, has linear pharmacokinetics, long terminal half-life and is extensively distributed in tissues (15).

Some interesting applications for this drug may be in surgical wound infections (particularly following abdominal surgery), and as alternative therapeutic agent in patient with serious allergies to β-lactam antibiotics (10).

Results from Phase III clinical studies in the treatment of complicated skin and skin structure infection (cSSSI) and complicated intra-abdominal infection (cIAI) have demonstrated the potential of tigecycline used as monotherapy for the treatment of this infections: the drug showed equivalence to imipenem in cIAI and to vancomycin plus aztreonam in cSSSI (12, 16, 4, 19).

The *in vitro* and *in vivo* studies points out that, tigecycline, with an expanded broad-spectrum antimicrobic activity against Gram positive and negative bacteria, offers a new alternative for the treatment of infections caused by clinically relevant pathogens in which the emergence of resistance to previously active antibiotics has created to the physicians limitations in therapeutic options.

Table 3. In vitro *activity of tigecycline and comparative antimicrobial agents against* Enterobacteriaceae *clinical pathogens*.

Microrganisms	Drugs	MIC 50	MIC 90	MIC Range
		μg/ L		
E. coli	Tigecycline	0.5	1	0.06 - 8
	Amikacin	8	16	1 - ≥64
	Amoxicillin Clavulanic Acid	16	32	4 - ≥32
	Ampicillin	≥32	≥32	1 - ≥32
	Cefepime	≤0.,5	≥32	4 - ≥32
	Ceftazidime	≤8	≥32	≤8 - ≥32
	Ceftriaxone	0.25	≥64	≤0.06 - ≥64
	Levofloxacin	8	≥8	0.015 - ≥8
	Meropenem	≤0.06	0.12	≤0.06 – 0.5
	Minocycline	8	≥16	1 ≥16
	Piperacillin Tazobactam	≥128	≥128	0.06 - ≥128
Klebsiella spp.	Tigecycline	0.5	2	0.25 – 2
	Amikacin	2	32	1 – 32
	Amoxicillin Clavulanic Acid	2	32	1 – ≥32
	Ampicillin	≥32	≥32	≥32
	Cefepime	≤0.05	≥32	≤0.05- ≥32
	Ceftazidime	≤8	≥32	≤8- ≥32
	Ceftriaxone	≤0.06	64	≤0.06 - ≥64
	Levofloxacin	0.12	≥8	0.03 - ≥8
	Meropenem	≤0.06	0.25	≤0.06 -1
	Minocycline	4	16	1 - ≥16
	Piperacillin Tazobactam	2	64	1 - ≥128
Enterobacter spp.	Tigecycline	1	4	0.5 - ≥16
	Amikacin	2	64	1 - ≥64
	Amoxicillin Clavulanic Acid	≥32	≥32	32 - ≥32
	Ampicillin	≥32	≥32	16 - ≥32
	Cefepime	≤0.5	≥32	≤0.5 - ≥32
	Ceftazidime	≤8	≥32	≤8 - ≥32
	Ceftriaxone	2	≥64	0.12 - ≥32
	Levofloxacin	0.12	8	0.03 - ≥8
	Meropenem	0.25	8	≤0.06 – 8
	Minocycline	8	≥16	2 - ≥16
	Piperacillin Tazobactam	4	≥128	1 - ≥128
S. marcescens	Tigecycline	1	2	0.5 - 4
	Amikacin	2	8	1 – 16
	Amoxicillin Clavulanic Acid	≥32	≥32	8 - ≥32
	Ampicillin	32	≥32	≤0,5 - ≥32
	Cefepime	≤0.5	≤0,5	≤0.5 - 1
	Ceftazidime	≤8	≤8	≤8
	Ceftriaxone	0.5	16	≤0.06 -16
	Levofloxacin	1	4	0.25 - 8
	Meropenem	4	≥16	0.06 - ≥16
	Minocycline	8	8	4 - 16
	Piperacillin Tazobactam	1	8	0.25- 32

Table 4. In vitro *activity of tigecycline and comparative antimicrobial agents against other Gram negative clinical pathogens.*

Microrganisms	Drugs	MIC 50	MIC 90	MIC Range
		μg/ L		
A. baumannii	Tigecycline	1	2	0.25 – 8
	Amikacin	≥64	≥64	≤0.5 - ≥64
	Amoxicillin Clavulanic Acid	≥32	≥32	≤8 - ≥32
	Ampicillin	≥32	≥32	8 - ≥32
	Cefepime	≥32	≥32	≤0.06 - ≥32
	Ceftazidime	≥32	≥32	≤8 - ≥32
	Ceftriaxone	≥64	≥64	4 - ≥64
	Levofloxacin	≥8	≥8	0.06 - ≥8
	Meropenem	≥16	≥16	0.12 - ≥16
	Minocycline	16	≥16	≤0.05 - ≥16
	Piperacillin Tazobactam	≥128	≥128	≤0.06 - ≥128
P. aeruginosa	Tigecycline	8	16	8 - ≥16
	Amikacin	8	≥64	2 - ≥64
	Amoxicillin Clavulanic Acid	≥32	≥32	≥32
	Ampicillin	≥32	≥32	≥32
	Cefepime	8	≥32	2 - ≥32
	Ceftazidime	16	≥32	≤8 - ≥32
	Ceftriaxone	≥64	≥64	64 - ≥64
	Levofloxacin	4	≥8	0.25 - ≥8
	Meropenem	4	16	≤0.06 - ≥16
	Minocycline	≥16	≥16	4 - ≥16
	Piperacillin Tazobactam	16	≥128	2 - ≥128
H. influenzae	Tigecycline	0.25	0.25	0.12 – 0.25
	Amikacin	2	4	2 – 8
	Amoxicillin Clavulanic Acid	1	2	0.25 - 2
	Ampicillin	≤0.5	4	≤0.5 - 8
	Cefepime	≤0.5	≤0.5	≤0.5
	Ceftazidime	≤8	≤8	≤8 - ≥32
	Ceftriaxone	≤0.06	0.5	≤0.06 - 16
	Levofloxacin	0.03	0.03	0.015 – 0.25
	Meropenem	≤0.06	0.25	≤0.06 – 0.25
	Minocycline	≤0.5	1	≤0.5 - 1
	Piperacillin Tazobactam	≤0.6	0.25	≤0.06 - 8

Table 5. In vitro *activity of tigecycline and comparative antimicrobial agents against* Enterococcus *spp. and* Staphylococcus aureus.

Microrganisms	Drugs	MIC 50	MIC 90	MIC Range
		μg/ L		
Enterococcus spp.	Tigecycline	0.12	0.25	0.03 – 0.5
	Amoxicillin/Clavulanic Acid	1	≥8	0.5 -≥8
	Ampicillin	2	≥16	1 -≥16
	Ceftriaxone	≥64	≥64	0.5 - ≥64
	Levofloxacin	≥32	≥32	0.5 - ≥32
	Linezolid	2	4	0.5 - 4
	Meropenem	8	≥16	4 - ≥16
	Minocycline	≥8	≥8	≤0.25 - ≥8
	Penicillin	8	≥8	2 - ≥8
	Piperacillin/Tazobactam	8	≥16	4 - ≥16
	Vancomycin	1	4	1 - ≥32
S. aureus Met R	Tigecycline	0.25	0.5	0.12 - 16
	Amoxicillin/Clavulanic Acid	8	≥8	0.12 - ≥8
	Ampicillin	≥16	≥16	≤0.06 - ≥16
	Ceftriaxone	64	≥64	4 - ≥64
	Levofloxacin	16	≥32	0.25 - ≥32
	Linezolid	4	4	≤0.5 - 4
	Meropenem	4	≥16	≤0.12 - ≥16
	Minocycline	0.5	≥8	≤0.25 - ≥8
	Penicillin	≥8	≥8	≤0.06 - ≥8
	Piperacillin/Tazobactam	8	≥16	1 - ≥16
	Vancomycin	1	2	1 - ≥32
S. aureus Met S	Tigecycline	0.12	0.5	0.12 - 2
	Amoxicillin/Clavulanic Acid	4	≥8	2 - ≥8
	Ampicillin	≥16	≥16	≥16
	Ceftriaxone	16	≥64	4 - ≥64
	Levofloxacin	16	32	0.25 - ≥32
	Linezolid	8	≥8	2 - ≥8
	Meropenem	1	≥16	≤0.12 - ≥16
	Minocycline	0.5	2	≤0.25 - 4
	Penicillin	≥8	≥8	≥8
	Piperacillin/Tazobactam	8	≥16	2 - ≥16
	Vancomycin	1	1	1

Table 6. In vitro *activity of tigecycline and comparative antimicrobial agents against* Streptococci.

Microrganisms	Drugs	MIC 50	MIC 90	MIC Range
		μg/ L		
S. pneumoniae PEN- R(5)	Tigecycline	1	1	1-2
	Amoxicillin/Clavulanic Acid	2	4	1 – 4
	Ampicillin	4	4	4
	Ceftriaxone	2	8	1-8
	Levofloxacin	1	1	1
	Linezolid	1	1	1
	Meropenem	1	1	0.5 - 1
	Minocycline	≥8	≥8	≥8
	Penicillin	4	4	2 - 4
	Piperacillin/Tazobactam	4	4	4 - 4
	Vancomycin	0.5	1	0.5 - 1
S. pneumoniae PEN-S(10)	Tigecycline	0.25	0.5	0.25 - 1
	Amoxicillin/Clavulanic Acid	≤0.03	≤0.03	≤0.03 – 0.12
	Ampicillin	≤0.06	≤0.06	≤0.06 – 0.25
	Ceftriaxone	≤0.03	≤0.03	≤0.03 - 1
	Levofloxacin	1	1	1
	Linezolid	≤0.5	1	≤0.5 - 1
	Meropenem	≤0.12	≤0.12	≤0.12
	Minocycline	2	8	0.25 - 8
	Penicillin	≤0.06	≤0.06	≤0.06 – 0.25
	Piperacillin/Tazobactam	≤0.25	≤0.25	≤0.25
	Vancomycin	0.5	0.5	0.25 – 0.5
S. agalactiae	Tigecycline	≤0.03	0.25	≤0.008 – 0.25
	Amoxicillin/Clavulanic Acid	0.06	0.06	≤0.03 – 0.06
	Ampicillin	≤0.06	≤0.06	≤0.06 –0.12
	Ceftriaxone	0.06	0.06	≤0.03 -1
	Levofloxacin	1	1	0.5 - 4
	Linezolid	≤0.5	1	≤0.5 -2
	Meropenem	≤0.12	≤0.12	≤0.12
	Minocycline	2	≥8	≤0.25 - ≥8
	Penicillin	≤0.06	≤0.06	≤0.06
	Piperacillin/Tazobactam	≤0.25	≤0.25	≤0.25
	Vancomycin	2	0.5	≤0.12 – 0.5

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