Original Article

Microbiology Section

Invitro Activity of Tigecycline Against Gram Positive and Gram Negative Isolates in a Tertiary Care Hospital

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ABSTRACT

Background: Resistance to multiple anti-microbial agents among gram positive and gram negative pathogens is high worldwide. Tigecycline, a glycylcycline antibiotic is a promising advancement in the treatment of infections caused by multidrug resistant organisms.

Objectives: To evaluate the invitro activity of tigecycline against a spectrum of Gram positive and Gram negative pathogens

Materials and Methods: A total of 195 non -repetitive, clinically significant isolates obtained from various clinical specimens from hospitalised patients were included in the study. The organisms isolated include methicillin resistant *Staphylococcus aureus* (MRSA) (n=40), *Enterococcus fecalis* (n=15), *Streptococcus pneumoniae* (n=10), Extended Spectrum Beta Lactamase (ESBL) producing *Escherichia coli*(n=40), ESBL producing *Klebsiella pneumoniae* (n=40), ESBL producing *Enterobacter* spp (n=15), *Serratia marcesens* (n=5), *Acinetobacter baumannii* (n=25) and *Haemophilus influenzae* (n=5). Minimum inhibitory concentrations (MIC) were determined for various classes of anti-microbial agents including tigecycline using broth micro-dilution methodology as defined by the Clinical laboratory Standards Institute (CLSI) using Microscan panels. Interpretation of the anti-microbial susceptibility testing was done as per CLSI criteria. For tigecycline, interpretative criteria was as per the United States Food and Drug Administration breakpoints. MRSA and ESBL screening were performed in accordance with CLSI guidelines.

Results: Tigecycline exhibited good activity against all the isolates tested in the study. The three most active agents *in vitro* against MRSA and *Enterococcus fecalis* isolates in this study were tigecycline, vancomycin and linezolid with 100 % susceptibility. In the case of ESBL producing *Enterobacteriaceae,* meropenem and tigecycline were the most active agents. Tigecycline was the most effective anti-microbial agent against the multidrug resistant *Acinetobacter baumannii* including the meropenem resistant isolates.

Conclusion: Tigecycline is an alternative option for the treatment of multi-drug resistant pathogens causing complicated skin and soft tissue and intra-abdominal infections.

Key Words: Anti-microbial resistance, Tigecycline, In vitro susceptibility

KEY MESSAGE

- Tigecycline is a potent anti-microbial agent against MRSA,VISA,ESBL and carbapenem resistant Gram negative pathogens
- Useful in the treatment of complicated skin and soft tissue and intra-abdominal infections

INTRODUCTION

Treatment of serious life threatening infections due to multi-drug resistant (MDR) pathogens presents a difficult challenge due to limited therapeutic options. Increased resistance to anti-bacterial agents among clinically important organisms, particularly non-fermentative Gram negative bacilli (including *Acinetobacter* spp. and *Pseudomonas aeruginosa*), extended spectrum beta lactamase (ESBL) producing Enterobacteriaceae and Gram positive organisms such as *Staphylococcus aureus* and *Enterococcus* spp is of great concern [1]. Infections caused by these organisms leads to prolonged hospitalisation, high treatment cost, increased morbidity and mortality [2]. With the emergence and spread of carbapenem resistance among *Pseudomonas aeruginosa*, *Acinetobacter spp* and members of Enterobacteriaceae, the only available treatment options remaining is the polymyxin group of antibiotics. Methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant *Enterococcus* (VRE) spp are also on rise in many parts of the world. [3]

In Intensive care units (ICU) carbapenems and vancomycin are used as the last resort in the treatment of MDR Gram negative and Gram positive infections respectively. Currently, carbapenem resistance is increasingly reported among Gram negative bacteria. The prevalence of vancomycin intermediate *Staphylococcus aureus* (VISA) strains in India is reported to be 6.3% [3,4]. Clearly there is a need for new anti-microbial agents with novel mechanisms of actions to keep in pace with the emergence and spread of MDR pathogens.

Tigecycline, a newer semi-synthetic gylcylcycline derived from minocycline is a promising molecule in the treatment of infections caused by MDR organisms. Tigecycline is a bacteriostatic agent and has potent invitro activity against several Gram positive and

Gram negative aerobic and anaerobic bacteria including MRSA, VRE, *Streptococcus pneumoniae, Neisseria gonorrhoeae, Moraxaella catarrhalis, Haemophilus influenzae*, ESBL producing Enterobacteriaceae and carbapenem resistant *Acinetobacter* spp. Furthermore, it is not affected by the known mechanisms of resistance to tetracycline and minocycline such as efflux pumps and ribosomal protective mechanisms. In addition it does not present cross resistance with other antibiotics such as beta lactams, aminoglycosides and fluoroquinolones. However it is affected by the intrinsic multidrug pumps of *Pseudomonas aeruginosa* and *Proteae* and it is not useful to treat infections caused by them [5,6,7]. Because of this promising microbiological, pharmacodynamics and pharmacokinetic profile, tigecycline is a good alternative to treat infections due to MDR pathogens. As of now, tigecycline is approved for the treatment of complicated skin and soft tissue and intra-abdominal infections [8].

We evaluated the *invitro* activity of tigecycline against a spectrum of Gram positive and Gram negative pathogens

MATERIALS AND METHODS

Bacterial isolates: The study was conducted in a 1600 bedded university teaching hospital from August 2007- May 2008. A total of 195 non-repetitive, clinically significant isolates from hospitalised patients were included in the study. The source of these isolates included pus (n=58), blood (n=42), bronchoalveolar lavage [BAL] (n=29)urine (n=25), wound swab (n=23), sputum (n=11), ear swab (n=2), cerebrospinal fluid [CSF] (n=2), bile (n=1), pleural fluid (n=1), and peritoneal fluid (n=1). The organisms were identified either by conventional methods or Microscan walkway system (Dade Behring Inc., USA) using Gram negative and Gram positive panels. The organisms which were tested included MRSA (n=40), *Enterococcus fecalis* (n=15), *Streptococcus pneumoniae* (n=10), ESBL producing *Escherichia coli (*n=40) , ESBL producing *Klebsiella pneumoniae* (n=40), ESBL producing Enterobacter spp (n=15), *Serratia marcesens* (n=5) ,*Acinetobacter baumannii* (n=25) and *Haemophilus influenzae* (n=5).

Anti-microbial susceptibility testing: Minimum inhibitory concentrations (MIC) were determined using broth microdilution methodology as defined by the CLSI using Microscan panels [9]. The test panel for Gram negative isolates included (concentration given in µg/ml): amikacin (0.5-64), amoxicillin-clavulanic acid (0.12/0.06-32/16), ampicillin (0.5-32), cefepime (0.5-32) ceftazidime (8-32), cefotaxime (0.06-64), levofloxacin (0.008-8) meropenem (0.06-16), minocycline (0.5-16), piperacillin-tazobactam (0.06/4-128/4) and tigecycline (0.008-16).The gram positive organisms were tested against the following anti-microbials: amoxicillin-clavulanic acid (0.03/0.0015-8/4), ampicillin (0.06-16), penicillin (0.06-8), linezolid (0.5-8), cefotaxime (0.03-64), levofloxacin (0.06-32), minocycline (0.25-8) ,vancomycin (0.12-32) and tigecycline (0.008-16). MIC determination was carried out using freshly prepared cation adjusted Mueller-Hinton broth to prevent oxidative degradation of tigecycline in aqueous solution [10]. For *Streptococcus pneumoniae* and *Haemophilus influenzae* Mueller Hinton broth with 3% lysed horse blood was used. Broth microdilution panels inoculated with Gram negative organisms were incubated in ambient air at 35°C for 16-20 hours. *Staphylococcus aureus* and *Enterococcus* spp were incubated in ambient air at 35ºC for 24 hours. Panels with *Streptococcus pneumoniae* and *Haemophilus influenzae* were incubated at 35ºC for 16-20 hours in CO_2 incubator. Quality control strains were used in the study of *E.coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213 and *Enterococcus fecalis* ATCC 29212. Interpretation of the anti-microbial susceptibility testing was done as per CLSI criteria [9]. Since there were no CLSI recommended interpretative criteria for tigecycline, the United States Food and Drug Administration (FDA) breakpoints: *Staphylococcus aureus* (susceptible ≤0.5 µg/ml), *Enterococcus* (susceptible ≤0.25 µg/ml), Enterobacteriaceae (susceptible ≤ 2µg/ml, intermediate 4µg/ml, resistant ≥8µg/ml) were used. The FDA had not established breakpoints for *Acinetobacter baumannii*, therefore MIC interpretation was done using the breakpoints criteria listed for *Enterobacteriaceae* as per previous studies done in centers in India and other countries in the world [2,9,11,12].

Anti-bacterial resistance determination: Methicillin resistance in *Staphylococcus aureus* was detected using cefoxitin (30µg) (Himedia laboratories, Mumbai, India) disc by diffusion method and interpreted in accordance with CLSI criteria [9].

The presence of ESBL among *E.coli, K. pneumoniae* and *Enterobacter spp* was detected according to CLSI methodology for which cefotaxime 30 µg, cefotaxime–clavulanic acid (30/10µg), ceftazidime (30 µg) and ceftazidime-clavulanic acid (30/10 µg) discs (Himedia laboratories, Mumbai, India) were used. An increase of ≥ 5 mm in inhibition zone on the combination disc was compared to the cephalosporin alone indicated ESBL production [9].

RESULTS

Bacterial isolates: Gram positive (n=65): The MRSA (n=40) isolates were from pus (n=17), wound swab (n=9), blood (n=9), BAL (n=2), ear swab (n=2) and peritoneal fluid (n=1). *Streptococcus pneumoniae* (n=10) were from sputum (n=8), BAL (n=1) and pleural fluid (n=1). *Enterococcus fecalis* (n=15) were isolated from pus (n=5), urine (n=4), wound swab (n=3) and blood (n=3).

Gram negative (n=130): ESBL producing *Escherichia coli* (n=40) were isolated from pus (n=16) , blood (n=8), urine (n=6) wound swab (n=5) BAL (n=4) and bile (n=1).The source for ESBL producing *Klebsiella pneumoniae* (n=40) were pus (n=15), blood (n=11),BAL (n=6), wound swab (n=5) and urine (n=3). *Acinetobacter baumannii* included in the study were isolated from BAL (n=14), blood (n=6), urine (n=2), CSF (n=1) wound swab (n=1) and pus (n=1). Out of the 15 *Enterobacter* spp, 8 were from urine, 4 from blood, 2 from BAL and 1from pus. There were 3 *Serratia marcesens* isolated from pus and 2 from urine specimens. Five isolates of *Haemophilus influenzae* were tested, which were obtained from sputum (n=3), blood (n=1) and CSF (n=1).

Susceptibility to tigecycline: All MRSA were susceptible with MIC ranging from 0.03-0.25µg/ml. The ESBL producing *K. pneumoniae, E.coli* and the *Enterobacter species* were all susceptible to tigecycline. Among the *A. baumannii* isolates (n=25), 20 were susceptibile to tigecycline and in 5 isolates the MIC was in intermediate range.

Susceptibility to other classes of Antimicrobial agents: [Table/Fig-1] shows the susceptibility pattern, the MIC_{50} and MIC_{90} values of the Gram positive isolates included in the study.

All the MRSA isolates were susceptible to tigecycline, minocycline, vancomycin and linezolid. Among the *E. fecalis* and *Streptococcus pneumoniae* isolates, there was uniform susceptibility to tigecycline, vancomycin and linezolid

The susceptibility profile of Gram negative isolates is shown in [Table/Fig-2]

Antimicrobial agent	MRSA (n=40)					Enterococcus fecalis (n=15)					Streptococcus pneumoniae (n=10)				
	S	I	R	MIC $_{50}$ µg/ml	MIC $_{90}$ µg/ml	S	I	R	MIC $_{50}$ µg/ml	MIC $_{90}$ µg/ml	S	I	R	MIC $_{50}$ µg/ml	MIC $_{90}$ µg/ml
Tigecycline	40	-	-	0.12	0.25	15	-	-	0.03	0.03	10	-	-	0.25	0.25
Penicillin	-	-	40	8	>8	8	-	7	8	>8	10			2	2
Ampicillin	-	-	40	>16	>16	10	-	5	8	16	10	-	-	1	2
Cefotaxime	-	-	40	64	>64	-	-	-	-	-	10			1	2
Amoxycillin-clavulanic acid	-	-	40	8	8	-	-	-	-	-	10	-	-	2	4
Minocycline	39	1	-	<0.25	<0.25	14	1	-	4	1	3	4	3	1	4
Levofloxacin	10	8	22	4	16	3	-	12	32	>32	8	-	2	0.25	0.5
Vancomycin	40	-	-	0.25	0.5	15	-	-	1	0.25	10	-	-	0.25	0.25
linezolid	40	-	-	1	1	15	-	-	0.5	0.5	10	-	-	<0.5	<0.5

[Table/Fig-1]: Antimicrobial susceptibility pattern and MIC_{50} and MIC_{90} values of the anti-microbials tested against Gram positive cocci
S-susceptible, I-intermediate, R-resistan.

Antimicrobial agent	Escherichia coli (n=40)					Klebsiella pneumoniae (n=40)					Enterobacter species (n=15)					Acinetobater baumannii (n=25)				
	S	I	R	MIC_{50} µg/ml	MIC_{90} µg/ml	S	I	R	MIC_{50} µg/ml	MIC_{90} µg/ml	S	I	R	MIC_{50} µg/ml	MIC_{90} µg/ml	S	I	R	MIC_{50} µg/ml	MIC_{90} µg/ml
Tigecycline	40	-	-	0. 12	0. 25	39	1	-	0. 25	0.5	15	-	-	0. 25	0.5	20	5	-	1	2
Levofloxacin	3	-	37	8	8	16	1	23	8	>8	8	1	6	1	4	5	4	16	4	>8
Cefotaxime	-	-	40	> 64	> 64	-	1	39	> 64	> 64	-	1	14	64	> 64	-	1	24	64	> 64
Ceftazidime	-	-	40	32	> 32	-	-	40	> 32	> 32	-	2	13	32	> 32	2	-	23	32	> 32
Cefepime	12	2	26	16	16	12	-	28	16	32	6	2	7	16	32	3	4	18	16	32
Amikacin	40	-	-	4	4	26	1	13	4	8	12	-	3	2	8	7	3	15	32	64
Piperacillin tazobactam	40	-	-	4	16	20	10	10	16	32	12	3	-	8	16	5	8	12	32	128
Meropenem	40	-	-	<0.06	<0.06	40	-	-	0. 06	0. 12	15	-	-	<0.06	<0.06	16	1	8	2	4
Minocycline	26	1	13	2	16	23	4	13	2	8	11	2	2	1	2	17	2	6	2	4

[Table/Fig-2]: Anti-microbial susceptibility pattern and MIC_{50} and MIC_{90} of the anti-microbials tested against Gram negative bacilli
S-susceptible, I-intermediate, R-resistant.

The ESBL producing *E.coli* and *Enterobacter spp*, were susceptible to amikacin, piperacillin– tazobactam, meropenem and tigecycline. Levofloxacin and cefepime showed poor activity against these organisms. In the case of ESBL producing *K. pneumoniae*, meropenem and tigecycline were the most active agents. Amikacin, pipercillin-tazobactam, cefepime and levofloxacin exhibited high MIC in most of the isolates tested in the study.

With the exception of Ampicillin and Amoxycillin clavulanic acid, *Serratia marcesens* isolates were susceptible to all the antimicrobial agents in the panel.

Haemophilus influenzae isolates were susceptible to all the anti-microbials tested in the study

Among the *A. baumannii* (n=25), amikacin, levofloxacin, cefepime and piperacillin-tazobactam showed poor activity with only few isolates being susceptible. Meropenem resistance was encountered in 8/25 isolates. Tigecycline was the most effective anti-microbial agent against the multidrug resistant *Acinetobacter baumannii* including the meropenem resistant isolates.

DISCUSSION

Bacterial resistance to the commonly used anti-microbial agents is increasing and it is a matter of concern, particularly in patients with serious and complicated nosocomial infections. Emergence and spread of methicillin resistance among *Staphylococcus aureus*, ESBL production in Enterobacteriaceae and carbapenem resistance among Gram negative bacteria have led to the limited therapeutic options, resulting in increased morbidity and mortality. The development of new ant-imicrobial agents with novel modes of action is critically needed to keep in pace with the development and spread of drug resistance mechanisms among bacteria [11].

Tigecycline is a glycylcycline compound with broad spectrum of bacteriostatic activity against gram positive pathogens including MRSA, VISA (Vancomycin intermediate *Staphylococcus aureus*)VRE and penicillin resistant *Streptococcus pneumoniae*; against Gram negative organisms like ESBL producing Enterobacteriaceae, Multi-drug resistant *Acinetobacter* species including the carbapenem resistant isolates, anaerobes such as *Bacteriodes fragilis* group, atypical organisms like *Mycoplasma* spp, *Chlamydia* spp and rapidly growing Mycobacteria [5]. It acts by inhibiting the protein synthesis in the bacterial cell by binding to the 30S subunit of the ribosome. In comparison with tetracycline, tigecycline exhibits its bacteriostatic effects by binding to corresponding ribosomal sites with greater affinity and irrespective of the mutations that confer resistance to tetracycline and also it evades the tetracycline efflux pumps. Tigecycline does not exhibit co-resistance with known mechanisms of resistance. Its capacity to penetrate into various tissues, makes it useful in the treatment of infections of the skin and soft tissues as well as intra -abdominal infections, whereas its low serum concentrations compromise its use in bloodstream

infections. It is not useful in the treatment of nosocomial pneumonia as indicated by poor results in the study of ventilator associated pneumonia [13, 14].

This study was done to evaluate the invitro activity of tigecycline against MRSA, ESBL producing Enterobacteriaceae, multi-drug resistant *Acinetobacter baumannii* by determining their MIC to tigecycline. The other organisms tested were *Streptococcus pneumoniae* and *Haemophilus influenzae.*

MRSA is a global problem with treatment options limited to glycopeptides (vancomycin, teicoplanin), oxazolidinones (linezolid), streptograminins (quinupristin-dalfopristin), and polycyclic compounds (tetracycline, tigecycline).The prevalence of MRSA from several centres in India as reported ranges from 20-80%. Emergence of vancomycin and linezolid resistance among *Staphylococcus aureus* is an alarming threat. The prevalence of vancomycin intermediate *Staphylococcus aureus* (VISA) strains in India is reported to be 6.3% [4]. Later there were sporadic reports of vancomycin resistant *Staphylococcus aureus* (VRSA) from India [15,16]. More recently, a study conducted in a tertiary care centre to identify the emergence of vancomycin resistance in south India, reported 4.46% of VISA and 1.95% of VRSA [17]. The three most active agents in vitro against MRSA isolates in this study are tigecycline, vancomycin and linezolid with 100% susceptibility. Hence tigecycline plays a very important role in the treatment of infections caused by MRSA and is currently the drug of choice against the VISA and VRSA isolates [13,15].

Tigecycline demonstrated excellent activity against the *Streptococcus pneumoniae, Haemophilus influenzae* isolates. In India till date multi-drug resistance is not a significant problem in these pathogens. Hence tigecycline is not an optimal choice for the management of infections caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*.

Tigecyline was highly active against the ESBL producing Enterobacteriaceae. Although carbapenems are widely regarded as the drugs of choice for treatment of infections caused by ESBL producing organisms, production of beta lactamases capable of hydrolyzing carbapenems have been reported from Enterobacteriaceae [19]. The available alternative treatment options in such infections are the tigecycline and the polymyxin B. However in this study, we did not encounter carbapenem resistance in the Enterobacteriaceae. In a multi-centric study from India, regardless of the presence or absence of ESBL, tigecycline exhibited good activity against Enterobacteriaceae [11].

A baumannii is one of the commonly isolated nosocomial pathogen, mainly from the patients in the ICU. These isolates are resistant to multiple anti-microbial agents including the carbapenems .Treatment options for carbapenem resistant *Acinetobacter baumannii* are limited to polymyxin and tigecycline. In the study isolates tigecycline demonstrated good activity against the *Acinetobacter baumannii* with MIC ≤2µ/ml in 80% (n=20) and in the remaining 20% (n=5) the MIC was in intermediate range (4µ/ml). A tigecycline susceptibility report from a tertiary care hospital in India reported a low rate of susceptibility (42%) to tigecycline among *Acinetobacter* species, where the organisms were totally unexposed to tigecycline and also to the tetracycline group of antibiotics [2]. In another study from India, 70.6% of MDR *Acinetobacter* species were susceptible to tigecycline [11]. In a study on 224 urine isolates from complicated urinary tract infections, the overall resistance to tigecycline in *Acinetobacter* spp was 14.2% and among the carbapenem resistant isolates, 32% were resistant to tigecycline [20]. Hence the use of tigecycline should be strictly monitored to prevent the development and dissemination of resistance against tigecycline, which is the last resort in the treatment of MDR *Acinetobacter baumannii* infections.

To conclude, the present study shows tigecycline is a potent anti-microbial agent against MRSA, ESBL producing *Enterobacteriaceae* and multi-drug resistant *Acinetobacter baumannii.* Due to its long half-life and large volume of distribution, it can be an important lifesaving agent in the treatment of polymicrobial intra-abdominal, skin and soft tissue infections. It is not useful in bloodstream infections and nosocomial pneumonia. In view of its excellent activity against MDR pathogens, it is prudent to reserve tigecycline for life threatening infections when other options fail. This will minimise the emergence of resistance to tigecycline.

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