In vitro activity of tigecycline against patient isolates collected during phase 3 clinical trials for hospital acquired pneumonia

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Abstract

The *in vitro* activity of tigecycline was evaluated against 819 baseline pathogens isolated from 383 patients enrolled in the phase 3 clinical trial investigating the efficacy of tigecycline in hospital acquired pneumonia (HAP). The trials were global, enrolling patients in 27 countries. Tigecycline was active against the most prevalent pathogens in HAP, including gram-positive and gram-negative strains (90% of MICs ≤ 2 $\mu\text{g/mL}$ for the entire collection). The spectrum of activity of tigecycline included important pathogens such as *Staphylococcus aureus* (including methicillin-resistant *S. aureus*), *Enterococcus faecalis*, *Streptococcus pneumoniae*, *Acinetobacter baumannii/calcoaceticus* complex, *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*. As reported previously, a few genera, such as *Pseudomonas aeruginosa* and the *Proteaeae*, were generally less susceptible to tigecycline by comparison to other gram-negative pathogens. The excellent *in vitro*, expanded, broad-spectrum activity of tigecycline in the clinical isolates confirmed the potential utility of tigecycline for pathogens associated with hospital acquired pneumonia infections.

Introduction

The glycylicycline class of antibiotics was developed by Wyeth in response to the threat of emerging antibiotic resistance throughout the world.¹ Tigecycline, the first in the class glycylicycline, received market approvals for treatment of complicated skin and skin structure infections (cSSSI) and complicated intra-abdominal infections (cIAI) in 2005 and community acquired bacterial pneumonia (CABP) in 2008 (see Tygacil Label at http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021821s013s017s018b1.pdf).²⁻⁶ Tigecycline binds to the 30S ribosomal subunit blocking access of amino-acyl tRNA molecules to the A site,⁷ and is not affected by tetracycline resist-

ance mechanisms: efflux pumps and ribosomal protection.⁸⁻¹⁰ The expanded broad spectrum of activity of tigecycline includes a broad range of antibiotic-susceptible and -resistant gram-positive and gram-negative aerobes, anaerobes, and "atypical" bacteria.⁴

Hospital acquired pneumonia (HAP) is second only to urinary tract infections as the most common nosocomial infection contracted, especially among patients admitted to the ICU.¹¹ In critical care settings and following surgical treatment, nosocomial pneumonia is reported in approximately 20% of patients and mortality rates range from 20-70%. Methicillin-resistant *Staphylococcus aureus* (MRSA) as well as gram-negative pathogens – *Acinetobacter spp.*, *Escherichia coli*, *Pseudomonas aeruginosa* – are predominant pathogens in HAP; in addition, antibiotic resistance rates are elevated in these organisms complicating therapeutic decision-making. To evaluate the safety and efficacy of tigecycline in treatment of HAP infections a randomized, double-blind trial was conducted with imipenem/cilistatin as the active comparator.¹² This analysis was conducted in order to evaluate the susceptibility of the clinical isolates to tigecycline and selected comparator agents.

Materials and Methods

Clinical isolates

Baseline pathogens from all patients enrolled in the clinical trial were included in the analysis of susceptibility data. Site laboratories processed patient specimens and cultured bacterial pathogens according to local practices. Acute HAP was defined as pneumonia with onset of symptoms ≥ 48 hours after admission to an acute care hospital or chronic care facility (such as a skilled nursing home facility or rehabilitation unit), or < 7 days after the subject was discharged from the hospital. The initial hospitalization must have been of ≥ 3 days duration. Subjects must have had the presence of a new or evolving infiltrate on chest X-ray and the chest X-ray must have been obtained ≥ 48 hours after the subject was admitted to the hospital or chronic care facility. Diagnosis required that the subjects have the presence of fever within 24 hours prior to randomization into the trial and leukocytosis or increased bands or leukopenia. In addition, subjects must have had at least two of the following: cough, dyspnea or tachypnea, pleuritic/inspiratory chest pain, auscultatory findings on pulmonary examination or rales and/or evidence of pulmonary consolidation, hypoxemia, purulent sputum or respiratory secretion or a change in sputum character occurring ≥ 48 hours after hospitalization, or respiratory failure requiring mechanical ventilation (in lieu

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Conflict of interest: HJ and PP were employees of Wyeth when the manuscript was drafted. HJ and PP are currently employees of Pfizer, and HJ holds stock in the company. MT has no conflicts of interest to declare.

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of having two of the clinical signs and symptoms listed above). Respiratory tract specimens were obtained for Gram stain and culture at randomization. The majority of specimens submitted for culture were from: bronchoscopy, deep expectoration, or endotracheal aspiration; although it must be acknowledged that not all isolates described in the study were clinically relevant. Bacterial pathogens were sent to a central laboratory for identification and susceptibility testing. MICs were determined in Mueller-Hinton II broth (MHB); for streptococci MHB containing 5% lysed horse blood was used. MICs were determined using custom-prepared dehydrated microdilution panels (Trek Diagnostics, Westlake, OH, USA) and followed reference methodology as described by the CLSI.^{13,14} Methicillin resistance of staphylococci was determined by MIC tests for oxacillin supplemented with 2% NaCl and interpreted according to CLSI interpretive criteria.^{13,14}

Confirmation of extended spectrum β -lactamase

For those isolates of *E. coli*, *Klebsiella pneumoniae* or *Proteus mirabilis* resulting in a cef-tazidime MIC of ≥ 2 $\mu\text{g/mL}$, confirmation of the presence of an extended spectrum β -lactamase (ESBL) was performed using Etest ESBL

strips containing either ceftazidime or cefotaxime with and without clavulanic acid, according to the manufacturer's instructions (ABBIODISK, Solna, Sweden).

PCR analysis of resistance determinants

Methicillin (*S. aureus*) and tetracycline resistance determinants (*S. aureus*, *E. coli*) were identified using diagnostic PCR assays as previously described.^{9,10} In addition, confirmed ESBL containing isolates were further examined by PCR to determine the class(es) of β -lactamase (e.g. TEM, SHV, CTX, OXA) encoded using protocols previously described.¹⁵

Results

The most prevalent pathogens isolated from patients during the clinical trials (2004-2006) for HAP, including patients with ventilator associated pneumonia (VAP), are listed in Table 1. The distribution of pathogens was representative for the infection type and similar to reports from recent studies.¹⁶ A summary of the tigecycline susceptibility for the predominant baseline isolates obtained is presented in Table 2. The most prevalent pathogens isolated were *Staphylococci* spp. (287 isolates) with *S. aureus* represented by 75 methicillin-resistant (MRSA) and 130 methicillin-sensitive (MSSA) isolates (Tables 1, 2). *Acinetobacter baumannii/calcoaceticus* complex was the most prevalent gram-negative pathogen isolated (82 baseline isolates), followed by *E. coli* (75 isolates), *K. pneumonia* (75 isolates), and *P. aeruginosa* (54 isolates) (Table 1, 2).

As shown in Table 2 and Supplementary Table, 92% of the MRSA isolates were susceptible to tigecycline (MIC₉₀ 0.5 μ g/mL). In the case of the MSSA isolates, 100% of the isolates were susceptible to tigecycline (MIC₉₀ 0.25 μ g/mL), and susceptibility rates for comparator agents were in excess of 91% with the exception of azithromycin (88%) and ceftazidime (73%) in the VAP population. Twenty-two MRSA and five MSSA isolates were resistant to minocycline (MIC $\geq$ 8 μ g/mL); of these, 24 isolates encoded tet(M), two isolates encoded tet(K) and tet(M), and a single isolate encoded tet(K) alone as determined by PCR analysis as previously described (Supplementary Table and data not shown).⁹ In addition, 10 isolates were minocycline susceptible (MIC $\leq$ 4 μ g/mL) and tetracycline resistant (MIC $\geq$ 8 μ g/mL); of these, four isolates encoded tet(M), five isolates encoded tet(K), and a single isolate encoded both determinants. All of the methicillin susceptible isolates of *Staphylococcus epidermidis* were fully susceptible to 0.5 μ g/mL of tigecycline (MIC₉₀

Table 1. Etiology of organisms cultured from patients with hospital acquired pneumonia.

Organism	Non-VAP		VAP	
	N (%)	Multi-drug resistant isolates (%) ^a	N (%)	Multi-drug resistant isolates (%) ^a
Gram-positive aerobes	297 (36%)	101 (34%)	100 (12%)	42 (42%)
<i>Staphylococcus aureus</i>	147 (18%)	50 (34%)	58 (7%)	25 (43%)
<i>Staphylococcus epidermidis</i>	37 (4.5%)	28 (76%)	12 (1.5%)	10 (83%)
<i>Enterococcus faecalis</i>	37 (4.5%)	7 (19%)	7 (0.8%)	3 (43%)
<i>Streptococci pneumoniae</i>	22 (2.7%)		5 (0.6%)	
<i>Staphylococcus haemolyticus</i>	20 (2.4%)	16 (80%)	4 (0.5%)	4 (100%)
<i>Enterococcus faecium</i>	4 (0.5%)		2 (0.25%)	
Gram-negative aerobes	268 (33%)		154 (18%)	
<i>Acinetobacter baumannii / calcoaceticus</i> complex	34 (4.5%)	27 (79%)	48 (6%)	25 (52%)
<i>Escherichia coli</i>	58 (7%)	12 (21%)	17 (2%)	1 (6%)
<i>Klebsiella pneumoniae</i>	61 (7%)	8 (13%)	14 (1.7%)	
<i>Pseudomonas aeruginosa</i>	30 (3.6%)	4 (13%)	24 (3%)	7 (29%)
<i>Enterobacter cloacae</i>	19 (2.3%)		3 (0.4%)	
<i>Haemophilus influenzae</i>	13 (1.5%)		9 (1.0%)	
<i>Klebsiella oxytoca</i>	11 (1.3%)		2 (0.2%)	
<i>Stenotrophomonas maltophilia</i>	5 (0.6%)		7 (0.8%)	
<i>Proteus mirabilis</i>	6 (0.7%)	2 (33%)	6 (0.7%)	2 (33%)
<i>Enterobacter aerogenes</i>	4 (0.5%)	1 (25%)	7 (0.8%)	2 (28%)
<i>Serratia marcescens</i>	6 (0.7%)	1 (16%)	4 (0.5%)	1 (25%)

^a Multidrug resistant strains are methicillin-resistant *Staphylococcus aureus* (MRSA) and *S. Epidermidis* (MRSE) isolates by default and pathogens having resistance to three classes of antibacterial agent. VAP, ventilator associated pneumonia.

0.5 μ g/mL). Among the 38 isolates of MRSE there were three isolates with a tigecycline MIC of 1 μ g/mL resulting in an overall susceptibility rate for these isolates of 92% (MIC₉₀ 0.5 μ g/mL). When considering all 287 strains of *Staphylococcus* spp., the tigecycline MIC₉₀ was 0.5 μ g/mL.

Tigecycline had good activity against all 50 isolates of *Enterococcus* spp. collected (Table 2). The predominant species obtained was *Enterococcus faecalis* (44 isolates) and all of the isolates were susceptible to 0.25 μ g/mL (FDA susceptible breakpoint). By contrast, the MIC₉₀s for both levofloxacin (>16 μ g/mL) and minocycline (16 μ g/mL) were at the resistant breakpoints for the *E. faecalis* isolates (Supplementary Table).

Tigecycline activity was determined against 27 isolates of *Streptococcus pneumoniae* that included two isolates that were penicillin intermediate and two isolates that were penicillin resistant according to the recently changed penicillin breakpoints for this organism.¹³ All of the isolates were susceptible to $\leq$ 0.12 μ g/mL tigecycline.

Tigecycline showed good activity against gram-negative organisms of which *A. baumannii/calcoaceticus* complex was the predominant pathogen isolated (Supplementary Table). The MIC₉₀s for all of the comparator agents were above the respective resistance breakpoints except for imipenem for the non-VAP isolates (MIC₉₀ 2 μ g/mL). CLSI or FDA breakpoints for tigecycline have not been

established for this organism.

For the 75 baseline patient isolates of *E. coli*, 100% were susceptible to 2 μ g/mL tigecycline (MIC range 0.12-2 μ g/mL) with an MIC₉₀ of 0.5 μ g/mL (Supplementary Table). Thirteen (17%) of these isolates were multidrug resistant (MDR) strains showing resistance to ceftazidime, levofloxacin, and tetracycline with MIC₉₀s of >64, 16, and >64 μ g/mL, respectively. The *E. coli* collection included 48 tetracycline resistant (MIC $\geq$ 8 μ g/mL) strains, 26 of which were also resistant (MIC $\geq$ 8 μ g/mL) to minocycline. The tetracycline resistance determinants in these isolates were identified by PCR as previously described.¹⁰ Twenty-five of the minocycline resistant isolates were found to encode tet(B), with two isolates also encoding tet(A) and a single isolate also encoding tet(C). One minocycline resistant isolate encoded only tet(A). Twenty-two isolates were found to be susceptible to minocycline (MIC $\leq$ 4 μ g/mL) and resistant to tetracycline (MIC $\geq$ 8 μ g/mL). All 22 isolates were found to encode tet(A), with four isolates also encoding tet(M) and two isolates also encoding tet(B). As previously shown, the presence of tetracycline-resistance determinants, specifically mono-specific tetracycline efflux pumps, had no impact on tigecycline susceptibility of the isolates.¹⁰

Twenty-one *E. coli* isolates were identified as encoding ESBLs owing to a ceftazidime MIC $\geq$ 2 μ g/mL and confirmed using E-test strips. As previously described,¹⁵ the class of β -lactamase responsible for the ESBL phenotype was deter-

Table 2. *In vitro* activity of tigecycline against bacterial isolates cultured from patients with hospital acquired pneumonia.

Organism (no. of strains)	MIC ₅₀	MIC ₉₀	% S ^a	No. of isolates with MIC (μg/mL) of									
				≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8
Gram-negative aerobes													
<i>Citrobacter freundii</i> complex (5)	0.5	NA ^b	100				1	4					
<i>Enterobacter aerogenes</i> (11)	1	2	91				1	4	4	1			1
<i>Enterobacter cloacae</i> (22)	0.5	1	100				3	10	8	1			
<i>Escherichia coli</i> (75)	0.25	0.5	100			13	36	23	2	1			
<i>Klebsiella oxytoca</i> (13)	0.25	2	100			1	5	4	1	2			
<i>Klebsiella pneumoniae</i> (75)	0.5	2	96				4	46	13	9	3		
<i>Proteus mirabilis</i> (12)	4	8	42							5	5	2	
<i>Serratia marcescens</i> (10)	1	2	100						8	2			
<i>Haemophilus influenzae</i> (22)	0.25	0.5	100		2	6	10	4					
<i>Acinetobacter calcoaceticus</i> / <i>baumannii</i> complex (82)	1	4	NA				3	9	11	21	26	11	1
<i>Burkholderia cepacia</i> (6)	2	NA	NA							1	3	2	
<i>Pseudomonas aeruginosa</i> (54)	16	32	NA										6 48
<i>Stenotrophomonas maltophilia</i> (12)	1	2	NA				1	3	5	3			
Gram-positive aerobes													
<i>Staphylococcus aureus</i> (MRSA) (75)	0.25	0.5	92		1	25	33	10	4	2			
<i>Staphylococcus aureus</i> (MSSA) (130)	0.12	0.25	100		4	100	25	1					
<i>Staphylococcus epidermidis</i> (MRSE) (38)	0.25	0.5	92		2		22	11	3				
<i>Staphylococcus epidermidis</i> (MSSE) (11)	0.12	0.5	100		4	4	1	2					
<i>Staphylococcus haemolyticus</i> (24)	0.5	1	88			4	6	11	1	2			
Coagulase-negative <i>Staphylococcus</i> ^c (9)	0.25	NA	100		1	2	4	2					
<i>Enterococcus faecalis</i> (VSE) (44)	0.12	0.25	100		9	29	6						
<i>Enterococcus faecium</i> (VSE) (6)	0.12	NA	100		2	3	1						
<i>Streptococcus anginosus</i> group ^d (5)	0.06	NA	100		2	3							
<i>Streptococcus</i> spp. <i>viridans</i> group ^e (16)	0.06	0.12	100	2	11	3							
<i>Streptococcus pneumoniae</i> ^f (27)	0.06	0.12	100	8	14	5							

^a%S is the percent of strains susceptible at FDA susceptibility breakpoints for tigecycline: ≤2 g/mL for *Enterobacteriaceae*, ≤0.5 for *Staphylococcus* spp., ≤0.25 g/mL for *Streptococcus* spp., ≤0.25 g/mL for *Enterococcus* spp. and ≤4 g/mL for anaerobes. ^bNA, not applicable owing to number of strains or no approved interpretive criteria are available. ^c*S. capitis* (2), *S. hominis* (4), *S. saprophyticus* (1), *S. warneri* (2). ^d*S. anginosus* (2), *S. constellatus* (2), *S. intermedius* (1). ^e*S. mitis* (2), *S. oralis* (8), *S. parasanguis* (1), *S. salivarius* (4), viridans *Streptococcus* (1). ^f Pen-S (23), Pen-I (2), Pen-R (2). MSSA, methicillin-sensitive *Staphylococcus aureus*; MSSE, Methicillin-sensitive *Staphylococcus Epidermidis*; VSE, vancomycin-sensitive enterococci.

mined by PCR. Nineteen (90%) of the isolates were found to encode a *bla*_{CTX} family enzyme with various combinations of *bla*_{TEM}, *bla*_{SHV}, and *bla*_{OXA} genes with fourteen isolates encoding the combination of *bla*_{CTX}, *bla*_{TEM}, and *bla*_{OXA} genes. One isolate was found to carry both a *bla*_{TEM} and *bla*_{SHV} gene, whereas another isolate encoded an AmpC β-lactamase of the *bla*_{CMY} family. As previously described, *E. coli* encoding ESBLs are as susceptible as non-ESBL isolates to tigecycline.¹⁵

When tested against *K. pneumoniae*, tigecycline performed well with 96% of isolates susceptible and an MIC₉₀ of 2 μg/mL for the 75 isolates tested (Table 2). Whereas in earlier studies *K. pneumoniae* had shown a tendency for elevated tigecycline MICs, only three isolates in the present study had an MIC of 4 μg/mL. Eight (11%) of the baseline isolates were MDR strains, resistant to a β-lactam and at least two other classes of agents, in this case levofloxacin and minocycline. The ESBL status of 31 isolates was confirmed (ceftazidime MIC ≥2 μg/mL and Etest positive) and the class of determinant responsible for the ESBL status identified by PCR.¹⁵ Twenty-four isolates encoded a *bla*_{SHV} gene with 23 of the isolates encoding additional determinants in various combinations of the *bla*_{TEM}, *bla*_{CTX}, and *bla*_{OXA}

classes. In the case of *bla*_{CTX}, 19 (79%) isolates encoded this determinant with 16 isolates encoding both the *bla*_{SHV} and *bla*_{CTX} determinants. Two isolates encoded AmpC β-lactamases of the *bla*_{DHA} family.

The 54 *P. aeruginosa* isolates collected during the clinical trial had MIC₉₀s in the resistant range for all of the comparator agents for which a breakpoint has been established. The tigecycline MIC₉₀ was 32 μg/mL, which is reflective of earlier studies demonstrating reduced susceptibility of this organism to tigecycline.¹⁷ *P. aeruginosa* expresses a family of multidrug efflux pumps (Mex pumps) that efficiently remove tigecycline from the cytoplasm, reducing its effectiveness. As would be expected, *P. aeruginosa* displayed low levels of susceptibility to ceftazidime (63-73%; non-VAP, VAP), levofloxacin (57-63%), and aminoglycosides (63-73%) (Supplementary Table).

The activity of tigecycline was evaluated against 22 *Enterobacter cloacae* isolates with the result that all isolates were susceptible to 1 μg/mL. The findings were similar for the small collection (11) of *Enterobacter aerogenes* isolates: 10 of the 11 isolates were susceptible to 2 μg/mL tigecycline with one isolate having an MIC = 8 μg/mL. Prior mechanistic studies revealed that a multidrug efflux system, AcrAB,

is responsible for reduced tigecycline susceptibility in *Enterobacter* spp.¹⁸

Against the small collection of 12 *P. mirabilis* isolates, tigecycline showed results in agreement with what has been seen in prior studies: MIC₉₀ 8 μg/mL.¹⁹ All of the *P. mirabilis* isolates were resistant to minocycline (MIC range 16 – >64 μg/mL). In addition, two baseline isolates were found to express the ESBL phenotype (ceftriaxone MIC ≥2 μg/mL and Etest positive), and PCR analysis revealed that one of the isolates encoded *bla*_{TEM}, *bla*_{CTX}, and *bla*_{OXA} family enzymes whereas the other isolate only encoded a *bla*_{TEM} family enzyme.

Discussion

Tigecycline was specifically designed to overcome the two classical tetracycline resistance mechanisms, ribosomal protection proteins and monospecific tetracycline efflux pumps, while maintaining the broad spectrum of activity of the tetracycline class.¹ During preclinical development, tigecycline was shown to have activity against a broad range of clinically important pathogens, including MRSA, VRE, and antibiotic resistant gram-neg-

ative pathogens, as well as anaerobes and atypical bacteria. Tigecycline has demonstrated clinical utility and gained approval for use in treatment of cSSSI, cIAI, and CABP indications.^{2,6} The potent antibacterial activity of tigecycline demonstrated in our study echoed that seen in earlier clinical studies for the approved indications as well as during preclinical development.^{2,6} As expected, tigecycline activity in our study was not impacted by the presence of the classical tetracycline resistance mechanisms in *E. coli* and *S. aureus* or ESBL in *E. coli*, *K. pneumonia*, or *P. mirabilis*.

Clinical isolates were obtained from patients enrolled in 27 countries in North America, Latin America, Eastern Europe, Western Europe, Asia, South Africa, and Australia. There were no regional differences in the MICs of tigecycline noted for isolates from the various regions providing isolates. These results are in agreement with results obtained previously from a number of large *in vitro* susceptibility studies that included isolates from North America, Latin America, Europe, the Middle East, and Asia.²⁰

Our study examined pathogens from both non-VAP and VAP patients and, for the most part, tigecycline activity was similar in both patient populations. The only exception to this finding for tigecycline was with *P. aeruginosa*. Owing to the fact that 9% (24 isolates) of VAP isolates were *P. aeruginosa* and the tigecycline MIC₉₀ for those isolates was 32 µg/mL, this pushed the tigecycline MIC₉₀ for the 255 VAP isolates to 8 µg/mL. By comparison, for the non-VAP population, *P. aeruginosa* is only 5% (30 isolates) of isolates and, although the tigecycline MIC₉₀ for these isolates is 32 µg/mL, has less of an impact on the MIC₉₀ for the 566 non-VAP isolates: MIC₉₀ 2 µg/mL. In the case of *A. calcoaceticus/baumannii* complex, the imipenem MIC₉₀ was 2 µg/mL for the non-VAP population and 32 µg/mL for the VAP population with 94% and 77% corresponding imipenem susceptibility. Tigecycline was the only agent tested with good activity (MIC₉₀ 2 µg/mL) against the *A. calcoaceticus/baumannii* complex isolates from VAP patients. Tigecycline has been shown to be safe and effective in double-blind, multicenter, global clinical trials for cSSSI, cIAI, and, most recently, CABP (see Tygacil label at http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021821s013s017s0181bl.pdf).^{2,3,6} In summary, the *in vitro* activity of tigecycline against a broad spectrum of gram-positive and gram-negative pathogens isolated from patients enrolled in phase 3 clinical trials conducted worldwide for HAP showed an excellent susceptibility profile and suggests utility in the treatment of patients with this disease.

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