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Tigecycline
A Novel Glycylcycline

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Abstract

Antibacterials have been in clinical use for almost 60 years; however, the effectiveness of these valuable agents has been diminished by widespread emergence of bacterial resistance. Tigecycline is the first in a new class of glycylcyclines with activity against a wide range of clinically important pathogens. Tigecycline has demonstrated potent microbiological activity and excellent therapeutic response in animal infection models and in recently reported phase III human clinical trials. It is effective against intra-abdominal and skin and soft tissue infections caused by susceptible or multidrug-resistant staphylococci, enterococci or streptococci as well as most Enterobacteriaceae and anaerobic pathogens. In clinical trials nausea and vomiting were the most common adverse events and were of a magnitude typical of those observed with tetracyclines in general. Additionally, tigecycline has proven to be efficacious in animal models of infection, including pneumonia, endocarditis and peritonitis.

Tigecycline is only available as an intravenous agent and distributes extensively in tissues. Administration of a 100mg loading dose of tigecycline followed by twice-daily doses of 50mg yielded an apparent volume of distribution of 7–10 L/kg. Systemic clearance ranged from 0.2 to 0.3 L/h/kg and its half-life varied from 37 to 67 hours. The pharmacokinetics of tigecycline appear unaffected by sex, age, renal disease or the presence of food. Data from animal studies would suggest that time above the minimum inhibitory concentration is the pharmacodynamic factor that best correlates with bacterial eradication.

The efficacy, safety profile and pharmacodynamic attributes of tigecycline support its continuing clinical development as empirical parenteral treatment of challenging nosocomial and community-acquired infections, including those caused by proven or suspected resistant pathogens.

Since their discovery, antimicrobials have been used largely successfully in the treatment of a wide variety of infectious diseases. More recent classes of antibacterials (e.g. macrolides, fluoroquinolones and carbapenems) exhibited a broader range of activity against pathogenic organisms, including Gram-positive and -negative bacteria, atypicals (e.g. *Chlamydia pneumoniae*, *Legionella pneumophila* and *Mycoplasma pneumoniae*) and anaerobes, as well as against certain mycobacteria. Bacterial resistance is a growing global concern within both the hospital and community setting, and reports of decreased activity of commonly used agents such as β-lactams, aminoglycosides, glycopeptides, macrolides and fluoroquinolones against challenging pathogens are becoming more frequent.[1-6]

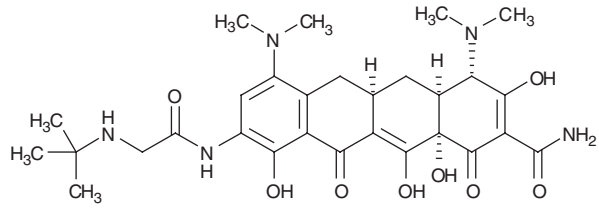

Fig. 1. Chemical structure of tigecycline.

In response to the challenge of bacterial resistance, a newly introduced, semi-synthetic class of broad-spectrum antibacterials, the glycylcyclines, has been developed. Tigecycline (figure 1), the first of these novel antibacterials, has been shown to be a potent glycylcycline with activity against a wide range of bacteria, including methicillin-susceptible and -resistant *Staphylococcus aureus* (MSSA and MRSA), methicillin-susceptible and -resistant *S. epidermidis*, penicillin-susceptible and -resistant *Streptococcus pneumoniae* and enterococci, both vancomycin-susceptible and -resistant strains of *Enterococcus faecalis* and *E. faecium*.[7-11] The activity of tigecycline against glycopeptide-intermediate resistant *S. aureus* (GISA) has also recently been reported.[12,13] Tigecycline also demonstrates activity against most clinically relevant species of Enterobacteriaceae, *Bacteroides*, *Clostridia* and anaerobic cocci. In addition, tigecycline possesses activity against clinical isolates resistant to tetracyclines expressing *tet* genes for either efflux or ribosomal protection resistance mechanisms.[14,15]

The objective of this paper is to review the mechanisms of action and resistance, *in vitro* antibacterial activity, pharmacokinetics, pharmacodynamics and therapeutic efficacy of tigecycline in animal studies and human clinical trials. Data from published literature and from presentations at recent scientific conferences have been reviewed as principle source documentation.

1. Mechanism of Action

Tigecycline is a bacteriostatic agent that induces its antibacterial effect by binding to a single high-affinity intracellular site on the bacterial 30S-ribosome, blocking entry of amino-acyl transfer molecules and, thus, preventing further protein synthesis.[16] Of the two distinct transfer RNA binding sites (A and P) within the large ribosomal subunit, tigecycline interacts with a helical region (H34) of the A-site, in a unique mechanism of action relative to other class A-site binding antibacterials.[17-19] Associative interactions between tigecycline and the ribosome are reversible, which is likely to be an underlying mechanism responsible for the observed bacteriostatic action of this agent.[18,20,21] In Gram-negative enteric bacteria, tigecycline is first thought to enter the cell via the OmpF and OmpC outer membrane porins, most probably as positively charged cation-tigecycline complexes. Subsequently, the complex dissociates yielding free tigecycline, which diffuses through the inner cytoplasmic membrane. It is also assumed that the unbound lipophilic tigecycline molecules cross the cytoplasmic membrane of Gram-positive bacteria. Intracellularly, tigecycline is thought to chelate with Mg^{2+}, forming the active Mg-tigecycline complex that actively binds to the ribosome. A more complete physicochemical description of this process is given in a recent review.[22]

Current evidence suggests that glycylcyclines inhibit not only wild-type ribosomes but also *tetM*-protected and other tetracycline-resistant ribosomes.[12,16,23] Glycylcyclines bind strongly to the ribosome and this enhanced binding is thought to be responsible for the ability of tigecycline to overcome the ribosomal protection mechanism expressed by tetracycline-resistant organisms.[12,16,18]

2. Tigecycline and Antimicrobial Resistance

Recent surveillance initiatives point to an increased prevalence of resistance to antimicrobials, with a specific emphasis on the increase in reports of

MRSA.[1,24,25] Over a recent 4-year period, MRSA rates increased in Europe (23–34%), the US (26–36%) and the Asia-Pacific region (49–54%). Furthermore, methicillin resistance among staphylococci has been associated with higher rates of co-resistance to fluoroquinolones, macrolides and, to a lesser extent, clindamycin, with the majority of MRSA isolates exhibiting resistance to three or more antimicrobial classes.[1,11] The emergence of community-acquired MRSA strains with distinct phenotypes to the more established nosocomial strains has also been observed.[26]

Tigecycline activity against staphylococci is completely unaltered by the presence of methicillin or glycopeptide resistance genes, and remains fully effective against enterococci expressing one or more vancomycin resistance determinants.[11,12,14] Among Gram-negatives, tigecycline activity is only marginally affected by the presence of extended-spectrum β-lactamases (ESBLs) or AmpC-producing strains and, for the latter, remains one of the most potent agents tested.[11,27] Since genes encoding both ESBLs and plasmid-mediated AmpC β-lactamases are usually located on large multidrug resistance plasmids, tigecycline activity against such strains may be of clinical significance.[27] However, the activity of tigecycline against *Pseudomonas aeruginosa* is modest at best.

Tigecycline is active against *tetM*-resistant organisms. It is thought the product of the *tetM* gene is either unable to disrupt the tight glycylcycline-ribosomal bond or is unable to interact with the ribosome to allow protein synthesis to occur.[16,18,25] Bacteria displaying efflux-mediated resistance are also susceptible to tigecycline. This enhanced activity results either from the inability of tigecycline to induce efflux proteins or simply because the efflux pump is ineffective in transporting glycylcyclines out of the cell.[18,23]

It should be noted that neither laboratory-derived nor naturally occurring tigecycline-resistant isolates have been observed to date with >1600 patient exposures from completed and ongoing phase III clinical trials. However, recent work has shown that the presence of the *AcrAB* multidrug efflux pump found in *P. mirabilis* reduces the susceptibility of these organisms to tigecycline, with minimum inhibitory concentrations (MICs) of 4 μg/mL typically observed.[28]

3. Microbiological Activity

The *in vitro* potency of tigecycline as assessed by current National Committee for Clinical Laboratory Standards (NCCLS) methodologies is shown in tables I, II and III.[29,30] Overall, tigecycline is a broad-spectrum antimicrobial agent with high potency against a range of clinically important Gram-negative and -positive pathogens with particularly notable potency against both susceptible and resistant strains of staphylococci, enterococci and streptococci. It has been reported that tigecycline may be sensitive to oxidative degradation when the NCCLS broth microdilution MIC assay is performed as a result of higher levels of dissolved oxygen in stored broth media.[11]

Consequently, published tigecycline MIC values may actually be elevated relative to MICs determined using freshly prepared media. Proposed tigecycline breakpoints are ≤2 (susceptible), 4 (intermediate) and ≥8 μg/mL (resistant).

3.1 Gram-Negative Bacilli

The potency of tigecycline against Gram-negative clinical isolates is shown in table I,[31-36] where tigecycline MIC_{90} values were in the range of 0.25–2 μg/mL. Tigecycline displayed equivalent potency to imipenem against *Escherichia coli*, but both agents were 4-fold less potent than ceftriaxone or levofloxacin. Minocycline was moderately active against *E. coli*.

Both *E. aerogenes* and *E. cloacae* were susceptible to tigecycline (MIC_{90} of 0.5 and 1.0 μg/mL, respectively) and, with the exception of levofloxacin, tigecycline displayed the highest potency against both *Enterobacter* spp. with 4- to 128-fold greater *in vitro* activity than minocycline, ceftriaxone or imipenem.

Tigecycline, ceftriaxone, imipenem and levofloxacin had comparable MIC_{90} values against *Citrobacter koseri* (range 0.12–0.5 μg/mL) and

Table I. *In vitro* activities of tigecycline[a] and comparator agents against Gram-negative clinical isolates[b]

Organism (no. of isolates tested)	Antibacterial	MIC (μg/mL)		
		range	50%	90%
Escherichia coli (100)	Tigecycline	0.06–0.5	0.12	0.25
	Ceftriaxone	≤0.06–>128	≤0.06	≤0.06
	Imipenem	≤0.06–1	0.12	0.25
	Levofloxacin	≤0.06–16	≤0.06	≤0.06
	Minocycline	0.12–32	0.5	8
Enterobacter aerogenes (100)	Tigecycline	0.03–2	0.25	0.5
	Ceftriaxone	≤0.06–>128	0.12	32
	Imipenem	0.12–2	1	2
	Levofloxacin	≤0.06–16	≤0.06	≤0.06
	Minocycline	≤0.06–16	1	2
E. cloacae (100)	Tigecycline	0.25–2	0.5	1
	Ceftriaxone	≤0.06–>128	0.5	128
	Imipenem	0.12–2	1	1
	Levofloxacin	≤0.06–1	≤0.06	0.12
	Minocycline	1–32	2	4
Citrobacter koseri (54)	Tigecycline	0.12–2	0.25	0.5
	Ceftriaxone	≤0.06–>128	≤0.06	0.5
	Imipenem	≤0.06–0.5	0.12	0.25
	Levofloxacin	≤0.06–4	≤0.06	0.12
	Minocycline	0.5–32	1	4
C. freundii (100)	Tigecycline	0.03–1	0.25	0.5
	Ceftriaxone	≤0.06–>128	32	128
	Imipenem	0.12–2	1	1
	Levofloxacin	≤0.06–32	≤0.06	1
	Minocycline	0.12–64	2	8
Klebsiella pneumoniae (100)	Tigecycline	0.25–4	0.5	0.5
	Ceftriaxone	≤0.06–128	≤0.06	0.12
	Imipenem	≤0.06–2	0.25	0.5
	Levofloxacin	≤0.06–16	≤0.06	0.25
	Minocycline	1–64	2	4
K. pneumoniae AmpC (29)	Tigecycline	0.5–2	1	2
	Ceftriaxone	8–>128	16	128
	Imipenem	0.5–64	1	32
	Levofloxacin	1–64	1	64
	Minocycline	2–32	4	16
K. pneumoniae ESBL (56)	Tigecycline	0.12–4	0.5	1
	Ceftriaxone	2–>128	16	64
	Imipenem	≤0.06–2	0.25	0.5
	Levofloxacin	≤0.06–8	0.12	1
	Minocycline	0.5–>64	2	16
K. oxytoca (101)	Tigecycline	0.12–1	0.25	0.25
	Ceftriaxone	≤0.06–>128	≤0.06	4
	Imipenem	0.12–4	0.25	0.5

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Table I. Contd

Organism (no. of isolates tested)	Antibacterial	MIC (μg/mL)		
		range	50%	90%
	Levofloxacin	≤0.06–4	≤0.06	≤0.06
	Minocycline	0.5–8	1	2
Serratia marcescens (100)	Tigecycline	0.25–8	1	1
	Ceftriaxone	≤0.06–16	0.25	1
	Imipenem	≤0.06–4	0.5	1
	Levofloxacin	≤0.06–12	≤0.06	0.25
	Minocycline	1–16	2	4
Acinetobacter baumannii (97)	Tigecycline	0.03–4	0.25	2
	Ceftriaxone	2–>128	32	>128
	Imipenem	≤0.06–32	0.25	32
	Levofloxacin	≤0.06–64	4	16
	Minocycline	≤0.06–16	0.12	8
Burkholderia cepacia (18)	Tigecycline	0.06–8	1	4
	Ceftriaxone	1–>128	16	>128
	Imipenem	≤0.06–>128	8	32
	Levofloxacin	≤0.06–8	1	2
	Minocycline	≤0.06–16	0.5	2
S. maltophilia (100)	Tigecycline	0.12–4	0.5	2
	Ceftriaxone	4–>128	>128	>128
	Imipenem	8–>128	>128	>128
	Levofloxacin	≤0.06–128	0.5	2
	Minocycline	≤0.06–2	0.12	0.5
Pseudomonas aeruginosa (100)	Tigecycline	0.25–32	8	16
	Ceftriaxone	4–>128	32	128
	Imipenem	0.25–64	1	16
	Levofloxacin	≤0.06–64	0.25	4
	Minocycline	0.25–64	8	32
Pasteurella multocida (30)	Tigecycline	≤0.015–0.12	0.03	0.12
	Ceftriaxone	≤0.06–0.12	≤0.06	≤0.06
	Imipenem	≤0.06–1	0.12	0.5
	Levofloxacin	≤0.06–0.15	≤0.06	≤0.06
	Minocycline	≤0.06–8	≤0.06	0.5
Haemophilus parainfluenzae (37)	Tigecycline	0.12–1	0.25	0.5
	Ceftriaxone	≤0.06–0.12	≤0.06	≤0.06
	Imipenem	≤0.06–2	1	2
	Levofloxacin	≤0.06	≤0.06	≤0.06
	Minocycline	1–4	2	4
H. influenzae (100)	Tigecycline	0.06–1	0.25	0.5
	Ceftriaxone	≤0.06–0.12	≤0.06	≤0.06
	Imipenem	≤0.06–4	1	2
	Levofloxacin	≤0.06–0.12	≤0.06	≤0.06
	Minocycline	0.25–16	1	2
Moraxella catarrhalis (27)	Tigecycline	0.03–0.06	0.03	0.06

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Table I. Contd

Organism (no. of isolates tested)	Antibacterial	MIC (μg/mL)		
		range	50%	90%
	Ceftriaxone	≤0.06–1	≤0.06	0.5
	Imipenem	≤0.06–0.12	≤0.06	≤0.06
	Levofloxacin	≤0.06	≤0.06	≤0.06
	Minocycline	≤0.06	≤0.06	≤0.06

a *In vitro* antibacterial activity of tigecycline has been assessed against recent clinical isolates of listed pathogens collected from North American and European medical institutions as part of the ongoing T.E.S.T. initiative. The T.E.S.T. programme is a 3-year global surveillance initiative sponsored by Wyeth Pharmaceuticals being conducted at 690 hospitals in approximately 35 countries. T.E.S.T. data have been gathered by the Jones Group, BSAC, etc., and have been presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID).[31-36]

b MICs for tigecycline were determined by broth microdilution according to National Committee for Clinical Laboratory Standards methodology using freshly prepared media to avoid oxidative degradation.[29]

ESBL = extended-spectrum β-lactamase; **MIC** = minimum inhibitory concentration; **T.E.S.T.** = Tigecycline Evaluation Surveillance Trial.

these agents were 8- to 32-fold more active than minocycline. Against *C. freundii*, tigecycline (MIC_{90} 0.5 μg/mL) had similar potency to imipenem and levofloxacin, but was ≥16-fold more potent than minocycline and ceftriaxone.

Ceftriaxone, levofloxacin, imipenem and tigecycline had comparable activities against *Klebsiella pneumoniae* (MIC_{90} range 0.12–0.5 μg/mL). However, for AmpC-producing strains of *K. pneumoniae*, tigecycline was 8- to 64-fold more active than all other antimicrobials tested in this study. Isolates of *K. pneumoniae* expressing ESBL were all susceptible to imipenem (MIC_{90} 0.5 μg/mL), with similar potencies observed for tigecycline (MIC_{90} 1.0 μg/mL) and levofloxacin (MIC_{90} 1.0 μg/mL). Tigecycline was one of the more effective agents against *K. oxytoca* (MIC_{90} 0.25 μg/mL). Tigecycline, ceftriaxone and imipenem exhibited identical MIC_{90} values against *Serratia marcescens* (MIC_{90} 1.0 μg/mL) and were 4-fold more potent than minocycline, but 4-fold less potent than levofloxacin.

MIC_{90} values for all agents versus non-fermentative Gram-negative species (*Acinetobacter baumannii*, *Burkholderia cepacia*, *S. maltophilia* and *P. aeruginosa*) were generally ≥2 μg/mL. Tigecycline was the most active compound tested against *A. baumannii* (2 μg/mL), being 4-fold more potent than minocycline and ≥8-fold more active than all other comparators. Tigecycline, minocycline and levofloxacin were the most effective agents against *B. cepacia* and *S. maltophilia*, with tigecycline, levofloxacin and imipenem displaying modest but higher activities against *P. aeruginosa* than minocycline or ceftriaxone.

Against fastidious Gram-negative organisms (*Pasteurella multocida*, *Haemophilus parainfluenzae*, *H. influenzae* and *Moraxella catarrhalis*) tigecycline MIC_{90} values ranged from 0.06 to 0.5 μg/mL, and this *in vitro* activity was, in general, comparable with the potencies observed for ceftriaxone, imipenem, levofloxacin and minocycline.

Data for tigecycline have been collected for recent clinical isolates of *Morganella morganii*, *Proteus vulgaris*, *P. mirabilis*, *Providentia rettgeri* and *P. stuartii* obtained from medical institutions in the US and Europe.[14,38] Tigecycline exhibited moderate potency against these organisms with MIC_{90} values of 4–8 μg/mL.

3.2 Gram-Positive Cocci

Table II summarises the activity of tigecycline against Gram-positive clinical isolates.[31-36] The *in vitro* microbiological efficacy of tigecycline against MSSA (MIC_{90} 0.25 μg/mL) is similar to the activities observed with levofloxacin and minocycline (MIC_{90} values of 0.5 and 0.12 μg/mL, respectively), but 4-fold lower than the activity of imipenem (MIC_{90} ≤0.06 μg/mL). Vancomycin was the least active agent with an MIC_{90} of 1 μg/mL. Against

Table II. *In vitro* activities of tigecycline[a] and comparator agents tested against Gram-positive clinical isolates[b]

Organism (no. of isolates tested)	Antibacterial	MIC (μg/mL)		
		range	50%	90%
MRSA (100)	Tigecycline	0.06–0.5	0.12	0.25
	Levofloxacin	0.12–>128	8	32
	Minocycline	≤0.06–16	0.12	4
	Vancomycin	0.5–2	1	1
MSSA (100)	Tigecycline	0.06–0.25	0.12	0.25
	Imipenem	≤0.06	≤0.06	≤0.06
	Levofloxacin	≤0.06–16	0.12	0.5
	Minocycline	≤0.06–8	0.12	0.12
	Vancomycin	0.5–1	0.5	1
MSSE (54)	Tigecycline	0.03–0.5	0.12	0.25
	Imipenem	≤0.06	≤0.06	≤0.06
	Levofloxacin	0.12–8	0.12	4
	Minocycline	≤0.06–0.5	0.12	0.25
	Vancomycin	0.5–2	1	2
MRSE (94)	Tigecycline	0.06–0.5	0.12	0.5
	Levofloxacin	≤0.06–>128	4	16
	Minocycline	≤0.06–0.5	0.12	0.5
	Vancomycin	1–2	1	2
Community-acquired MRSA (10)	Tigecycline	0.12–0.25	0.12	0.25
	Imipenem	0.12–32	0.25	1
	Levofloxacin	0.12–0.25	0.12	0.12
	Minocycline	0.12	0.12	0.12
	Vancomycin	0.5–2	1	1
GISA MRSA (19)	Tigecycline	0.0.06–1	0.12	0.25
	Levofloxacin	0.25–32	8	32
	Minocycline	≤0.06–16	≤0.06	0.5
	Vancomycin	1–8	4	8
Staphylococcus haemolyticus (74)	Tigecycline	0.03–1	0.25	0.5
	Imipenem	≤0.06–128	16	128
	Levofloxacin	≤0.06–32	0.12	32
	Minocycline	≤0.06–2	0.25	0.5
	Vancomycin	0.25–16	2	2
Vancomycin-resistant *Enterococcus faecalis* (12)	Tigecycline	≤0.015–0.06	0.03	0.06
	Imipenem	0.5–128	1	128
	Levofloxacin	0.5–64	1	64
	Minocycline	≤0.06–16	≤0.06	16
	Vancomycin	>64	>64	>64
Vancomycin-susceptible *E. faecalis* (100)	Tigecycline	0.03–0.12	0.06	0.12
	Imipenem	≤0.06–4	1	2
	Levofloxacin	10.5–64	1	32
	Minocycline	≤0.06–16	4	16
	Vancomycin	0.25–4	1	2
Vancomycin-resistant *E. faecium* (95)	Tigecycline	≤0.015–0.12	0.03	0.06

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Table II. Contd

Organism (no. of isolates tested)	Antibacterial	MIC (μg/mL)		
		range	50%	90%
	Imipenem	≤0.06–>128	>128	>128
	Levofloxacin	0.5–128	16	64
	Minocycline	≤0.06–16	2	8
	Vancomycin	>64	>64	>64
Vancomycin-susceptible *E. faecium* (51)	Tigecycline	0.03–0.12	0.03	0.06
	Imipenem	0.12–128	4	128
	Levofloxacin	0.12–128	1	32
	Minocycline	≤0.06–16	≤0.06	16
	Vancomycin	0.25–4	1	2
Penicillin-susceptible *Streptococcus pneumoniae* (100)	Tigecycline	≤0.004–0.06	0.015	0.03
	Imipenem	≤0.06–0.12	≤0.06	≤0.06
	Levofloxacin	0.25–4	0.5	1
	Minocycline	≤0.06–8	≤0.06	≤0.06
	Vancomycin	0.12–0.5	0.25	0.25
Penicillin-resistant *S. pneumoniae* (14)	Tigecycline	0.008–0.015	0.015	0.015
	Imipenem	≤0.06–0.5	0.12	0.25
	Levofloxacin	0.5–1	0.5	0.5
	Minocycline	≤0.06–16	0.12	2
	Vancomycin	0.12–0.25	0.12	0.25
S. pyogenes (56)	Tigecycline	0.015–0.06	0.015	0.03
	Imipenem	≤0.06	≤0.06	≤0.06
	Levofloxacin	0.25–1	0.5	0.5
	Minocycline	≤0.06–8	≤0.06	4
	Vancomycin	0.25–2	0.25	0.25
S. agalactiae (55)	Tigecycline	0.015–0.06	0.03	0.03
	Imipenem	≤0.06	≤0.06	≤0.06
	Levofloxacin	0.25–1	0.5	0.5
	Minocycline	≤0.06–16	8	16
	Vancomycin	0.212–0.5	0.25	0.5

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b MICs for tigecycline were determined by broth microdilution according to National Committee for Clinical Laboratory Standards methodology using freshly prepared media to avoid oxidative degradation.[29]

GISA = glycopeptide-intermediately resistant *Staphylococcus aureus*; **MIC** = minimum inhibitory concentration; **MRSA** = methicillin-resistant *S. aureus*; **MRSE** = methicillin-resistant *S. epidermidis*; **MSSA** = methicillin-susceptible *S. aureus*; **MSSE** = methicillin-susceptible *S. epidermidis*; **T.E.S.T.** = Tigecycline Evaluation Surveillance Trial.

methicillin-resistant strains of *S. aureus*, the *in vitro* efficacy of tigecycline remains unaffected (MIC_{90} 0.25 μg/mL) as does the activity of vancomycin (MIC_{90} 1 μg/mL), while the potency of imipenem, levofloxacin and minocycline was decreased by ≥32-fold. Tigecycline also retains activity against GISA strains and was the most potent antimicrobial agent tested against this pathogen.

A recent Spanish study assessed the microbiological effectiveness of tigecycline in comparison with linezolid, moxifloxacin and quinupristin/dalfopristin against clinical isolates of *Staphylococcus* spp.,

Table III. *In vitro* activities of tigecycline and comparator agents tested against anaerobes (data adapted from Mikels et al.[37])

Organism (no. of isolates tested)	Antibacterial	MIC (μg/mL)		
		range	50%	90%
Bacteroides fragilis group (400)	Tigecycline	≤0.01–>16	1	8
	Metronidazole	≤0.06–8	1	2
	Chloramphenicol	0.125–8	4	8
	Imipenem	≤0.06–128	0.25	2
	Piperacillin/tazobactam	≤0.06–>256	1	16
B. fragilis (272)	Tigecycline	≤0.01–>16	1	8
	Metronidazole	≤0.06–8	1	2
	Chloramphenicol	0.125–8	4	8
	Imipenem	≤0.06–128	0.25	1
	Piperacillin/tazobactam	≤0.06–>256	1	4
B. thetaiotaomicron (40)	Tigecycline	≤0.01–16	1	8
	Metronidazole	0.5–2	1	2
	Chloramphenicol	0.125–8	4	8
	Imipenem	≤0.06–32	0.5	2
	Piperacillin/tazobactam	≤0.5–>256	8	32
B. ovatus (40)	Tigecycline	0.125–>16	2	16
	Metronidazole	0.5–4	2	4
	Chloramphenicol	2–8	4	8
	Imipenem	0.125–2	0.5	2
	Piperacillin/tazobactam	1–32	8	16
B. uniformis (27)	Tigecycline	≤0.06–>16	2	8
	Metronidazole	0.5–4	2	4
	Chloramphenicol	2–8	4	8
	Imipenem	≤0.06–4	0.25	1
	Piperacillin/tazobactam	0.125–32	8	32

MIC = minimum inhibitory concentration.

principally *S. aureus* and coagulase-negative staphylococci.[39] Quinupristin/dalfopristin and tigecycline were the most potent agents tested with MIC_{90} values of 0.12 and 0.5 μg/mL for oxacillin-susceptible *S. aureus* and 0.12 and 0.25 μg/mL for coagulase-negative staphylococci, respectively. Against oxacillin-resistant isolates, MIC_{90} values for both agents remained the same or increased by a single tube dilution. Data from an earlier Spanish study compared the potency of tigecycline with that of comparator agents against 1087 recent clinical isolates from 12 Spanish medical centres.[40] Tigecycline MIC_{90} values ranged from 0.125 to 0.5 μg/mL for Gram-positives, from 0.5 to 16 μg/mL for Gram-negatives, including *Acinetobacter* spp. and *S. maltophilia* for which tigecycline was among the most potent agent, and from 0.125 to 8 μg/mL for anaerobes.

Against enterococci, MIC_{90} values for tigecycline range from 0.06 to 0.12 μg/mL and were unaffected by the presence of resistance determinants. Tigecycline displayed the most potent activity of all the tested antibacterials against both susceptible and resistant strains of *E. faecalis* and *E. faecium*. Tigecycline was ≥16-fold more active than vancomycin, imipenem, minocycline and levofloxacin against vancomycin-susceptible *E. faecalis* and was ≥16-fold more potent than vancomycin, minocycline and levofloxacin against vancomycin-susceptible *E. faecium*. Imipenem was ineffective against vancomycin-susceptible strains of *E. faecium*.

All tested antimicrobials displayed activity against penicillin-susceptible *S. pneumoniae*, with MIC_{90} values ranging from 0.03 to 0.25 μg/mL. The rank order of potency was tigecycline > imipenem,

minocycline > vancomycin > levofloxacin. Against penicillin-resistant isolates tigecycline had an MIC_{90} of 0.015 μg/mL and was ≥16-fold more active than all other antibacterials tested.

In comparison with tetracyclines, tigecycline demonstrated broad-spectrum activity against Gram-positive cocci and Enterobacteriaceae, including those resistant to tetracycline and minocycline.

Agents such as tigecycline that incorporate stability to MRSA, vancomycin-resistant enterococci (VRE) and the commonly occurring tetracycline resistance mechanisms should be a valuable addition to the clinician's empirical armamentarium.

3.3 Anaerobes

Recent *in vitro* data confirm the potency of tigecycline against *Nocardia* spp.[41] A tigecycline MIC_{90} value of 4 μg/mL against a group of *Nocardia* spp., including *N. asteroides*, *N. farcinia*, *N. otitidis-cavarium* and *N. nova*, was comparable with MIC_{90} values observed for linezolid, imipenem, meropenem and ertapenem of 1, 2, 8 and 32 μg/mL, respectively.

In table III the potency of tigecycline against *Bacteroides* spp. is compared with various antimicrobials. Although tigecycline MIC_{90} values of 8–16 μg/mL were comparable with those of chloramphenicol and are 2- to 4-fold better than piperacillin/tazobactam, the potency of tigecycline against *Bacteroides* spp. would be considered marginal. MIC_{90} values for imipenem and metronidazole ranged from 4- to 8-fold lower than corresponding values for tigecycline.[42,43]

Published data on the potency of tigecycline against *Clostridium difficile* and *C. perfringens* revealed MIC_{90} values of 0.12 and 0.25 μg/mL, respectively.[10,14,40]

4. Pharmacokinetic and Pharmacodynamic Properties

The pharmacokinetic properties of tigecycline in healthy volunteers and in patients with renal disease, intra-abdominal or skin and skin structure infections are summarised in table IV. Data on morbidly obese individuals or patients with liver disease have not been assessed. Both maximum serum concentration (C_{max}) and area under the plasma concentration-time curve (AUC) vary proportionately with dose, and the pharmacokinetics are minimally affected by the presence of food or diminished renal capacity. At all dosages >25mg, tigecycline has a large volume of distribution (>6.4 L/kg) relative to values for single oral or intravenous doses of tetracycline, doxycycline or minocycline (range of 0.14–1.6 L/kg).[44] *In vitro* protein binding of tigecycline measured by ultrafiltration ranged from 71% at 0.1 μg/mL to 87% at 1 μg/mL. Using ultracentrifugation techniques, protein binding values of 73% and 79% were observed at tigecycline concentrations of 0.1 and 1 μg/mL.[45] Concomitant multiple-dose administration of tigecycline and digoxin in healthy male volunteers revealed no drug interactions as measured by standard pharmacokinetic parameters.[46]

Radiolabeled experiments in rats have shown that elimination of tigecycline was slower from tissues than from plasma yielding high tissue to plasma ratios, particularly in bone, bone marrow, thyroid, spleen and liver.[54] A bronchoalveolar lavage study showed high tigecycline concentrations in alveolar cells (77.5-fold higher than serum) and epithelial lining fluid (32% higher than serum).[55] Tigecycline has a half-life of 36 hours, which is longer than that of tetracycline (10 hours), doxycycline (12–22 hours) and minocycline (11–26 hours). The major pathway of tigecycline excretion in humans appears to be be biliary excretion.[45] No major metabolites have been found to date. Less than 15% of tigecycline is excreted unchanged in the urine.

Two recent studies have investigated the pharmacodynamic properties of tigecycline.[7,56] Using a neutropenic murine thigh infection model, the activity of tigecycline was evaluated against *S. pneumoniae*, *S. aureus*, *E. coli* and *K. pneumoniae*.[7] All isolates were susceptible to tigecycline with MIC values ranging from 0.06 to 0.5 μg/mL and minimum bactericidal concentrations typically 1–2 dilutions higher than the MIC. The data revealed nonlinear pharmacokinetics that differed from the linear pharmacokinetics observed in humans.[47] The re-

Table IV. Pharmacokinetic properties of intravenous tigecycline administered as single dose (SD) or multiple doses (MD) to healthy volunteers or to patients with renal disease, or intra-abdominal or skin and skin structure infections[45,47-50]

Tigecycline dose (mg)[a]	C_{max} (ng/mL)	AUC (ng • h/mL)	$t_{1/2}$ (h)	CL (L/h/kg)	Vd (L/kg)
12.5 SD	109 (10)[b]	753 (68)	11 (84)	0.29 (67)	2.8 (34)
25 SD	252 (25)	2 255 (45)	32 (64)	0.20 (50)	6.4 (20)
50 SD	383 (17)	2 558 (21)	18 (21)	0.28 (14)	6.4 (31)
75 SD	566 (14)	3 658 (27)	21 (25)	0.29 (16)	7.5 (10)
100 SD	911 (29)	6 396 (10)	38 (14)	0.20 (13)	8.6 (18)
200 SD	1643 (18)	12 426 (23)	42 (28)	0.25 (22)	11 (25)
200 SD fed	1528 (22)	11 719 (19)	54 (28)	0.22 (12)	13 (18)
300 SD fed	2817 (17)	17 856 (10)	46 (13)	0.25 (11)	12 (20)
25 MD	324 (17)	1 482 (18)	49.3 (72)	0.20 (17)	8.6 (23)
50 MD	621 (15)	3 069 (12)	36.9 (32)	0.20 (9)	7.2 (7)
100 MD	1173 (15)	4 980 (19)	66.5 (34)	0.24 (20)	9.1 (32)
100 SD renal impaired[c]	961	4 041	NA	NA	NA
25 SD q12h 7–14d[d]	265 (78)	1 430 (47)	NA	0.25 (46)	NA
50 SD q12h 7–14d[d]	403 (45)	2 240 (40)	NA	0.31 (40)	NA
100 LD + 50 q12h 4–14d[e]	633.4	2 185	NA	0.22 (28)	NA
100 LD + 50 q12h 5–14d[e]	483 (42)	2 880 (31)	NA	0.24 (34)	NA

a All doses administered to fasting individuals unless otherwise indicated.

b Percentage coefficient of variation.

c Creatinine CL <30 mL/min.

d Data from patients with skin and skin structure infections.[51,52]

e Data from patients with intra-abdominal infections.[53]

AUC = area under the plasma concentration-time curve; **CL** = clearance; **C_{max}** = maximum serum concentration; **LD** = loading dose; **NA** = not applicable; **q12h** = every 12 hours; **$t_{1/2}$** = serum half-life; **Vd** = volume of distribution.

sults also suggested that tigecycline activity was dependent on the time above MIC, and the concentration should be maintained above the MIC for at least 50% of the dose interval for optimal activity. The AUC/MIC was also important in predicting activity. Using a 3 mg/kg dose, tigecycline demonstrated a postantibiotic effect (PAE) of 8.9 hours against *S. pneumoniae* and 4.9 hours against *E. coli*.

In a second study,[56] the effect of different dosing regimens was evaluated for efficacy against a clinical *vanA* strain of *E. faecium* HB217, which had a tigecycline MIC of 0.06 μg/mL. Rabbits with aortic valve endocarditis received intravenous doses of tigecycline of 14 mg/kg twice daily, 14 mg/kg once daily or 7 mg/kg once daily for 5 days. Serum concentrations were maintained at all times above the MIC with twice daily dosing and below the MIC for 50% of the time with either of the two once-daily regimens. Reductions in bacterial counts of 3.7 ± 0.9 $\log_{10}$ colony forming units (cfu)/g of vegetation were noted for the twice-daily regimen versus 3.2 ± 1.2 and 3.1 ± 1.0 $\log_{10}$ cfu/g reductions for the 14 and 7 mg/kg once-daily regimens, respectively. No difference in effectiveness was noted between the regimen that maintained serum concentrations above the MIC at all times and the regimens where the serum concentration fell below the MIC for 50% of the time.

5. Efficacy in Animal Models

The efficacy of tigecycline has been evaluated in several animal models of infection. The results from these studies have been summarised in a recent comprehensive review.[44]

One guinea pig and two murine pneumonia/lung infection models evaluated the efficacy of tigecycline and comparator agents in the eradication of *L. pneumophila*,[57] *P. aeruginosa*[37] or penicillin-susceptible and penicillin-resistant strains of *S. pneumoniae*.[58] In the guinea pig Legionnaire's disease model, tigecycline administered as a single

subcutaneous dose of 7.5 mg/kg had similar activity to erythromycin and azithromycin, as assessed by end of therapy bacterial loads (cfu/g), and survival rates were comparable across all treatment groups.

In the first murine pneumonia model, tigecycline, piperacillin and gentamicin, either alone or in combination, were evaluated for activity against infection by *P. aeruginosa*. Efficacy was assessed by measuring $\log_{10}$ reductions in bacterial counts relative to control animals. The results of this study indicated that tigecycline demonstrated excellent activity with mean change from control ($\log_{10}$ cfu) ranging from −1.02 to −3.75 $\log_{10}$ cfu over a dosing range of 0.5–50 mg/kg/day against *P. aeruginosa* in the murine model. Given the marginal *in vitro* potency of tigecycline against *P. aeruginosa*, the observed *in vivo* efficacy may result from more extensive tissue concentrations of tigecycline relative to measured plasma concentrations.[54] Furthermore, while glycylcyclines are subject to efflux from *P. aeruginosa*, they are generally inferior substrates to pseudomonal efflux pumps than doxycycline or minocycline.[59] Tigecycline activity was comparable with the activities of gentamicin and piperacillin, and an additive effect was observed with tigecycline and gentamicin when administered together either once or twice daily. A similar additive effect was seen with tigecycline/piperacillin combinations when administered twice daily, but not for the once-daily regimen.

In the second murine pneumonia model, the therapeutic efficacy of tigecycline was compared with that of vancomycin, amoxicillin and minocycline against both penicillin-susceptible and -resistant strains of *S. pneumoniae*. Against susceptible strains the concentration of antimicrobial (mg/kg) required to prevent death in 50% of the test population was 0.4 for tigecycline, 0.5 for amoxicillin, 1.9 for vancomycin and 3.3 for minocycline. In pneumococcal infection caused by penicillin-resistant *S. pneumoniae*, tigecycline retained high activity at both single and twice-daily dosing (0.5 and 0.2 mg/kg, respectively). Tigecycline was effective at much lower concentrations than vancomycin (1.8 and 1.6 mg/kg for the single and twice-daily dose administration, respectively) and amoxicillin (13.1 and 2.8 mg/kg for the single and twice-daily dosing regimens, respectively).

Two rabbit studies and one rat endocarditis model assessed the efficacy of tigecycline in the treatment of infection caused by *E. faecalis*, *E. faecium* or MRSA. The first rabbit endocarditis study in which animals were inoculated with a *vanA* strain of *E. faecium* has been described in section 4.[56] Infection in the second rabbit study was induced by *E. faecalis* or *E. faecium*.[60] High activity, as measured by colony count reductions, was seen for a 5-day tigecycline regimen at a dosage of 14 mg/kg. Tigecycline was also homogeneously distributed within cardiac vegetations. In the rat endocarditis model, animals were inoculated with either *E. faecalis* or MRSA and the efficacy of tigecycline at dosages of 0.5–80 mg/kg/day were compared with the activity of vancomycin administered at 40–240 mg/kg/day.[61] Overall, tigecycline at dosages of ≥14 mg/kg/day was more effective than vancomycin at any concentration in reducing bacterial cardiac tissue loads for all three strains of *E. faecalis* tested. For vancomycin-susceptible *E. faecalis*, tigecycline treatment resulted in an average $\log_{10}$ decrease of >2 cfu/heart relative to controls at 24 hours compared with <1.5 cfu/heart for vancomycin relative to 24-hour controls. Against vancomycin-resistant *E. faecalis* (*vanA*), tigecycline therapy at 14 mg/kg/day elicited 24-hour reductions from controls of 2.68 cfu/heart, while vancomycin at 240 mg/kg/day was ineffective against this strain. Tigecycline therapy of 2, 7 and 14 mg/kg/day against *E. faecalis* (*vanB*)-induced endocarditis resulted in 2.8, 3.7 and 4.7 $\log_{10}$ cfu/heart 24-hour reductions, respectively. Against MRSA, tigecycline doses of 14 mg/kg/day were significantly better than vancomycin at 40 mg/kg/day in reducing bacterial load with observed reductions of 4.5 and 0.69 $\log_{10}$ cfu/heart, respectively.

Two murine neutropenic thigh infection model studies have been reported. The first study, in which infection was initiated with *E. coli*, *K. pneumoniae*, *S. pneumoniae* or *S. aureus*, has been described in section 4.[7] In the second study, tigecycline again

demonstrated high efficacy against both penicillin-susceptible and -resistant strains of *S. pneumoniae*, with bacteriostatic doses of 5.2 and <1 mg/kg, respectively.[58] Potent tigecycline activity was also noted in the treatment of infection caused by vancomycin-resistant *E. faecalis* and *E. faecium* (static doses of <1 and 11 mg/kg, respectively), and good activity was seen against methicillin-susceptible and methicillin-resistant strains of *S. aureus* (16 and 23 mg/kg, respectively). Finally, a broader range of therapeutic efficacy was observed for tigecycline against *E. coli* and *K. pneumoniae* infections (12–76 mg/kg).

The *in vivo* efficacy of tigecycline has also been compared with tetracycline, minocycline, ampicillin, vancomycin and quinupristin/dalfopristin in a murine peritonitis model.[62] Infection was induced using strains of *E. faecalis* or *E. faecium* in which resistance mechanisms (*vanA*, *vanB*, *ermB* or tetR) could be present. Tigecycline activity was superior to both tetracycline and minocycline, and retained high activity against all strains including those with tetracycline or vancomycin resistance determinants.

6. Clinical Trials

Data from tigecycline clinical trials are summarised in table V. Phase I studies of tigecycline have examined the pharmacokinetics, safety and tolerability in healthy male volunteers,[47] the impact of age and sex of healthy volunteers on tigecycline pharmacokinetic parameters,[48] and the effects of renal disease on the pharmacokinetic profile of tigecycline.[49]

In the first study[47] tigecycline was administered to eight volunteers as both a 1-hour infusion of different doses (12.5, 25, 50, 75, 100, 200 and 300mg) and as a 4-hour infusion (200 and 300mg). Groups taking the higher 200 and 300mg doses received the drug under both fed and fasted conditions. Results from this study suggested that tigecycline was well tolerated over the dose range examined. Common adverse effects of nausea, vomiting and headache were somewhat relieved by food, but not by longer infusion times. Tigecycline pharmacokinetics were unaffected by food, and the measured C_{max} and AUC values appeared to be dose proportional, varying respectively from 0.11 μg/mL and 0.9 μg • h/mL for the 12.5mg dose to 2.8 μg/mL and 17.9 μg • h/mL, respectively, for the 300mg dose. Tigecycline exhibited a half-life of 36 hours and was extensively distributed into the tissues with a volume of distribution at steady state >10 L/kg.

In an open-label, single 100mg dose study, tigecycline was administered as a 1-hour infusion to healthy male and female volunteers classified into three age groups (18–50 years, 65–75 years and >75 years).[48] The results of this study showed that tigecycline was well tolerated in both sexes and by all age groups, with nausea, vomiting and headache reported as the principal adverse events. The mean C_{max} values for both sexes ranged from 0.85 to 1 μg/mL. AUC values were lowest in males <50 years (4.2 μg • h/mL) and highest in males >75 years (5.8 μg • h/mL). The AUC was approximately 5 μg • h/mL for all three female groups. Tigecycline was extensively distributed in tissues, and the pharmacokinetics following a single 100mg dose appeared unaffected by sex or age in this population.

A recent phase I study evaluated the impact of severe and end-stage renal disease (ESRD) on tigecycline pharmacokinetics, and the effect of haemodialysis on tigecycline clearance.[49] Six healthy volunteers, six renally impaired patients (creatinine clearance <30 mL/min) and eight patients with ESRD received 100mg of tigecycline by infusion over 1 hour. Half of the ESRD patients were given tigecycline 2 hours before haemodialysis, while the remaining four patients received the tigecycline dose after haemodialysis. The mean C_{max} in ESRD patients post-infusion was 961 versus 604 ng/mL for healthy volunteers. However, AUC values were not dramatically different between ESRD patients and healthy volunteers with observed values of 4041 and 3330 ng • h/mL, respectively. Renally impaired patients had similar mean C_{max} values to healthy volunteers but higher mean AUC values (4758 ng • h/mL). No appreciable level of tigecycline was recovered in the dialysate fluid, and no difference in pharmacokinetics was observed when tigecycline was administered to ESRD pa-

Table V. Summary of tigecycline (T) clinical trials

Study	Dose	Clinical indication (volunteers/patients)	Duration of treatment	Clinical cure	Microbiological cure	Common adverse events
Phase I						
Muralidharan et al.[47]	12.5, 25, 50, 100, 200 and 300mg	Healthy male volunteers	1 or 4h	NA	NA	Nausea: 48.5%[a] Vomiting: 29.4%[a]
Muralidharan et al.[48]	100mg	Effect of age and sex	1h	NA	NA	
Troy et al.[49]	100mg	Effect of renal disease	1h	NA	NA	
Phase II						
Postier et al.[51]	T: 25mg[b] q12h	Skin and skin structure infections	7–14d	T: 37/55 (67%) [95% CI 53.5, 79.3][c]	T: 25/45 (56%) [95% CI 40.0, 70.4][d]	Nausea: 22% T Vomiting: 13% T
	T: 50mg[e] q12h			T: 40/54 (74%) [95% CI 60.3, 85.0][c]	T: 32/46 (69%) [95% CI 54.2, 82.3][d]	Nausea: 28% T Vomiting: 15% T
Murray et al.[53]	T: 50mg[e] q12h	Intra-abdominal infections	5–14d	T: 44/66 (67%) [95% CI 54.0, 77.8][c]	T: 44/66 (66.7%) [95% CI 54.0, 77.8][d]	Nausea: 42.3% T Vomiting: 27.0% T
Phase III						
Dartois et al.[63]	T: 50mg[e] q12h V/A: 1g/2g q12h	Skin and skin structure infections	5–14d	T: 201/224 (90%) [95% CI 85.0, 93.4][c] V/A: 203/215 (94%) [95% CI 90.5, 97.1][c]	T: 109/165 (66%) [95% CI 58.3, 73.2][d] V/A: 112/148 (76%) [95% CI 67.9, 82.3][d]	Nausea: 25.2% T; 5.2% V/A Vomiting: 12.0% T; 2.2% V/A Rash: 1.1% T; 3.7% V/A Elevated AST: 1.5% T; 5.2% V/A Elevated ALT: 1.8% T; 6.7% V/A
Dartois et al.[64]	T: 50mg[e] q12h I/C: 500mg/500mg q6h	Intra-abdominal infections	5–14d	T: 279/322 (86.6%) [95% CI 82.4, 90.2][f] I/C: 270/319 (84.6%) [95% CI 80.2, 88.4][f]	T: 242/265 (91.3%) [95% CI 87.3, 94.4][d] I/C: 232/258 (89.9%) [95% CI 85.6, 93.3][d]	Nausea: 17.6% T; 13.3% I/C Vomiting: 12.6% T; 9.2% I/C

a Most common adverse events for all three phase I studies combined.

b Tigecycline 25mg preceded by a 50mg loading dose.

c Clinically evaluable population.

d Microbiologically evaluable population.

e Tigecycline 50mg preceded by a 100mg loading dose.

f Microbiologically modified intent-to-treat population.

A = aztreonam; **I/C** = imipenem/cilastatin; **NA** = not applicable; **qxh** = every *x* hours; **V** = vancomycin.

tients before or after haemodialysis. Tigecycline AUC and C_{max} values were slightly to moderately elevated in ESRD patients relative to healthy volunteers, but the higher exposure did not affect the safety and tolerability profile.

All phase I pharmacokinetic data covering doses ranging from 12.5 to 300mg as a single dose and 25 to 100mg twice-daily as multiple doses have been collected and analysed using noncompartmental methods and the results presented at a recent conference.[50] Overall, tigecycline demonstrated approximately linear pharmacokinetics across all dose ranges of the multiple-dose studies. Tigecycline had a long half-life and a large volume of distribution, and the pharmacokinetic parameters were unaffected by food, age or sex.

Data from two phase II clinical trials have also been reported.[51,53] In the most recent report, the efficacy and safety of tigecycline has been studied in hospitalised patients with complicated skin and skin structure infections.[51] Two doses of tigecycline (25mg with a loading dose of 50mg, and 50mg with a loading dose of 100mg) were administered intravenously every 12 hours for 7–14 days. A total of 164 patients were enrolled yielding an intent-to-treat (ITT) population of 160, of whom 79 were in the 25mg group and 81 in the 50mg group. The principal diagnoses were infected ulcer (35%) and major abscess (31%).

At the test-of-cure visit (7–21 days post-treatment) 67% of the 25mg group (95% CI 53.3, 79.3) and 74% of the 50mg group (95% CI 60.3, 85.0) were rated as cured. In microbiologically evaluable patients (45 and 46 patients in the 25 and 50mg groups, respectively) end-of-treatment eradication rates were 62% (95% CI 46.5, 76.2) in the 25mg group and 74% (95% CI 58.9, 85.7) in the 50mg group. *In vitro* susceptibility tests of baseline infecting pathogens including MRSA, MSSA, *S. pyogenes*, *E. coli*, *E. faecalis* and *E. faecium* yielded MIC_{90} values for both dosages ranging from 0.06 to 0.5 μg/mL. In the microbiologically evaluable patients, eradication rates for MRSA (2 of 4 [50%] and 1 of 4 [25%]), MSSA (13 of 19 [68%] and 14 of 20 [70%]), *S. pyogenes* (1 of 3 [33%] and 5 of 7 [71%]), *E. coli* (3 of 5 [60%] and 3 of 3 [100%]), *E. faecalis* (4 of 6 [67%] and 3 of 3 [100%]) and *E. faecium* (1 of 1 [100%] and not applicable) were observed for the 25 and 50mg dose of tigecycline, respectively. Tigecycline had an acceptable safety profile, with the most frequent treatment-associated adverse events being nausea, vomiting and diarrhoea.

Preliminary phase II data on the clinical efficacy of tigecycline in the treatment of complicated intra-abdominal infections in hospitalised patients has also been reported.[53] In a randomised open-label study, patients with intra-abdominal infections requiring surgical excision and drainage plus antimicrobial therapy were treated intravenously with an initial loading dose of tigecycline 100mg followed by a 50mg dose every 12 hours. Therapy was continued for a minimum of 5 days and did not exceed 14 days.

A total of 111 patients, 77 men and 34 women, ranging in age from 18 to 80 years old were enrolled, of whom 66 were clinically evaluable. Fifteen patients were lost to follow-up and were not included in the clinical efficacy analyses. Principal diagnoses included perforated and gangrenous appendicitis, complicated cholecystitis, perforated diverticulitis and peritonitis. Of the clinically evaluable population, cure rates at the test-of-cure and end of treatment were 67% (95% CI 54.0, 77.8) and 76% (95% CI 63.6, 85.5), respectively. Cure rates in the ITT group were 55% (61 of 111 patients; 95% CI 45.2, 64.4) at the test-of-cure visit and 72% (80 of 111 patients; 95% CI 62.8, 80.2) at the end of treatment assessment. Per-pathogen response rates at the test-of-cure visit were measured for *Bacteroides* spp. (49 of 63 [77.8%]), *Citrobacter* spp. (4 of 4 [100%]), *Clostridium* spp. (8 of 10 [80%]), *Enterobacter* spp. (5 of 6 [83.3%]), *Enterococcus* spp. (10 of 14 [71.4%]), *E. coli* (44 of 54 [81.5%]) and *K. pneumoniae* (6 of 8 [75%]). Nausea and vomiting were the most common adverse events and tigecycline appeared to be well tolerated in this study population.

Results from two phase III studies have recently been reported that compared the safety and efficacy of tigecycline with vancomycin/aztreonam in the

treatment of complicated skin and skin structure infections,[63] and investigated the activity of tigecycline compared with imipenem/cilastatin in patients with intra-abdominal infections.[64]

In the first study,[63] 557 hospitalised adult men or women were screened and 546 were evenly randomised to receive intravenous therapy with tigecycline (100mg loading dose followed by 50mg every 12 hours) or vancomycin 1g/aztreonam 2g every 12 hours yielding 436 clinically evaluable and 313 microbiologically evaluable patients. Patients not meeting severity criteria (n = 23) or evaluability requirements (n = 84) were withdrawn from the study. At the test-of-cure visit, cure rates for the clinically evaluable populations were 90% for tigecycline (201 of 224 patients; 95% CI 85.0, 93.4) and 94% for vancomycin/aztreonam combination therapy (203 of 215 patients; 95% CI 90.5, 97.1). Microbiological eradication rates at the end of treatment were 66% for tigecycline (109 of 165 patients; 95% CI 58.3, 73.2) and 76% for vancomycin/aztreonam (112 of 148 patients; 95% CI 67.9, 82.3). A statistical test for non-inferiority revealed that tigecycline therapy was non-inferior ($p < 0.001$) to combination vancomycin/aztreonam regimens. The adverse event profiles were similar in both groups, with nausea and vomiting more common in the tigecycline arm but with rash and increased liver transaminases more frequently reported in vancomycin/aztreonam-treated patients.

In the second study,[64] 824 patients with intra-abdominal infections were stratified by disease severity (Apache II score ≤15 vs >15 to ≤30) and randomly assigned to intravenous tigecycline (100mg loading dose followed by 50mg every 12 hours) or intravenous imipenem/cilastatin (500mg/500mg every 6 hours) for 5–14 days. The primary diagnoses were complicated appendicitis, cholecystitis and intra-abdominal abscess. At the test-of-cure visit, cure rates for the clinically evaluable populations were 86.6% for tigecycline (279 of 322 patients; 95% CI 82.4, 90.2) and 84.6% for imipenem/cilastatin combination therapy (270 of 319 patients; 95%CI 80.2, 88.4). Microbiological eradication rates at the test-of-cure were 91.3% for tigecycline (242 of 265 patients; 95% CI 87.3, 94.4) and 89.9% for imipenem/cilastatin (232 of 258 patients; 95% CI 85.6, 93.3). Overall, the clinical efficacy of tigecycline was statistically non-inferior ($p < 0.0001$) to regimens of imipenem/cilastatin. Adverse events were equivalent across both treatment groups. The most commonly reported adverse events for tigecycline and imipenem/cilastatin were nausea (17% and 13.6%, respectively) and vomiting (12.6% and 9.2%, respectively). The majority of patients were withdrawn because they did not meet severity (n = 23) or evaluability (n = 153) criteria.

7. Discussion

Tigecycline, the first in a new class of broad-spectrum glycylcycline antibacterials, addresses a growing medical need for empirical monotherapy in the treatment of infections caused by community- and hospital-acquired pathogens that have become resistant to commonly used agents. It is currently undergoing phase III clinical development in 44 countries worldwide with a target recruitment of approximately 5000 patients.

The *in vitro* activity of tigecycline is unaffected by resistance mechanisms, including those displayed by methicillin-resistant staphylococci, glycopeptide-intermediate and -resistant *S. aureus*, VRE, penicillin-resistant pneumococci and β-lactamase-producing respiratory pathogens.[8,9,11-13] Additionally, the mutation frequency for laboratory-derived strains against tigecycline is $<10^{-9}$.[18] Comparative *in vitro* susceptibility data have also demonstrated that tigecycline has good activity against anaerobic pathogens.[10,42-44]

Newly published data from European surveillance initiatives have also demonstrated the activity of tigecycline and comparator antimicrobials against recently collected clinical isolates.[38,65] In the first European study, tigecycline activity was compared with conventional agents against a wide range of clinical pathogens,[38] while the second study focussed more specifically on clinical isolates of *Acinetobacter* spp. and *P. aeruginosa*.[65] Tigecycline MIC_{90} values were ≤1 μg/mL for all Gram-positive cocci and ≤2 μg/mL for most species of

Enterobacteriaceae. MIC_{90} values of 2 μg/mL were reported for all strains of *Acinetobacter* spp. and *S. maltophilia*. Tigecycline potency against *Acinetobacter* spp. was confirmed in the second study, in which the MIC_{90} of ≤2 μg/mL for tigecycline was 8- to 32-fold more active than comparator agents. Tigecycline potency against *P. aeruginosa* (MIC_{90} of 16 μg/mL) was equal to or better than comparator agents, but clearly less potent than the *in vitro* potency demonstrated against *Acinetobacter* spp. Increasing multidrug resistance among nosocomial pathogens, particularly MRSA and VRE, is a major contributor to treatment failure, patient morbidity, mortality and costs. The potency of tigecycline against 2206 recent bacteraemia isolates from patients at 25 centres in the UK and Ireland has recently been documented.[66-68]

The enhanced activity of tigecycline compared with tetracyclines is derived from an increased binding affinity of the drug for the *tetM*- and *tetO*-protected ribosomes and from the inhibition of tetracycline efflux determinants.[16,17] A recent investigation assessed the *in vitro* potency of tigecycline against 6309 Enterobacteriaceae, of which 2059 were resistant to tetracycline via *tetA*, *tetB*, *tetM* or *tetO* resistance determinants.[15] Strains included *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *P. mirabilis*, *Proteus* (indole-positive), *Serratia* spp., *Citrobacter* spp., *Salmonella* spp. and *Shigella* spp. For all Enterobacteriaceae, tigecycline MIC_{90} values ranged from 0.25 to 4 μg/mL. Against strains with known resistance mechanisms, the MIC_{90} values again ranged from 0.25 to 4 μg/mL. Apart from a 4-fold increase in MIC_{90} for *Klebsiella* spp. and *Citrobacter* spp., all other MIC_{90} values were a ≤2-fold increase from that observed in the total bacterial population studied.

Tigecycline, along with clindamycin, linezolid and other antibacterials, is a bacteriostatic agent. Tigecycline has broad tissue penetration and achieves high drug concentrations, particularly in bone. Effective therapeutic outcomes with tigecycline were noted for pneumococci and enterococci with known resistance mechanisms that were refractive to traditional antimicrobial therapies. Data from the ongoing T.E.S.T. (Tigecycline Evaluation Surveillance Trial) clearly demonstrate the *in vitro* antibacterial potency of tigecycline against a broad range of Gram-positive and -negative pathogens,[31] and recent studies illustrate the potency and spectrum of tigecycline against bloodstream infection isolates,[32] community-acquired respiratory tract infection and nosocomial pneumonia pathogens,[33] and a large international collection of resistant pathogens.[34] Additionally, the potency of tigecycline against bacterial pathogens from intensive care units[35] and an international collection of pathogens causing skin and soft tissue infections has recently been documented.[36]

Data from phase II and III clinical trials support the therapeutic use of tigecycline in the treatment serious intra-abdominal and skin/skin structure infections. In both open-label and randomised controlled studies, tigecycline-treated patients exhibited high clinical cure and microbiological eradication rates. Tigecycline was moderately well tolerated, with the most frequent adverse events being gastrointestinal in nature, of mild-to-moderate severity and not requiring discontinuation of therapy in most instances. In a recent report, the tolerability of tigecycline in healthy volunteers was investigated using pooled pharmacokinetic/pharmacodynamic phase I data.[69] Of 136 individuals studied, single occurrences of nausea were reported in 51 (38%) individuals and single incidents of vomiting in 25 (18%). Two nausea or vomiting occurrences were reported in four individuals. Nausea and vomiting were reported in 12% and 4% of the placebo group, 17% and 0% in the tigecycline 25mg group, and 33% and 0% in the tigecycline 50mg group, respectively. Most occurrences of nausea were mild (49%) or moderate (27%). Similarly, most cases of vomiting were mild to moderate (20–44%). Overall, the data suggested that tigecycline exposure ($AUC > C_{max}$) was predictive of the likelihood of nausea and vomiting events in phase I study participants. The predicted rates were comparable with those seen with tetracyclines in general, with tolerable rates predicted for the 50mg dose administered twice daily.

8. Conclusion

Tigecycline, currently undergoing phase III clinical development, is a novel glycylcycline with a broad spectrum of activity. Its potent antibacterial activity is largely unaffected by the more commonly occurring resistance phenotypes including MRSA and GISA, methicillin-resistant coagulase-negative staphylococci, VRE, penicillin-resistant *S. pneumoniae*, ESBL-producing *E. coli* and *Klebsiella* spp., bacterial resistance due to β-lactamases, penicillin-binding protein modifications, gyrase mutations, or efflux- or ribosomal change-mediated tetracycline resistance.

The microbiological efficacy of tigecycline coupled with its excellent pharmacokinetic and pharmacodynamic properties, and efficacy and safety in both animal studies and clinical trials support the use of this agent as a viable therapeutic regimen for the treatment of a wide range of infections requiring initial or extended parenteral therapy. However, caution should be exercised to avoid widespread use of this agent to minimise the potential development of resistant organisms.

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