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Affiliations

[†]Author for correspondence
University of Manitoba,
Department of Medical
Microbiology, Faculty of Medicine,
Departments of Medicine,
Clinical Microbiology, Health
Sciences Centre, Winnipeg,
Manitoba, Canada
Tel.: +1 204 787 4902
Fax: +1 204 787 4699
ggzhanel@pcs.mb.ca

KEYWORDS:
clinical trials, complicated
intra-abdominal infections,
complicated skin and skin-
structure infections,
glycylcyclines, *in vitro* activity,
pharmacokinetics,
safety, tigecycline

Tigecycline: a novel glycylcycline antibiotic

George G Zhanel[†], James A Karlowsky, Ethan Rubinstein
and Daryl J Hoban

Tigecycline, the first-in-class glycylcycline, was developed to recapture the broad spectrum of activity of the tetracycline class and to treat patients with difficult-to-treat bacterial infections. Tigecycline's *in vitro* spectrum of activity encompasses aerobic, facultative and anaerobic Gram-positive and -negative bacteria, including antimicrobial-resistant bacteria such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*, and extended-spectrum β -lactamase-producing Enterobacteriaceae. Clinical trials involving patients with complicated skin and skin-structure infections and complicated intra-abdominal infections, including patients infected with methicillin-resistant *S. aureus*, demonstrated that tigecycline was bacteriologically and clinically effective with mild-to-moderate gastrointestinal adverse events (i.e., nausea, vomiting and diarrhea) the most commonly reported. Tigecycline is a promising new broad-spectrum parenteral monotherapy for the treatment of patients with Gram-positive and -negative bacterial infections.

Expert Rev. Anti Infect. Ther. 4(1), 9–25 (2006)

The gradual global escalation in both community- and nosocomial-acquired antibiotic (antibiotic and antimicrobial used interchangeably)-resistant bacteria is threatening our ability to effectively treat patients, underscoring the need for continued surveillance, more appropriate antibiotic prescribing and new treatment alternatives [1,2]. Many strains of Gram-positive bacteria (e.g., methicillin-resistant *Staphylococcus aureus* [MRSA], vancomycin-resistant enterococci [VRE] and penicillin-resistant *Streptococcus pneumoniae* [PRSP]), Gram-negative bacteria (e.g., extended-spectrum β -lactamase [ESBL]-producing *Escherichia coli* and *Klebsiella* spp.) and anaerobic bacteria (e.g., *Bacteroides fragilis*) have developed resistance to commonly used agents including β -lactams (penicillins and cephalosporins), fluoroquinolones and macrolides, and at times, present as multi-drug-resistant (MDR) strains [3–7]. Unfortunately, few novel antimicrobials (i.e., ones with unique mechanisms of action and a reduced propensity to develop resistance) have been discovered and developed for

clinicians to use in the management of infections caused by these difficult-to-treat Gram-positive and -negative bacteria [8].

Isolation of antibiotic-resistant bacterial strains has become of increasing prominence in patients with complicated skin and skin-structure infection (cSSSI) and complicated intra-abdominal infections. Especially noteworthy are rising rates of isolation of MRSA, VRE and MDR streptococci, Enterobacteriaceae and anaerobe-resistant strains from skin sites [9,10]. Furthermore, the recent emergence of community-acquired MRSA [11] and vancomycin-resistant *S. aureus* (VRSA) [12,13] escalates the need for alternative therapies that are effective against these and other resistant organisms [14]. The increasing prevalence of ESBL-producing Gram-negative bacteria such as *E. coli* and *Klebsiella* spp., as well as MDR *Acinetobacter* spp. from patients with complicated intra-abdominal infections, also suggest that new treatment options may be needed [15].

Tigecycline (formerly known as the 9-*tert*-butyl-glycylamido semisynthetic derivative of minocycline, TBG-MINO or GAR-936) is

the first-in-class glycylcycline, a synthetic analog of the tetracycline family [16]. This modification of the tetracycline nucleus led to a reduction in tetracycline-specific efflux and ribosomal protection resistance. Tigecycline remains susceptible to the chromosomally encoded multidrug efflux pumps of *Proteus* spp. and *Pseudomonas aeruginosa*, although the latter is outside the currently licensed indications [17,18]. Tigecycline exhibits broad-spectrum *in vitro* activity, and its spectrum of activity includes tetracycline-resistant bacteria containing genes responsible for efflux mechanisms or ribosomal protection [19], MRSA, methicillin-resistant *Staphylococcus epidermidis* (MRSE), PRSP, VRE [20–32] and certain resistant Gram-negative organisms (e.g., ESBL-producing Enterobacteriaceae and MDR *Acinetobacter baumannii*) [20,23–27,31,33–38]. Since these pathogens are becoming more frequently isolated from patients with both community- and nosocomial-acquired infections, potent combination antibiotic regimens are often recommended to manage these potentially serious infections [14,15].

Tigecycline (Tygacil™, Wyeth Pharmaceuticals) was recently approved (June, 2005) by the US Food and Drug Administration (FDA) for the treatment of cSSSIs caused by *E. coli*, vancomycin-susceptible *Enterococcus faecalis*, *S. aureus* (including MRSA), *Streptococcus agalactiae*, *Streptococcus anginosus* group, *Streptococcus pyogenes* and *B. fragilis*, and for complicated intra-abdominal infections caused by *Citrobacter freundii*, *Enterobacter cloacae*, *E. coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, vancomycin-susceptible *E. faecalis*, methicillin-susceptible *S. aureus*, *S. anginosus* group, *B. fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens* and *Peptostreptococcus micros* [39]. While the role of tigecycline against certain resistant organisms remains to be confirmed in clinical trials (e.g., in VRE and ESBL-producing Gram-negative bacteria), this novel glycylcycline is a new alternative to available broad-spectrum antibiotics, such as advanced-generation cephalosporins, carbapenems, fluoroquinolones, β -lactam/ β -lactamase inhibitor combinations and Gram-positive-directed agents (e.g., daptomycin, linezolid and quinupristin/dalfopristin), for these indications.

The purpose of this review is to present up-to-date data for tigecycline with a specific focus on its chemistry, mechanism of action and resistance, *in vitro* activity (with comparisons to agents including ceftriaxone, ertapenem, gentamicin, levofloxacin, linezolid, minocycline, piperacillin/tazobactam and vancomycin), pharmacokinetics, pharmacodynamics, clinical efficacy, safety and tolerability, and drug interactions. All information described in this review (data from 1990 to 2005) was obtained by searching for references in PubMed and Medline, other scientific journals and abstracts, with some references obtained directly from Wyeth Research. The search terms included 'glycylcycline', 'tigecycline', 'GAR-936' and 'new antibiotics'.

Chemistry

The discovery of tigecycline as the first-in-class glycylcycline emanated from several decades of research to identify new compounds intended to overcome mechanisms of microbial

resistance observed with the tetracycline family of antibiotics. Similar to the tetracycline family, glycylcyclines are characterized by a four-ring carbocyclic structure. Early structural modifications of the four-ring carbocyclic nucleus led to the development of semisynthetic derivatives, which contain the *N,N*-dimethylglycylamido (DMG) substituent at the ninth position of minocycline and 6-demethyl-6-deoxytetracycline (DMDOT) [40]. Specifically, the glycylcyclines are derivatives that contain the 9-glycylamido group. Subsequent structural modification led to the formation of tigecycline, which is the TBG derivative of minocycline (FIGURE 1) [16,41]. Tigecycline demonstrated better *in vitro* activity than previously reported for DMG–minocycline and DMG–DMDOT [41]. Tigecycline has a molecular weight of 585.65 Da and its molecular formula is $C_{29}H_{39}N_5O_8$ [19].

The structure–activity relationships observed with selected glycylcyclines have been discussed by a number of authors [16,40,41]. Tigecycline is formed by the addition of the *t*-butylglycylamido group at C-9; notably, the basic nitrogen of the glycyl unit is vital to the preservation of antibacterial activity (FIGURE 2). Derivatives with alkylamino (e.g., propyl, butyl, pentyl and hexyl) or cyclic amino groups in the glycyl unit enhance *in vitro* activity [40]. Replacement of the alkyl-substituted glycyl group with other amino acids (e.g., leucine, alanine and phenylalanine) results in compounds with significantly compromised activity [40].

Mechanisms of action & resistance

The glycylcycline family of antibiotics have a mechanism of action similar to that of the tetracyclines, but with some notable improvements. Tigecycline, like all tetracycline antibiotics, inhibits bacterial protein synthesis through its binding action on the bacterial 30S ribosomal subunit with subsequent blockage of entry of amino-acyl transfer RNA (tRNA) molecules into the A site of the ribosome, ultimately preventing the incorporation of amino acids into elongating peptide chains [16,19,42,43]. Although the tetracyclines and glycylcyclines share a common binding site on the ribosome [46], tigecycline's *in vitro* activity is explained by its much stronger ribosome binding affinity, which is fivefold higher than tetracycline and minocycline [40,45–48]. In general, both glycylcyclines and tetracyclines demonstrate bacteriostatic activity against susceptible organisms [40,45], likely due to the reversible affinity of these agents for the 30S ribosome subunit [19].



Figure 1. Tigecycline.

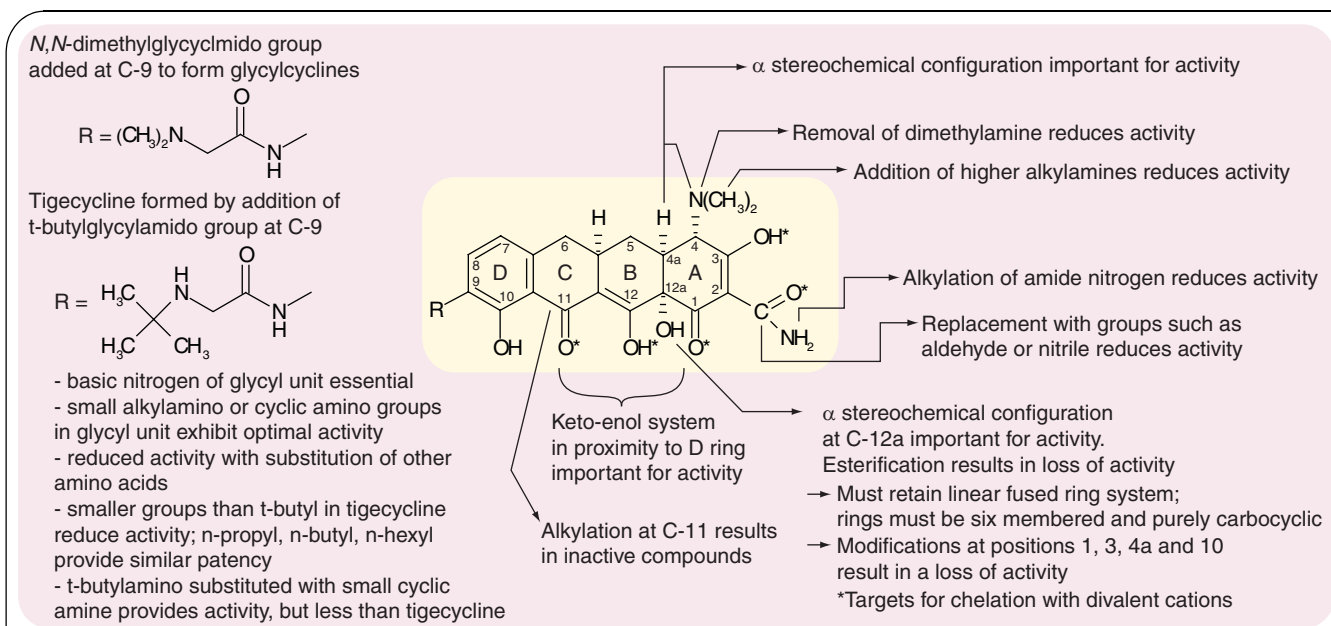


Figure 2. Structure–activity relationships of glycyclines.

A unique action of tigecycline is that it appears to circumvent resistance mechanisms that commonly affect the tetracycline family (i.e., active efflux of drug from inside the bacteria and ribosomal protection), thus retaining activity against both tetracycline- and minocycline-resistant bacterial strains [19,45]. Tigecycline's ability to overcome these two major determinants of tetracycline resistance appears to be the result of steric hindrance created by the large substituent at position 9. This assertion is supported by several lines of evidence: dimethyl-sulfate modification of tigecycline binding sites, mutational analysis of 16S ribosomal RNA (rRNA) and structural modeling of tigecycline at a binding site in the 30S ribosomal subunit [48].

Resistance to tetracyclines is well studied and occurs via the acquisition of tetracycline resistance genes. Different *tet* genes code for either efflux (e.g., *tet*[A] in Gram-negative bacteria and *tet*[K] in Gram-positive bacteria) or ribosomal protection (e.g., *tet*[M]) [19,40]. Occasionally, some strains of bacteria express both efflux and ribosomal protection *tet* genes [45]. Limited data suggest that the *in vitro* activity of glycycline antibiotics are not largely affected by *tet*-expressing efflux pumps, possibly due to the inability of the glycyclines to induce tetracycline efflux proteins, or because the efflux protein cannot export the glycyclines [45,49]. However, a recent investigation has shown that overexpression of *mepA*, a novel multidrug and toxic compound extrusion (MATE) family efflux pump, and not *tet*[M] may contribute to a decreased susceptibility of tigecycline in *S. aureus* [50].

There is also emerging data to suggest that tigecycline's activity may be somewhat compromised in certain Gram-negative organisms, specifically, those that express multidrug efflux pumps [17,18,51–53]. Tigecycline's *in vitro* activity was examined following exposure to strains of *E. coli* KAM3, which encodes several types of tetracycline-specific efflux transporter genes, *tet*(B), *tet*(C) and *tet*(K), as well as multidrug transporter genes, *acrAB*, *acrEF* and

bcr [42,43,51]. While tigecycline's potency was maintained against all strains expressing *tet* genes, fourfold increases in minimum inhibitory concentration (MIC) values were noted for strains containing the multidrug efflux proteins AcrAB and AcrEF. In two separate reports by Ruzin and colleagues, the activity of tigecycline was reduced in both *K. pneumoniae* and *Morganella morganii* strains with increased expression of the *acrAB* multidrug efflux pump [52,53]. The AcrAB transport system also appears to be associated with the intrinsic reduced susceptibility to tigecycline in *Proteus mirabilis* [17].

There is no current evidence to suggest that tigecycline's activity is reduced by *tet* genes which encode for ribosomal protection. The antibacterial activity of the glycyclines was preserved when exposed to tetracycline-resistant organisms that harbored *tet*(M)-protected ribosomes [47]. Although the precise mechanism through which the glycyclines overcome this type of resistance has not been elucidated, it is possible that these agents bind more avidly to the ribosomes such that the product of the *tet*(M) gene is unable to disrupt the tight bond, or that the product of the *tet*(M) gene is unable to interact with the ribosome to allow protein synthesis to occur in the presence of tigecycline [45–47].

As with all antimicrobials, increased usage of tigecycline in humans may eventually lead to the emergence of resistant strains. The authors believe that resistance, if it does occur, will likely arise via the acquisition of mutations within currently circulating efflux and ribosomal protection genes. No glycycline-resistant isolates have been created from initially susceptible ones to date.

In vitro activity

In general, the glycyclines have a spectrum of activity that is similar to the tetracyclines, but with more potent *in vitro* activity (MIC only) against several resistant Gram-positive

(e.g., MRSA, VRE and PRSP) and Gram-negative bacteria (e.g., ESBL-producing enterics). The *in vitro* activity of tigecycline against clinical isolates concurrently tested against comparator antibiotics is summarized in TABLES 1–3 [20,23–27,36,54–57]. The MIC₅₀ and MIC₉₀ values listed in each table for tigecycline represent the most common values obtained from several recently published reports that examined a large number of clinical isolates. Data presented solely at scientific meetings were not included in this analysis. For comparative purposes with other agents, FDA-approved tigecycline breakpoints were used to interpret MIC data [39]. Tigecycline breakpoints are 0.5 mg/l (susceptible) for *S. aureus* (including methicillin-resistant isolates), less than or equal to 0.25 mg/l (susceptible) for *Streptococcus* spp. (other than *S. pneumoniae*) and *E. faecalis* (vancomycin-susceptible isolates only), less than or equal to 2 mg/l (susceptible) and less than or equal to 8 mg/l (resistant) for Enterobacteriaceae, and less than or equal to 4 mg/l (susceptible) and greater than or equal to 16 mg/l (resistant) for anaerobes [39].

Gram-positive activity

Tigecycline has excellent potency (i.e., MIC₉₀ values ≤0.5 mg/l) against many Gram-positive cocci, including both methicillin-susceptible and -resistant *S. aureus*, coagulase-negative staphylococci, vancomycin-resistant staphylococci

and enterococci, penicillin-resistant *S. pneumoniae* and phenotypes inherently nonsusceptible to minocycline (TABLE 1) [20–31,33,34,37,58–66].

With respect to MRSA (256 isolates from 23 US sites), tigecycline was two- to 16-fold more active *in vitro* (MIC₉₀ 0.25 mg/l) than minocycline, vancomycin and linezolid [20]. In a global study of 25 MRSA isolates, tigecycline was two- to 256-fold more active (MIC₉₀ 0.25 mg/l) than comparator agents [23]. Tigecycline's activity against MRSA (MIC₉₀ 0.5 mg/l) was also reported in several recent *in vitro* investigations using isolates collected from patients (i.e., in intensive care units, and from those with skin and soft-tissue infection sites or bloodstream infections) [24,26,27]. These surveillance studies also provided evidence that tigecycline was two- to four-fold more active (MIC₉₀ 0.5 mg/l) than linezolid and vancomycin (MIC₉₀ 1 and 2 mg/l, respectively) against more than 13,000 methicillin-susceptible and -resistant *S. epidermidis* isolates [24,26,27].

Tigecycline also displays very potent activity compared with a variety of antimicrobial classes against *S. pyogenes*, *S. agalactiae*, *E. faecalis* and *E. faecium*. Against *S. agalactiae*, tigecycline had a MIC₉₀ of 1 mg/l, which is comparable with linezolid and vancomycin, and slightly higher than observed for imipenem/cilastatin, and substantially lower than minocycline (MIC₉₀ > 8 mg/l) [23]. Notably, tigecycline demonstrated a

Table 1. *In vitro* activity of tigecycline and selected comparator antimicrobials against Gram-positive aerobes.*

Organism	Tigecycline		Minocycline		Linezolid		Vancomycin		Ceftriaxone		Ertapenem		Piperacillin/tazobactam	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Staphylococcus aureus</i> (methicillin-susceptible)	0.12	0.5	≤0.25	4	2	4	1	1	2	8	0.12	0.25	1	>16
<i>S. aureus</i> (methicillin-resistant)	0.12	0.5	≤0.25	2	1	4	1	1	32	>64	4	>16	>16	>16
<i>Staphylococcus epidermidis</i> (methicillin-susceptible)	0.25	0.5	0.12	0.5	1	2	2	2	0.5 [‡]	4 [‡]	0.25 [‡]	4 [‡]	0.125 [‡]	1 [‡]
<i>S. epidermidis</i> (methicillin-resistant)	0.25	0.5	0.25	4	1	2	2	4	0.5 [‡]	4 [‡]	0.25 [‡]	4 [‡]	0.125 [‡]	1 [‡]
<i>Streptococcus pyogenes</i>	0.03	0.06	0.06	0.25	1	2	0.5	1	0.03	0.06	0.008	0.03	0.06	0.125
<i>Streptococcus agalactiae</i>	0.25	1	8	>8	1	2	0.5	0.5	0.03	0.12	0.06	0.06	0.25	0.25
<i>Streptococcus pneumoniae</i> (all)	0.12	0.5	≤0.25	8	≤0.5	1	0.25	0.5	≤0.03	0.5	0.03	0.5	≤0.25	1
<i>S. pneumoniae</i> (Pen R)	0.06	0.25	2	>8	≤0.5	1	0.5	0.5	1	2	0.2	2	4	8
<i>Enterococcus faecalis</i>	0.12	0.25	8	>8	2	2	1	2	>64	>64	8	>16	4	>16
<i>Enterococcus faecium</i>	0.06	0.25	4	>8	1	1	0.5	2	>32	>32	>16	>16	>128	>128

*Adapted from [20,23–27,54,55].

[‡]MIC values are reported for all *S. epidermidis* isolates regardless of susceptibility to methicillin.

MIC₅₀: Minimum inhibitory concentration (mg/l) of 50% of isolates; MIC₉₀: Minimum inhibitory concentration (mg/l) of 90% of isolates; Pen R: Penicillin resistant (penicillin MIC ≥ 2.0 mg/l).

Table 2. *In vitro* activity of tigecycline and selected comparator antimicrobials against Gram-negative aerobes.*

Organism	Tigecycline		Minocycline		Ceftriaxone		Ertrapenem		Piperacillin/ tazobactam		Gentamicin		Levofloxacin	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Acinetobacter</i> spp.	0.5	2	1	8	>64	>64	4	>16	64	128	-	1	8	>8
<i>Enterobacter aerogenes</i>	0.5	1	2	8	0.12	4	0.06	0.5	2	32	-	1	0.06	0.25
<i>Enterobacter cloacae</i>	0.5	2	2	16	0.25	>64	0.03	0.125	2	64	-	8	0.06	4
<i>Escherichia coli</i>	0.25	0.25	1	8	≤0.25	0.5	0.016	0.5	2	4	≤2	>8	0.03	>8
<i>Haemophilus influenzae</i> (all)	0.12	0.25	≤0.5	1	≤0.06	≤0.06	0.06	0.125	≤0.06	≤0.06	-	8	0.015	0.03
<i>H. influenzae</i> (β-lactamase positive)	0.12	0.25	0.5	1	≤0.06	≤0.06	-	-	≤0.06	≤0.06	-	8	0.015	0.015
<i>Klebsiella pneumoniae</i>	0.5	1	2	8	≤0.06	16	≤0.016	0.03	2	64	-	4	0.06	>8
<i>Klebsiella</i> spp.	0.5	1	3.1	-	0.25	>32	0.016	0.03	4	>64	≤2	>8	0.06	0.06
<i>Moraxella catarrhalis</i>	≤0.12	0.25	0.03	0.06	0.12	0.5	0.016	0.016	≤1	≤1	-	2	0.06	0.06
<i>Proteus mirabilis</i>	4	4	8	16	≤0.25	≤0.25	≤0.016	≤0.03	≤0.5	1	≤2	8	0.06	0.12
<i>Pseudomonas aeruginosa</i>	8	16	>16	>16	>64	>64	8	16	8	>64	≤2	>8	2	>8
<i>Serratia marcescens</i>	1	2	2	8	0.25	16	0.03	0.12	1	16	-	16'	0.25	1
<i>Stenotrophomonas maltophilia</i>	1	2	0.25	1	-	-	>16	>16	>64	>64	-	64	1	4

*Adapted from: [20,23–27,36,54,56,57].

BLP: β-lactamase positive; MIC₅₀: Minimum inhibitory concentration (mg/l) of 50% of isolates; MIC₉₀: Minimum inhibitory concentration (mg/l) of 90% of isolates.

MIC₉₀ of 0.25 mg/l against isolates of *E. faecalis*, irrespective of vancomycin susceptibility, and had MIC₉₀ values that were 130-fold lower than ampicillin against vancomycin-resistant strains [23]. Furthermore, tigecycline was 33-fold more potent than linezolid against vancomycin-resistant *E. faecium* and eightfold more potent against vancomycin-susceptible *E. faecium* than linezolid [23]. These findings confirmed an earlier report that tigecycline had potent activity against glycopeptide-resistant enterococci including *VanA*, *VanB* and *VanC* phenotypes [21].

Tigecycline is highly active against *S. pneumoniae* isolates, regardless of susceptibility or resistance to β-lactams or macrolides. Specifically, against penicillin-resistant strains of *S. pneumoniae*, tigecycline MIC₉₀ values were less than or equal to 0.25 mg/l compared with 2 mg/l for ceftriaxone, greater than 16 mg/l for imipenem/cilastatin and 8 mg/l for minocycline [20,26,28,30].

Gram-negative activity

Tigecycline's Gram-negative activity extends to many Enterobacteriaceae (MIC₉₀ ≤ 2 mg/l), as well as *Haemophilus influenzae* and *Moraxella catarrhalis*, and some opportunistic

pathogens such as *Acinetobacter* spp. and *Stenotrophomonas maltophilia* (TABLE 2) [20,23–27,31,33–38,58,62,65,67–69]. While tigecycline exhibits two- to eightfold greater activity against many Gram-negative bacteria compared with earlier generation tetracycline compounds, it has reduced *in vitro* activity against *Proteus* and *Providencia* spp., *Morganella morganii*, *Burkholderia cepacia* and *P. aeruginosa* [32]. *P. aeruginosa* MIC₉₀ values to tigecycline are uniformly greater than 16 mg/l.

In several recent US and global *in vitro* investigations involving over 30,000 clinical isolates, tigecycline exhibited excellent Gram-negative inhibitory activity against all phenotypes of Enterobacteriaceae regardless of degree or type of resistance mechanisms [20,23–27,36]. Tigecycline's MIC₅₀/MIC₉₀ values were similar to imipenem, but superior to ceftriaxone and piperacillin/tazobactam for all Enterobacteriaceae tested. The MIC₉₀ values of tigecycline were lower than the MIC₉₀ of imipenem against ESBL-producing isolates of *E. coli* and *K. pneumoniae* [20]. Against imipenem/cilastatin-nonsusceptible Enterobacteriaceae, tigecycline retained good activity (i.e., MIC₅₀/MIC₉₀ = 1/4 mg/l) [20]. Tigecycline was also highly potent against AmpC hyper-producers, as well as ESBL phenotypes of *Enterobacter* spp. and *S. marcescens* (MIC₉₀ ≤ 4 mg/l) [20].

Table 3. *In vitro* activity of tigecycline and selected antimicrobials against anaerobes.*

Organism	Tigecycline		Minocycline		Cefoxitin		Ertapenem		Piperacillin/ tazobactam		Clindamycin		Metronidazole	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Bacteroides fragilis</i>	2	8	8	≥8	8	16	0.125	1	1	4	1	≥128	1	2
<i>B. fragilis</i> group	1	8	≥2	≥4	16	32	0.25	2	2	16	1	>256	1	2
<i>Clostridium difficile</i>	0.06	0.125	0.03	4	>32	>256	≥4	16	8	16	-	32	0.5	1
<i>Clostridium perfringens</i>	0.5	1	≤0.06	4	0.5	1	≤0.06	≤0.06	0.25	0.5	-	2	-	1
<i>Fusobacterium</i> spp.	0.03	0.06	0.06	0.06	-	2	0.015	0.12	≤0.06	0.12	-	2	-	2
<i>Peptostreptococcus</i> spp.	0.06	0.125	0.125	8	-	2	0.06	0.5	0.06	0.25	-	2	-	32

*Adapted from [31,54,56,58,72–74].

MIC₅₀: Minimum inhibitory concentration (mg/l) of 50% of isolates; MIC₉₀: Minimum inhibitory concentration (mg/l) of 90% of isolates.

Tigecycline demonstrated excellent activity against *A. baumannii* with a MIC₅₀/MIC₉₀ of 0.5/2 mg/l, with only amikacin having greater activity than tigecycline [20].

Zhanel and colleagues recently assessed the activity of tigecycline against 1742 fluoroquinolone-resistant *E. coli* obtained from outpatient midstream urinary isolates in North America [70]. The MIC₅₀ and MIC₉₀ values of tigecycline against all isolates were 0.5 and 1 mg/l, respectively. These MIC values remained unaltered for the 1389 strains, with a fluoroquinolone/ampicillin resistance phenotype for 1165 isolates with a fluoroquinolone/trimethoprim–sulfamethoxazole resistance phenotype and for 1017 isolates with a MDR phenotype.

Postantibiotic effect

Another study examined the *in vitro* pharmacodynamics and postantibiotic effect (PAE) of tigecycline against four clinical isolates each of *E. coli*, *K. pneumoniae*, *E. cloacae* and ESBL-producing *K. pneumoniae* [71]. MIC and minimal bactericidal concentration (MBC) values were determined using standardized broth microdilution methods. Tigecycline demonstrated concentration-independent and bacteriostatic activity as evidenced by MIC values ranging from 0.25 to 64 mg/l, with MBCs greater than 64 mg/l for all isolates. None of the isolates developed resistance when exposed to concentrations of greater than or equal to 1 × MIC. Tigecycline exhibited a concentration-dependent PAE (mean 2–5 h) without any difference among the tested isolates.

Anaerobic activity

Tigecycline demonstrated activity against *B. fragilis* with typical MIC₉₀ values of less than or equal to 2 mg/l (i.e., fourfold greater potency compared with minocycline) [72]. Against *B. fragilis* group strains, tigecycline and minocycline had similar activity (MIC₉₀ 4 mg/l), although imipenem/cilastatin and piperacillin/tazobactam were slightly more active than the glycylicycline (TABLE 3) [72]. Tigecycline has also demonstrated *in vitro* activity against *Clostridium*, *Fusobacterium* and *Peptostreptococcus* spp. [31,58,73,74].

Miscellaneous activity

There are currently limited data that describe tigecycline's *in vitro* activity against atypical bacterial pathogens [75–79]. In general, tigecycline demonstrates similar or slightly improved activity against many atypical respiratory bacteria compared with minocycline, macrolides and fluoroquinolone agents. Tigecycline has potent activity against *Chlamydomphila pneumoniae* with MIC₉₀ values of 0.125 mg/l compared with doxycycline (0.25 mg/l), ofloxacin (0.25 mg/l) and clarithromycin (0.06 mg/l) [77]. Against *Mycoplasma pneumoniae*, tigecycline is more active *in vitro* (MIC₉₀ 0.25 mg/l) than minocycline, but has similar activity against *Mycoplasma hominis* (MIC₉₀ 0.5 mg/l) [76]. When tested against *Legionella pneumophila*, tigecycline appears to have less potent *in vitro* activity than azithromycin with MIC₉₀ values of 4–8 and 0.5 mg/l, respectively [75]. However, it should be noted that the activity of tigecycline against *L. pneumophila* was likely inaccurate as the test media employed (α -ketoglutarate [BYE α] growth medium) partially inactivated the drug [75]. *Ureaplasma urealyticum* is also generally less susceptible to tigecycline (MIC₉₀ 8 mg/l) than to minocycline (MIC₉₀ 0.25 mg/l) [76].

Tigecycline has also demonstrated activity against rapidly growing mycobacteria (*Mycobacterium fortuitum* group, *Mycobacterium abscessus*, *Mycobacterium chelonae*, *Mycobacterium immunogenum* and the *Mycobacterium smegmatis* group) with MIC₉₀ values (≤0.25 mg/l) several-fold lower than for minocycline and other tetracyclines [79]. However, tigecycline lacks activity against slowly growing mycobacteria (e.g., *Mycobacterium avium* complex, *Mycobacterium kansasii* and *Mycobacterium marinum*) [79]. No data are presently available for *M. tuberculosis*.

Pharmacokinetics

The pharmacokinetic parameters of tigecycline and selected comparator antimicrobials after multiple intravenous doses are summarized in TABLE 4 [39,56,80–85]. The following discussion focuses on the pharmacokinetic properties of tigecycline.

Table 4. Steady-state intravenous pharmacokinetic parameters of tigecycline and selected comparator antimicrobials.

Parameter	Tigecycline	Ceftriaxone	Ertapenem	Imipenem/ cilastatin	Piperacillin/ tazobactam	Levofloxacin	Linezolid	Vancomycin
Dose	100 mg x 1, then 50 mg every 12 h	1 g every 24h	1 g every 24 h	0.5 g every 6–8 h	3.375 g every 6 h	750 mg every 24 h	600 mg every 12 h	1 g every 12 h
C _{max} (mg/l)	0.63–0.87*	129	155	30–35	242	12.1	15.1	63
AUC [‡] (mg/h/l)	4.7	973	572	42	253	108	90	
t _{1/2} (h)	42	7.4	3.8	1	0.7–1.2	7.9	4.8	4–6
Vd (l)	639	7–13	8.2	0.23–0.31 l/kg	16–19	80	40–50	0.3–0.43 l/kg
Protein binding (%)	71–89	83–96 [†]	92–98 [†]	20	30	24–38	31	55
Excreted unchanged (%)	<15	60	44	60–70	70	77	30	70
Dose adjustment								
Renal	None	None	Yes	Yes	Yes	Yes	None	Yes
Hepatic	Yes [§]	None	Unknown	None	None	None	Unknown	None

Pharmacokinetic parameters reflect steady-state values after multiple dose.

*C_{max} reported following 60 and 30 min infusion, respectively.

[‡]AUC (mg/h/l) from 0–24 h except for imipenem/cilastatin and piperacillin/tazobactam where the AUC represents 0–6 h.

[§]Dose adjustment is recommended for patients with severe (Child-Pugh C) hepatic impairment.

[†]Concentration dependent.

AUC: Area under the curve; C_{max}: Maximum concentration t_{1/2}: Half-life; Vd: Volume of distribution.

Absorption, distribution, metabolism & elimination

Tigecycline is available as a parenteral agent (not likely to be available orally) due to its limited oral bioavailability, and is administered intravenously as a 30 min to 1 h infusion twice daily [39]. In a dose-escalation study in healthy males aged 18–50 years, a single 1 h intravenous infusion with increasing doses of 12.5–300 mg produced mean tigecycline maximum concentration (C_{max}) values ranging from 0.11 to 2.82 mg/l, respectively [86]. Corresponding mean area under the curve over 24 h (AUC)₂₄ values ranged from 0.8 to 17.9 mg/h/l. Both C_{max} and AUC values increased proportionally to the single-dose range studied, thus indicating that tigecycline has a linear pharmacokinetic profile. In a subset of patients who received a standard medium-fat breakfast after a single 200 mg dose, no significant difference in C_{max} values were observed between the fed and fasted groups (1.53 and 1.64 mg/l, respectively) [86]. A multiple-dose Phase I study investigated the steady-state pharmacokinetics of tigecycline in healthy male subjects who received 25, 50 or 100 mg doses as 1 h infusions twice daily for a total of 19 doses [86]. Steady-state C_{max} and AUC values were similar to those measured after each single dose studied, with evidence of dose proportionality. Mean steady-state C_{max} and AUC values following the 100 mg dose on day 10 were 1.2 mg/l and 5.0 mg/h/l, respectively. A similar study conducted in healthy Japanese male subjects revealed comparable tigecycline pharmacokinetic profiles with doses ranging from

25 to 150 mg [87]. In Japanese men who received a single 100 mg dose of tigecycline administered intravenously over 1 h, C_{max} was 0.85–1 mg/l and AUC was 4.2–5.8 mg/h/l [87].

Tigecycline is moderately bound to human plasma proteins (TABLE 4). In human plasma, binding was 71 and 89% by ultrafiltration at drug concentrations of 0.1 and 1.0 mg/l, respectively (i.e., those achieved in clinical trials), and ranged from 73 to 79%, respectively, over the same concentration range using ultracentrifugation [86]. Tigecycline has a very large volume of distribution (7–17 l/kg) that has been reported to be dose proportional and significantly greater than that of other tetracyclines [32,86,87]. These data imply that tigecycline should be extensively distributed throughout most tissue and body fluid compartments; however, presently there are limited human data available that describe the tissue penetration of tigecycline. In an inflammatory blister fluid model, tigecycline was shown to highly penetrate into inflammatory fluid (~78% of serum concentrations) after a 100 mg loading dose followed by 50 mg every 12 h, suggesting that this agent may be suitable for the treatment of skin and soft-tissue infections [88]. Administration of single doses of tigecycline (100 mg) to patients undergoing elective surgical/medical procedures found that the glycylicycline achieved high concentrations at 4 h from the start of the infusion in the gallbladder (38-fold), lung (8.6-fold) and colonic tissues (2.1-fold) relative to serum [89]. Distribution of tigecycline into bone and synovial fluid were lower (35 and

58% of serum concentrations, respectively), possibly due to the technical difficulties associated with extracting the drug from bone specimens [89]. In a bronchoalveolar lavage study in 33 healthy volunteers, concentrations of tigecycline in alveolar cells after a 100 mg loading dose followed by 50 mg/12 h were nearly 77.5-fold higher than serum values; corresponding concentrations in epithelial lining fluid were approximately 32% higher than serum [39]. In 30 subjects who received a similar tigecycline dosing regimen, tigecycline was found to concentrate highly in alveolar cells ($C_{\max}$ of 15.2 mg/l, AUC of 134 mg/h/l and half-life [$t_{1/2}$] of 24 h) compared with serum ($C_{\max}$ 0.72 mg/l, AUC 1.73 mg/h/l and $t_{1/2}$ of 15 h) [90]. Preliminary findings in 55 adults following a single 100 mg tigecycline dose, observed high lung tissue concentrations (380–761 ng/g from 4–24 h post dose), cerebrospinal fluid penetration (52.4% of serum in noninflamed meninges at 24 h post dose) and extremely high biliary levels (mean bile to serum ratio ranging from 606 to 1997) [91]. Although further data are needed to confirm steady-state concentrations in these tissues, these preliminary data suggest that tigecycline may be useful in the treatment of intra-abdominal and respiratory tract infections.

Tigecycline is eliminated primarily by the liver via biliary excretion of unchanged drug and glucuronidation [86]. Two major metabolic pathways of tigecycline have been identified including the glucuronidated parent drug, which accounts for 5–20% of radioactive metabolites in human serum, and its inactive epimer and *N*-acetyl-9-aminomincycline [92]. No active metabolites of tigecycline have been identified. Tigecycline's elimination $t_{1/2}$ ranges from 38 h following a single 100 mg dose to 67 h at steady state after 100 mg twice daily (TABLE 4) [86]. In healthy subjects, the mean total systemic clearance of tigecycline ranged from 0.2 to 0.3 l/h/kg across all dose groups [86]. Renal clearance is only a minor excretory pathway for tigecycline (~10–15% of total systemic clearance), with less than 22% of tigecycline excreted unchanged in the urine [39].

Special populations

Age and gender effects were evaluated in a single 100 mg intravenous dose study of tigecycline in 46 healthy young (18–50 years), elderly (65–75 years) and very elderly (>75 years) men and women [93]. The pharmacokinetic profile of tigecycline was generally similar across all three age and both gender groups. The mean AUC value in each of the three female age groups was approximately 5 mg/h/l. Young men (<50 years) had a slightly lower mean AUC value of 4.2 mg/h/l, whereas older men (>75 years) had slightly higher values (mean 5.5 mg/h/l), although these differences were not statistically significant. The volume of distribution was somewhat higher in men (6.2 l/kg) compared with women (5.8 l/kg; $p = 0.4$). The findings of this study suggest that dosage adjustments of tigecycline are not necessarily based upon age or gender.

Currently, there are no data which describe the disposition of tigecycline in children less than 18 years of age.

Data in patients with various degrees of renal impairment, as well as those on hemodialysis, suggest that no dose adjustments are necessary for patients with any degree of renal insufficiency. Tigecycline was administered as a single, 100 mg, 1 h intravenous infusion to patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) and end-stage renal disease [94]. Patients who were receiving hemodialysis were administered tigecycline either 2 h prior to dialysis or 1 h after dialysis. The mean tigecycline $C_{\max}$ was 60% higher in the end-stage renal disease cohort (0.96 mg/l) compared with age-matched healthy volunteers (0.60 mg/l). However, mean AUC was only 20% higher in the end-stage renal disease group (4.04 mg/h/l) versus those with normal renal function (3.33 mg/h/l). Tigecycline's pharmacokinetic profile in subjects who received tigecycline before or after a hemodialysis cycle did not differ, indicating that this agent is not significantly removed by hemodialysis. Thus, tigecycline can be administered without regard to a patient's hemodialysis schedule.

The pharmacokinetic disposition of a single intravenous dose (100 mg) of tigecycline in 25 patients with mild (Child–Pugh A, $n = 10$), moderate (Child–Pugh B, $n = 10$) and severe hepatic impairment (Child–Pugh C, $n = 5$) has been compared with 23 age- and weight-matched healthy volunteers [39]. Tigecycline's pharmacokinetic profile was unaltered in patients with mild hepatic dysfunction. In patients with moderate hepatic dysfunction, an approximate 25% reduction in the systemic clearance and elimination $t_{1/2}$ of tigecycline was observed compared with control subjects. These data suggest that no dosage adjustments for tigecycline are necessary in patients with mild-to-moderate liver impairment. However, as the systemic clearance and elimination $t_{1/2}$ of tigecycline were significantly reduced (55 and 43%, respectively) in patients with severe hepatic dysfunction, the dose of tigecycline should be reduced to 100 mg followed by 25 mg every 12 h [39]. Patients with severe hepatic impairment (Child–Pugh C) should be treated with caution and monitored for treatment response.

Drug interactions

At the time of writing, few drug–drug interaction studies with tigecycline have been conducted and published.

Zimmerman and colleagues evaluated the pharmacokinetics and pharmacodynamics of concomitantly administered tigecycline (100 mg followed by 50 mg every 12 h) and digoxin (0.5 mg followed by 0.25 mg/day) in 20 healthy male volunteers [95]. Steady-state AUC and total body clearance values of tigecycline were unaffected following digoxin administration. Although $C_{\max}$ values of digoxin were slightly reduced (13%), steady-state AUC and apparent oral-dose clearance of digoxin were not significantly changed in the presence of tigecycline. Furthermore, tigecycline did not induce any significant changes from baseline electrocardiogram measurements under steady-state digoxin conditions. Thus, unlike some members of the tetracycline family, tigecycline does not appear to inhibit the conversion of digoxin to inactive metabolites through alteration of the gut flora.

Coadministration of tigecycline (100 mg followed by 50 mg every 12 h) and warfarin (25 mg single dose) to healthy volunteers was associated with reduced clearance of R-warfarin (40%) and S-warfarin (23%), and corresponding increases in AUC of 68 and 29%, respectively [39]. The pharmacokinetic disposition of tigecycline was not affected in the presence of warfarin. While no patients had clinically altered coagulation, these findings suggest that prothrombin time or other suitable anticoagulation tests be monitored if tigecycline is administered concurrently with warfarin.

Since tigecycline is not predominately eliminated via hepatic metabolism, there is a low potential that it will induce or inhibit metabolic pathways of drugs which are dependent on these pathways leading to clinically important drug–drug interactions. Specifically, *in vitro* studies in human liver microsomes revealed that tigecycline does not inhibit metabolism mediated by any of the following six cytochrome P450 (CYP) isoforms: 1A2, 2C8, 2C9, 2C19, 2D6 and 3A4 [39]. In addition, since tigecycline is not extensively metabolized, clearance of tigecycline will not likely be affected by drugs that inhibit or induce the activity of these CYP isoforms.

Pharmacodynamics

Although the microbiologic and pharmacokinetic properties of an antimicrobial provide insight into an antimicrobial's bacteriological eradication from infectious sites, these parameters individually can not accurately predict bacteriological or clinical response. Accordingly, pharmacodynamic investigations that integrate both of these parameters (e.g., time above the MIC [$T > MIC$], peak serum antibiotic concentration [C_{max}/MIC] or AUC/MIC) are more useful in predicting bacteriological outcome [96]. When bacteriological eradication is based on optimizing the duration of antibiotic exposure (i.e., $T > MIC$), these antibiotics are categorized as providing time-dependent (concentration-independent) bactericidal activity. For antibiotics that display concentration-dependent killing, a C_{max}/MIC ratio greater than ten or an AUC/MIC ratio greater than 30–125 has been shown to correlate with bacteriological eradication. Bacteriological eradication for antibiotics that have moderate to prolonged persistent effects such as PAE are best predicted by AUC/MIC [97].

The pharmacodynamic properties of tigecycline have not been fully elucidated. Nonetheless, early *in vitro* experiments with tigecycline revealed time-dependent bactericidal activity against *S. pneumoniae*, *H. influenzae* and *Neisseria gonorrhoeae* [31]. Another study conducted in a neutropenic mouse thigh infection model suggested that both time- and concentration-dependent pharmacodynamic indices correlated with efficacy of tigecycline against selected Gram-negative and -positive bacteria [98]. Specifically, tigecycline in this animal model appeared to have time-dependent antimicrobial activity against several key pathogens (e.g., *S. pneumoniae*, *S. aureus*, *E. coli* and *K. pneumoniae*). That is, a tigecycline concentration above the MIC (ideally 4 × the MIC) for at least 50% of the dosing interval led to optimal activity [98]. The AUC/MIC ratio

was also important in predicting activity in this model. The authors also noted that tigecycline had a prolonged *in vivo* PAE for *S. pneumoniae* and *E. coli* (8.9 and 4.9 h, respectively). However, there are several reasons why the pharmacodynamic findings of this neutropenic murine model can not be extrapolated to humans:

- Tigecycline in the mouse exhibited nonlinear kinetics with relatively short elimination half-lives ranging from 1 to 2 h, whereas humans exhibit linear pharmacokinetics with very prolonged terminal half-lives [86]
- Efficacy was compromised in the mouse due to the lack of absolute and/or functional neutrophils
- In humans, tigecycline has extensive tissue distribution, therefore, serum concentrations may underestimate the concentration of drug at the clinical site of infection
- The susceptibility testing method for tigecycline was modified following the completion of this study (e.g., MIC values are likely to be one dilution lower than initially reported in the murine model)

Another study investigated the pharmacodynamics of tigecycline in an experimental animal model of endocarditis due to a VanA *E. faecium* strain, which was resistant to tetracycline [99]. *In vitro* pharmacodynamic studies demonstrated that tigecycline had bacteriostatic activity, which was not enhanced by increasing concentrations to more than 1 mg/l, and had a PAE ranging from 1 to 4.5 h. Rabbits with aortic endocarditis who received varying intravenous doses of tigecycline for 5 days (i.e., 14 mg/kg twice daily, 14 mg/kg once daily or 7 mg/kg once daily), demonstrated significant reductions of vegetative bacterial counts at the end of therapy, which was independent of the dose given. Tigecycline serum levels were constantly above the MIC with twice-daily dosing, and below the MIC 50% of the time with once-daily dosing, suggesting that glycylicycline exhibited concentration-independent effects. The authors concluded that tigecycline's prolonged $t_{1/2}$, significant PAE and excellent tissue distribution may explain its efficacy against enterococci resistant to glycopeptides and tetracyclines.

In summary, at the current time there are little data to definitely identify tigecycline's true pharmacodynamic profile. There is speculation that tigecycline data generated from clinical trials will ultimately find that the AUC/MIC ratio will most likely predict microbiologic eradication of tigecycline, based upon its prolonged *in vivo* PAE in key bacteria [98] and relatively long elimination $t_{1/2}$ in humans. Well-designed pharmacodynamic studies, ideally incorporated into clinical trials, are needed to fully characterize whether tigecycline's efficacy is best predicted based on concentration-independent or -dependent principles.

Clinical efficacy in complicated skin & skin-structure infections

Serious skin and skin-structure infections, especially those deemed to be complicated, are often caused by MDR pathogens, suggesting that new empirical treatment options are needed in high-risk patients (i.e., poor vascular perfusion,

pressure sores, abdominal wounds, complicating gastrointestinal surgery, fistulae from underlying infectious foci and a compromised immune system) [14]. Furthermore, the appearance of community-acquired MRSA and VRSA has escalated the need for new first-line therapies that are effective against suspected skin pathogens including resistant organisms [11–13]. One Phase II and two Phase III studies have established the efficacy of tigecycline in the treatment of cSSSIs [100,101].

The clinical and microbiological efficacy of tigecycline in hospitalized patients with cSSSIs was initially evaluated in a Phase II, open-label clinical trial [100]. Patients were randomly assigned to receive tigecycline 25 or 50 mg intravenously every 12 h for 7–14 days. A total of 109 patients were clinically evaluable, and 91 were microbiologically evaluable. At the test-of-cure visit, the clinical cure and microbiological eradication rates were 74 and 70% for those who received 50 mg every 12 h. Corresponding rates were 67 and 56%, respectively, for those given 25 mg every 12 h. These encouraging preliminary findings led to the initiation of Phase III trials.

Ellis-Grosse and colleagues recently described the findings of two Phase III, double-blind clinical trials, which were conducted in hospitalized adults with cSSSIs to determine tigecycline's efficacy compared with vancomycin/aztreonam (TABLE 5) [101]. Following randomization, patients received tigecycline (100 mg initial dose then 50 mg intravenously twice daily) or vancomycin (1 g intravenously twice daily) plus aztreonam (2 g intravenously twice daily) for up to 14 days. A total of 1057 patients (538 tigecycline and 519 vancomycin/aztreonam) met the protocol's minimal disease criteria and had a clinical response (clinically modified intent-to-treat population; i.e., those who received at least one dose of the study drug for a cSSSI that either involved deep soft tissue, required surgical intervention or was associated with significant underlying

disease) and 833 (422 tigecycline, 411 vancomycin/aztreonam) made up the clinically evaluable population. Clinical response rates in the tigecycline and vancomycin/aztreonam groups at the test-of-cure visit (12–92 days after therapy) were similar in the clinically modified intent-to-treat population (79.7 vs 81.9%, $p = 0.4183$) and clinically evaluable populations (86.5 vs 88.6%, $p = 0.4233$). Tigecycline was equally effective in patients who had monomicrobial and polymicrobial cSSSIs (each >86%). In addition, for patients with deep soft-tissue infection and abscesses, tigecycline provided greater than 86% clinical cure rates. Tigecycline was also effective in patients with diabetes mellitus (72%) and peripheral vascular disease (76%) in a rate similar to vancomycin/aztreonam (77 and 75%, respectively). Despite the small number of patients, tigecycline also cured greater than 82% (19 out of 23) of patients with bacteremia secondary to cSSSI similar to that of the vancomycin/aztreonam regimen (87.5%, 21 out of 24). Tigecycline was also very effective at eradicating MRSA (78%, 25 out of 32) in these two studies versus 76% (25 out of 33) with vancomycin/aztreonam. The authors concluded that tigecycline is an effective monotherapy for the treatment of cSSSI, especially when empirical coverage of Gram-positive and -negative pathogens is necessary.

Clinical efficacy in complicated intra-abdominal infections

Complicated intra-abdominal infections, which are typically characterized by a polymicrobial etiology, usually require a combination of appropriate broad-spectrum antimicrobial therapy and timely surgical intervention in order to achieve satisfactory clinical outcomes [15]. Since many bacteria comprising the gastrointestinal flora possess multiple resistance factors that express antimicrobial resistance patterns, potent antimicrobial combinations are often needed. The rapid and continuing

Table 5. Phase III clinical trial results.

Author	Regimen	n patients comprising intent-to-treat population	Mean duration of treatment (days)	Test of cure (no. of days post therapy)	Clinical outcomes for primary populations	Ref.
<i>Complicated skin and skin-structure infections</i>						
Ellis-Grosse et al.	Tigecycline 100 mg x 1, then 50 mg/12 h intravenous	566	8.2	12–92	c-mITT 79.7% (429/538) CE 86.5% (365/422)	[101]
	Vancomycin 1 g/12 h intravenous/aztreonam 2 g/12 h intravenous	550	8.3		c-mITT 81.9% (425/519) CE 88.6% (364/411)	
<i>Complicated intra-abdominal infections</i>						
Babinchak et al.	Tigecycline 100 mg x 1, then 50 mg/12 h intravenous	817	7.7	12–42	m-mITT 80.2% (506/631) ME 86.1% (441/512)	[103]
	Imipenem/cilastatin 500/500 mg/6 h intravenous	825	7.7		m-mITT 81.5% (514/631) ME 86.2% (442/513)	

CE: Clinically evaluable population; c-mITT: Clinically modified intent-to-treat population; ME: Microbiologically evaluable population; m-mITT: Microbiologically modified intent-to-treat population.

emergence of bacterial resistance over the last 10 years continues to spur efforts to identify new effective treatment options for complicated intra-abdominal infections.

Murray and colleagues reported the findings of a multicenter, Phase II, open-label trial, which evaluated tigecycline's efficacy in hospitalized patients who required surgery for complicated intra-abdominal infections [102]. Each patient received an intravenous 100 mg loading dose of tigecycline, followed by 50 mg every 12 h for 5–14 days. A total of 111 patients with perforated and gangrenous appendicitis, complicated cholecystitis or perforated diverticulitis and peritonitis were enrolled, of which 66 patients were evaluable for clinical efficacy. Clinical cure rates at the end-of-therapy and test-of-cure visits were 76 and 67%, respectively. Corresponding clinical cure rates for the intent-to-treat population were 72 and 55%, respectively. These preliminary findings, which found that tigecycline was effective in the treatment of patients with complicated intra-abdominal infections, paved the way for a Phase III trial.

Babinchak and coworkers recently summarized the findings of a pooled analysis of two Phase III double-blind trials that compared the efficacy of tigecycline and imipenem/cilastatin in more than 1600 patients with complicated intra-abdominal infections (TABLE 5) [103]. Each patient who satisfied the trial's entry criteria (i.e., had undergone a laparotomy, laparoscopy or percutaneous drainage of an intra-abdominal abscess and had a known or suspected complicated intra-abdominal infection) was randomly assigned to receive tigecycline (100 mg loading dose then 50 mg intravenously every 12 h) or imipenem/cilastatin (500/500 mg intravenously every 6 h) for 5–14 days. Clinical cure and microbiological eradication rates at the test-of-cure visit (12–42 days after therapy) were recorded for the two key patient populations, the microbiologically modified intent-to-treat population (i.e., those who received at least one dose of study drug and who had clinical evidence of a complicated intra-abdominal infection and a confirmed baseline isolate) and the microbiologically evaluable population (i.e., satisfied all protocol entry criteria, received at least 5 days of study antibiotic without any concomitant antibiotics and had a response recorded at the test-of-cure visit). Appendicitis complicated by perforation or a periappendiceal abscess was the most common intra-abdominal infection diagnosis (51%), followed by complicated cholecystitis (with evidence of empyema, perforation or gangrene [14%]). Clinical cure rates in the microbiologically modified intent-to-treat population were 80.2% for tigecycline versus 81.5% for imipenem/cilastatin (95% confidence interval [CI]: -5.8, 3.2). For the microbiologically evaluable group, clinical cure rates were 86.1% for tigecycline versus 86.2% for imipenem/cilastatin (95% CI: -4.5, 4.4). Tigecycline's clinical efficacy was equally effective across a variety of clinical diagnoses encountered when compared with the carbapenem, although clinical cure rates varied by the type of infection (e.g., higher clinical cure rates with complicated appendicitis vs lower clinical cure rates for intra-abdominal abscess). It was noted that patients with a monomicrobial infection had higher clinical cure rates (92%

tigecycline, 90% imipenem/cilastatin) compared with those with polymicrobial infections (83% tigecycline, 84% imipenem/cilastatin). This analysis also reported that tigecycline eradicated the majority of infections due to *E. coli* and *Klebsiella* spp. (>86%), and also, the majority of infections due to *Streptococcus* spp., methicillin-sensitive *S. aureus*, non-VRE enterococci and *B. fragilis* isolates. Although more data are needed to confirm tigecycline's efficacy against highly resistant isolates, this large pooled analysis supports that tigecycline monotherapy was efficacious and statistically equivalent to imipenem/cilastatin in the treatment of complicated intra-abdominal infections.

Safety & tolerability

The safety and tolerability of tigecycline can be assessed based upon several published Phase I–III trials, which involved nearly 1500 patients. Overall, gastrointestinal adverse events (i.e., nausea, vomiting and diarrhea) were reported most often, followed by local infusion-related irritations (e.g., injection site phlebitis) [86,100–103].

Muralidharan and colleagues reported the safety and tolerability of tigecycline in three Phase I, randomized, double-blind, placebo-controlled trials following single (12.5–300 mg as either a 1- or 4-h infusion rate) and multiple doses (25–100 mg every 12 h as a 1-h infusion or at variable infusion rates) [86]. The single-dose studies established that 100 mg was the maximum tolerated dose in healthy subjects during a fasting state, with tolerability increasing to 200 mg under fed conditions. Gastrointestinal adverse events, mainly nausea (48.5%) and vomiting (29.4%) were dose related, but not related to the length of intravenous infusion. The multiple-dose studies also observed that gastrointestinal intolerance (nausea) was dose related and that variable volume and infusion lengths failed to significantly alter the incidence of nausea and vomiting. These Phase I trials did not observe any clinically significant changes in routine laboratory parameters, blood pressure or QTc intervals, nor did any deaths or serious adverse events occur.

While Phase II trials with tigecycline administered in patients with skin and soft-tissue infections (25 or 50 mg every 12 h) [100] and intra-abdominal infections (50 mg every 12 h) [102] also observed that gastrointestinal intolerance was the most frequently reported adverse event, rates of nausea and vomiting were lower than observed in the Phase I trials. In the skin and soft-tissue infection study, nausea, vomiting and diarrhea were reported in 22, 13 and 11% of patients, respectively in the tigecycline 25 mg treatment group [100]. Corresponding adverse event rates in the 50 mg treatment group were 35, 19 and 9%, respectively. In the 50 mg group, three (<4%) patients discontinued therapy due to a gastrointestinal adverse effect (two nausea and vomiting, one diarrhea). Nine patients who received tigecycline had possibly drug-related abnormal laboratory test results, including elevated serum transaminases in five patients (four in the 50 mg group), elevated serum alkaline phosphatase in two patients (one per group), elevated blood urea nitrogen in one patient (50 mg group) and anemia in one patient (25 mg

group). In the Phase II clinical trial of patients with complicated intra-abdominal infections, nausea (42%) and vomiting (27%) were also the most commonly reported adverse effects [102]. One tigecycline-treated patient developed moderately severe *Clostridium difficile* colitis. No patient prematurely discontinued tigecycline in this study secondary to any adverse event.

The largest safety and tolerance experience with tigecycline following the approved dose for complicated skin and soft-tissue infections and intra-abdominal infections (100 mg loading, followed by 50 mg every 12 h) has been garnered from four Phase III trials [101,103]. Overall, 1415 patients were treated with tigecycline in these trials. Treatment-emergent adverse events, regardless of drug relatedness, were reported in 67.7% (383 out of 566) of tigecycline- and 61.1% (336 out of 550) of vancomycin/aztreonam-treated patients in the complicated skin and soft-tissue infection trials ($p = 0.024$) [99] and 73.8% (603 out of 817) of tigecycline-treated patients versus 71.6% (591 out of 825) of imipenem/cilastatin-treated patients in the complicated intra-abdominal studies [103]. In all four studies, tigecycline was prematurely discontinued for various reasons in 5% of patients compared with 4.7% in the control treatment groups (5.3% vancomycin/aztreonam vs 4.4% imipenem/cilastatin) [39].

In the complicated skin and soft-tissue infection studies, tigecycline was associated with a twofold higher rate of gastrointestinal-related adverse events compared with vancomycin/aztreonam (46 vs 21%, respectively; $p < 0.001$) [99]. Nausea (34.5%), vomiting (19.6%) and diarrhea (8.5%) occurred at significantly higher rates with tigecycline treatment compared with patients receiving vancomycin/aztreonam (8.2, 3.6 and 5.1%, respectively; $p \leq 0.032$). The incidence of rash, cardiovascular events and increases in alanine aminotransferase and/or aspartate aminotransferase levels were significantly higher in patients receiving the combination vancomycin/aztreonam group ($p \leq 0.003$) than for the tigecycline group. In the complicated intra-abdominal infection trial, tigecycline also had a significantly higher rate of gastrointestinal-related adverse events compared with imipenem/cilastatin (44.4 vs 39.4%, respectively; $p = 0.04$) [103]. Nausea (24.4% tigecycline, 19.0% imipenem/cilastatin; $p = 0.01$), vomiting (19.2% tigecycline, 14.3% imipenem/cilastatin; $p = 0.008$) and diarrhea (13.8% tigecycline, 13.2% imipenem/cilastatin; $p = 0.719$) were the most frequently reported adverse events in both treatment groups.

For the four Phase III studies combined, the most common drug-related adverse events following tigecycline therapy were nausea (20.4%) and vomiting (13.5%), of which approximately 95% were of mild-to-moderate severity [39]. Nausea and vomiting typically occurred after 1–2 days of tigecycline therapy. Early discontinuation of tigecycline therapy was most commonly due to nausea (1.3%) and vomiting (1%) [39]. Despite the high rate of nausea and vomiting associated with tigecycline, these adverse events may be minimized by administering the drug with food or metoclopramide.

Conclusion

Tigecycline, the first FDA-approved glycylcycline, is a new option for the management of serious infections caused by Gram-positive pathogens such as MRSA, Enterobacteriaceae and anaerobes including *B. fragilis* and *C. perfringens*. Phase III clinical trials demonstrated that tigecycline is effective in the treatment of patients with complicated skin and soft-tissue infections and complicated intra-abdominal infections, and led to FDA approval for these two indications. Tigecycline is available for intravenous administration and has a long elimination $t_{1/2}$ that permits twice-daily dosing. Gastrointestinal side effects (nausea and vomiting) were the most frequently reported adverse events in the clinical trials conducted; most episodes of nausea and vomiting (95%) were of mild-to-moderate severity. Currently available data suggest that tigecycline may play an important role in the future as a monotherapy alternative to older broad-spectrum antibiotics, such as advanced-generation cephalosporins, carbapenems, fluoroquinolones, piperacillin/tazobactam and Gram-positive-directed agents (e.g., daptomycin, linezolid and quinupristin/dalfopristin).

Expert commentary

The use of tetracyclines for treating bacterial infections is limited due to the emergence of resistant organisms with efflux and ribosomal protection mechanisms of resistance. Tigecycline, the first-in-class glycylcycline, is a synthetic analog of the tetracycline family that shares several structural features with minocycline but includes an *N*,*tert*-buthylglyclamido (TBG) substitution at the 9-position. *In vitro*, tigecycline demonstrates activity against tetracycline-resistant bacteria containing genes responsible for efflux mechanisms (e.g., tet[A] in Gram-negative bacteria and tet[K] in Gram-positive bacteria) and ribosomal protection (e.g., tet[M]).

Tigecycline demonstrates broad-spectrum antimicrobial activity against aerobic and anaerobic pathogens, as well as selected atypical pathogens, but possesses limited activity against *P. aeruginosa* and *Proteus* spp.

Tigecycline is a parenteral agent with moderate protein binding that extends its $t_{1/2}$ (nearly 42 h) and allows for twice-daily dosing. Studies in humans have shown that tigecycline is well distributed into inflammatory fluid, the gallbladder, lung, colonic tissues and bile. Prospective, multicenter randomized, double-blind, comparative clinical studies demonstrated that tigecycline monotherapy was clinically equivalent to current standard therapies. Clinical trials studying cSSSIs demonstrated that tigecycline has equivalent efficacy and safety compared with the combination of vancomycin and aztreonam and for complicated intra-abdominal infection, tigecycline was found to be as effective as imipenem/cilastatin. Tigecycline appears to be a promising new monotherapy with excellent efficacy and safety in the treatment of nosocomial infections for which it is indicated.

Several key issues regarding tigecycline need to be resolved, these include:

- Should tigecycline assume a first-line role directed against Gram-positive agents (e.g., daptomycin, linezolid and

quinupristin/dalfopristin) and other broad-spectrum agents for the treatment of hospital-acquired infections likely caused by MRSA and *Enterococcus* spp., and non-*Pseudomonas* Gram-negative nosocomial infections given the current climate of resistance, or should it be positioned as a second-line therapy when standard treatments fail or are found to be nonsusceptible?

- Will the equivalent efficacy and safety of tigecycline monotherapy compared with vancomycin/aztreonam for cSSSIs and imipenem/cilastatin for complicated intra-abdominal infections combined but with the advantage of twice-daily dosing make tigecycline a preferred agent to use for these infections?
- Will the intravenous-only dosage form and gastrointestinal intolerance limit tigecycline's usefulness?

Five-year view

Tigecycline has demonstrated a broad spectrum of antimicrobial activity against many Gram-positive and -negative aerobes and anaerobes. Its long $t_{1/2}$ permits twice-daily dosing. Several prospective, multicenter randomized, double-blind, comparative clinical studies demonstrated similar clinical efficacy of tigecycline compared with agents such as vancomycin/aztreonam and imipenem/cilastatin. Tigecycline has proven clinical efficacy and safety in the treatment of complicated skin and soft-structure infections and complicated intra-abdominal infections.

Disclosure

This paper was supported in part by Wyeth Research.

Key issues

- Tigecycline (Tygacil™, Wyeth Pharmaceuticals) is the first available agent in a new class of antibiotics known as glycyclines.
- Tigecycline has much stronger ribosome binding affinity (fivefold higher) compared with the tetracycline family of antibiotics, which may explain its superior *in vitro* activity.
- Tigecycline has broad-spectrum *in vitro* activity including aerobic, facultative and anaerobic Gram-positive and -negative bacteria.
- Tigecyclines novel mechanism of action allows for *in vitro* activity against tetracycline-resistant bacteria containing genes responsible for tetracycline efflux or ribosomal protection.
- Tigecycline has *in vitro* activity against many antibiotic-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* and extended spectrum β -lactamase-producing enteric Gram-negative bacilli.
- Tigecycline has a long serum elimination half-life (nearly 42 h) and thus can be administered twice daily.
- Tigecycline can only be administered intravenously as a 0.5–1 h infusion.
- Tigecycline is not extensively metabolized, thus lowering the potential of drug–drug interactions involving cytochrome P450 enzymes.
- Clinical trials to date have shown excellent efficacy in the treatment of complicated skin and skin-structure infections and complicated intra-abdominal infections, including patients with MRSA.
- Gastrointestinal adverse events (i.e., nausea, vomiting and diarrhea) were reported most commonly.

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Affiliations

- George G Zhanel
University of Manitoba, Department of Medical Microbiology, Faculty of Medicine, Departments of Medicine, Clinical Microbiology, Health Sciences Centre, Winnipeg, Manitoba, Canada
Tel.: +1 204 787 4902
Fax: +1 204 787 4699
ggzhanel@pcs.mb.ca
- James A Karlowsky
University of Manitoba, Department of Medical Microbiology, Faculty of Medicine, Departments of Medicine, Clinical Microbiology, Health Sciences Centre, Winnipeg, Manitoba, Canada

Tel.: +1 204 787 4597
Fax: +1 204 787 4699
jkarlowsky@hsc.mb.ca

- Ethan Rubinstein
University of Manitoba, Department of Medical Microbiology, Faculty of Medicine, Departments of Medicine, Clinical Microbiology, Health Sciences Centre, Winnipeg, Manitoba, Canada
Tel.: +1 204 977 5681
Fax: +1 204 789 3926
erubins@yahoo.com
- Daryl J Hoban
University of Manitoba, Department of Medical Microbiology, Faculty of Medicine, Departments of Medicine, Clinical Microbiology, Health Sciences Centre, Winnipeg, Manitoba, Canada
Tel.: +1 204 787 1191
Fax: +1 204 787 4699
dhoban@hsc.mb.ca