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Tigecycline

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Contents

Abstract

▲ Tigecycline is the first member of a new class of broad-spectrum antibacterials, the glycylcyclines, that has been specifically developed to overcome the two major mechanisms of tetracycline resistance (ribosomal protection and efflux).

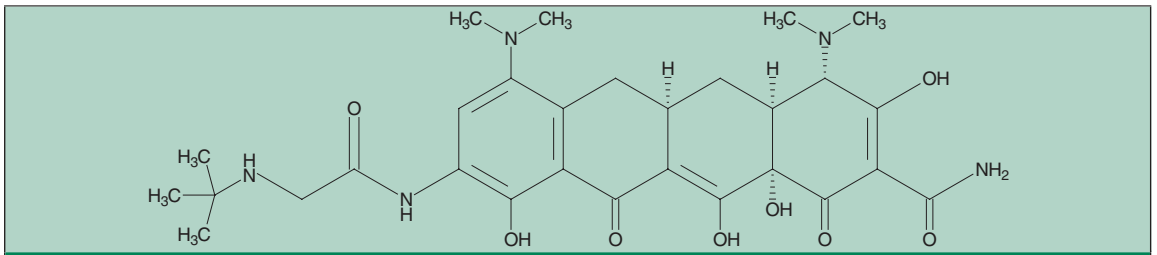
▲ *In vitro*, tigecycline was active against a wide range of Gram-positive and -negative aerobic and anaerobic bacteria implicated in complicated skin and skin structure infections (cSSSIs) and complicated intra-abdominal infections (cIAIs).

▲ Intravenously administered tigecycline (recommended dosage regimen 100mg initially, followed by 50mg every 12 hours for 5–14 days) has been approved by the US FDA for the treatment of cSSSIs and cIAIs.

▲ In well designed, pivotal phase III studies, tigecycline monotherapy was noninferior to combination therapy with vancomycin 1g plus aztreonam 2g every 12 hours in hospitalised adult patients with cSSSIs (two trials; pooled clinical cure rates, 86.5% vs 88.6%) or broad-spectrum therapy with imipenem/cilastatin 200–500mg/200–500mg every 6 hours in hospitalised adult patients with cIAIs (two trials; pooled clinical cure rates, 86.1% vs 86.2%).

▲ Tigecycline was generally well tolerated in phase III studies; nausea, vomiting and diarrhoea were the most frequent adverse events in patients treated with tigecycline or an active comparator (vancomycin plus aztreonam or imipenem/cilastatin).

Features and properties of tigecycline (Tygacil™)	
Indications	
Complicated skin and skin structure infections and complicated intra-abdominal infections	
Mechanism of action	
Protein 30S ribosomal subunit inhibitor	
Dosage and administration	
Recommended dosage	100mg initially, followed by 50mg every 12 hours
Recommended duration	5–14 days
Route of administration	30- to 60-minute intravenous infusion
Pharmacokinetic profile (100mg initially, followed by 50mg every 12 hours; infusions administered over 30–60 minutes). Mean steady state values in healthy volunteers	
Peak plasma concentration	0.87 μg/mL (30-minute infusion)
	0.63 μg/mL (60-minute infusion)
Area under the plasma concentration-time curve from 0–24h	4.7 μg • h/mL
Volume of distribution	639L
Elimination half-life	42.4h
Most common adverse events	
Nausea, vomiting and diarrhoea	



Tigecycline (Tygacil™)[1] is the first member of the glycylcyclines (a new class of broad-spectrum antibacterials structurally related to tetracyclines) to be licensed for clinical use. Glycylcyclines have been specifically developed to circumvent the two major mechanisms of resistance to tetracyclines (ribosomal protection and efflux), which have substantially decreased the effectiveness of these agents.[1,2]

Glycylcyclines, like tetracyclines, are generally bacteriostatic agents that inhibit protein synthesis in bacteria by reversibly binding to a single, high-affinity intracellular site (which the two drug classes share in common) on the 30S ribosomal subunit.[2] This action blocks the entry of amino-acyl transfer RNA molecules into the A-site of the ribosome, thus preventing the incorporation of amino acid residues into elongating peptide chains. However, glycylcyclines bind five times more effectively than tetracyclines to the ribosomal binding site;[3] this may account for their ability to overcome ribosome-based tetracycline resistance.[2] Moreover, tigecycline appears to interact with both the ribosomal binding site and the A-site in a manner distinct from that of tetracyclines.[4,5]

This profile reviews the *in vitro* antibacterial activity against clinically relevant bacteria (see section 5) and the pharmacology of tigecycline, and focuses on the clinical efficacy and tolerability of intravenous tigecycline in adult hospitalised patients with complicated skin and skin structure infections (cSSSIs) or complicated intra-abdominal infections (cIAIs).

1. Antibacterial Activity

In Vitro Activity

The following section focuses on the activity of tigecycline against a range of designated pathogens (i.e. susceptible strains of bacteria that cause infections in patients with cSSSIs or cIAIs as are specified in the US manufacturer's prescribing information;[6] see section 5).

The *in vitro* activity of tigecycline was assessed in terms of minimum inhibitory concentrations, e.g. those required to inhibit 50% (MIC_{50}) or 90% (MIC_{90}) of bacterial strains. Testing was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) [renamed Clinical and Laboratory Standards Institute; CLSI] dilution methods (broth, agar or microdilution).

In vitro activity has been evaluated in large studies (>5000 isolates)[7-12] from the two ongoing, global surveillance programmes (TEST [Tigecycline Evaluation Surveillance Trial][7,8] and SENTRY[9-12]) and several smaller studies (>300 isolates).[13-22] With two exceptions,[12] these studies have been published in full; additional results from the TEST initiative[23,24] are also available as posters/abstracts. Where specified, clinical isolates were obtained between 1998 and 2004.[7-9,11-15,17,19-22]

Proposed breakpoints in the US indicating susceptibility to tigecycline include ≤0.5 μg/mL for *Staphylococcus aureus* (including methicillin-resistant strains), ≤0.25 μg/mL for *Streptococcus* spp.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table I. *In vitro* activity (MIC values [μg/mL]) of tigecycline against designated[a] Gram-positive, -negative and anaerobic organisms in complicated skin and skin structure infections and complicated intrabdominal infections. The US susceptibility breakpoints for tigecycline were ≤0.5 μg/mL for *Staphylococcus aureus* (including methicillin-resistant strains), ≤0.25 μg/mL for *Streptococcus* spp. and vancomycin-susceptible *Enterococcus faecalis*, ≤2 μg/mL for Enterobacteriaceae and ≤4 μg/mL for anaerobes. Proposed intermediate susceptibility and resistance breakpoints for tigecycline were 4 and ≥8 μg/mL, respectively, for Enterobacteriaceae, and 8 and ≥16 μg/mL, respectively, for anaerobes.[6] Results from fully published studies evaluating tigecycline against clinical isolates collected from centres located worldwide,[7,13] or from centres in North America,[14,16,18,22] Asia[19] or Europe[15,17,20,21] (including the Middle East and South Africa[15]). Where stated, isolates were obtained over a ≥1-year period between 1998 and 2004[7,13-15,17,19-22]

Species (no. of isolates)	MIC_{50}	MIC_{90}	References
Aerobic facultative Gram-positive organisms			
Enterococcus faecalis [vancomycin-susceptible isolates] (527)	0.06–0.12	0.12–0.25	7,13,18
MRSA (1047)	0.12–0.25	0.25–0.5	7,13,15-17,19
MSSA (1737)	0.12–0.25	0.125–0.25	7,13,15-17,19
Streptococcus agalactiae (370)	0.06–0.12	0.12–0.25	7,13,14
S. anginosus group[b] (254)	0.06	0.06–0.12	13
S. pyogenes (114)	0.06–0.12	0.12	13,14
Aerobic facultative Gram-negative organisms			
Citrobacter freundii (90)	0.5	1–2	13,17,18
Enterobacter cloacae (501)	0.5–2	1–4	13,15,17-19
Escherichia coli[c] (2394)	0.12–0.25	0.25–0.5	7,13,15,17-19
Klebsiella oxytoca (285)	0.25–0.5	0.5–1	7,13,17,18
K. pneumoniae[c] (1268)	0.5	1–2	7,13,15,17-19
Anaerobic organisms			
Bacteroides fragilis (957)	0.12–2	0.25–16	13,18-22
B. thetaiotaomicron (340)	0.125–2	0.5–8	13,20-22
B. uniformis (113)	0.25–2	0.5–8	13,20-22
B. vulgatus (136)	0.25–1	2–8	13,20-22
Clostridium perfringens (91)	0.032–0.5	0.25–1	13,20
Peptostreptococcus micros (53)	0.032–≤0.06	≤0.06–0.25	13,20

a Those pathogens specified in the US manufacturer's prescribing information.[6]

b Includes *S. anginosus*, *S. intermedius* and *S. constellatus*.

c Extended spectrum β-lactamase-negative strains.[7,15]

MIC_x = minimum concentration required to inhibit *x*% of isolates; **MRSA** = methicillin-resistant *Staphylococcus aureus*; **MSSA** = methicillin-sensitive *Staphylococcus aureus*.

(other than *Streptococcus pneumoniae*) and vancomycin-susceptible *Enterococcus faecalis*, ≤2 μg/mL for Enterobacteriaceae and ≤4 μg/mL for anaerobes. The breakpoints indicating intermediate susceptibility and resistance to tigecycline are 4 and ≥8 μg/mL, respectively, for Enterobacteriaceae, and 8 and ≥16 μg/mL, respectively, for anaerobes.[6]

Gram-Positive and -Negative Aerobes

- Tigecycline is very active against most Gram-positive aerobes commonly associated with cSSSIs and cIAIs, including *Staphylococcus* spp., *Enterococcus* spp. and *Streptococcus* spp., according to data from *in vitro* studies,[7-11,13-19] including those from the TEST[7,8] and SENTRY[9-11] surveillance programmes. For the designated Gram-positive bacteria, MIC_{50} values were ≤0.25 μg/mL and MIC_{90} values were ≤0.5 μg/mL (see table I).

- Vancomycin-susceptible *E. faecalis* (n = 333), methicillin-susceptible *S. aureus* (MSSA; n = 489), methicillin-resistant *S. aureus* (MRSA; n = 348) and *S. agalactiae* (n = 328) were the designated organisms evaluated in the TEST programme;[7] 98.9–100% of these isolates were susceptible to tigecycline.

- As indicated by the results of the TEST programme[7,24] (and other studies[13,15-17,19]), tigecycline remains active against MRSA. Likewise, it

is active against tetracycline-[12] and oxacillin-[12] resistant strains of *S. aureus* (MIC_{90} 0.5 μg/mL). Tigecycline also retains its activity against vancomycin-resistant *E. faecalis*; tigecycline MIC_{90} values for these isolates (0.12–0.5 μg/mL)[7,14,18] were similar to those reported for vancomycin-susceptible isolates (see table I). Using a tigecycline susceptibility breakpoint of 2 μg/mL, all 22 vancomycin-resistant isolates of *E. faecalis* evaluated in the TEST programme were susceptible to the drug (MIC_{90} 0.12 μg/mL).[23]

- Tigecycline is active against most Enterobacteriaceae and non-fermentative Gram-negative organisms, according to data from *in vitro* studies,[7-10,13,15,17-19] including those from the TEST[7,8] and SENTRY[9,10] surveillance programmes. MIC_{50} values were ≤2 μg/mL and MIC_{90} values were ≤4 μg/mL for the designated Gram-negative bacteria (see table I).

- *Escherichia coli* (n = 893 extended spectrum β-lactamase [ESBL]-negative and 24 ESBL-positive isolates), *Klebsiella pneumoniae* (n = 655 ESBL-negative and 92 ESBL-positive isolates), *K. oxytoca* (n = 156) and *Enterobacter cloacae* (n = 597) were the designated Enterobacteriaceae evaluated in the TEST programme;[7] 91.3–100% of these isolates, including ESBL-positive isolates of *E. coli* (MIC_{90} 0.5 μg/mL) and *K. pneumoniae* (MIC_{90} 2 μg/mL), were susceptible to the drug.

- Results from the SENTRY programme showed that tigecycline had good activity against *Acinetobacter* spp. (n = 61, MIC_{90} 2 μg/mL; 96.7% susceptibility), less activity against *Proteus miribalis* (n = 91, 4 μg/mL; 52.7% susceptibility) and indole-positive *Proteae* spp. (n = 66, 4 μg/mL; 89.4% susceptibility), and little activity against *Pseudomonas aeruginosa* (n = 337, 16 μg/mL; 18.1% susceptibility).[11]

- Minimum inhibitory concentrations for aerobic organisms determined by broth dilution must use testing medium that is fresh (<12 hours old) or supplemented with the biocatalytic oxygen-reducing reagent Oxyrase.[25]

Gram-Positive and -Negative Anaerobes

- Tigecycline is active against most Gram-positive and -negative anaerobes;[13,18-22] tigecycline MIC_{50} and MIC_{90} values for designated anaerobic bacteria are shown in table I. Although there was a wide range of MIC_{90} values for *Bacteroides fragilis* (0.25–16 μg/mL) and, to a lesser extent, other designated *Bacteroides* spp. (0.5–8 μg/mL), MIC_{50} values for these organisms were ≤2 μg/mL (table I).

Post-Antibiotic Effect and Bacteriostatic/Bactericidal Activity

- At eight times the MIC, tigecycline had an *in vitro* post-antibiotic effect (PAE) of about 3–4 hours against *S. aureus* and about 2–3 hours against *E. coli*, including those strains carrying a tetracycline (M, B or K) resistance determinant.[5,26] Tigecycline 3 mg/kg demonstrated a PAE of 4.9 hours against *E. coli* in an *in vivo* animal infection model.[27]

- *In vivo*[27,28] and *in vitro*[5,26,29] studies have demonstrated that tigecycline is generally a bacteriostatic agent against the clinically relevant pathogens (see section 5); however, some bactericidal activity has been measured against *S. pneumoniae* and *Haemophilus influenzae*. Against *Staphylococcus* spp., at four times the MIC, tigecycline generally reduced the bacterial count by <3 log_{10} cfu/mL over 24 hours (bacteriostatic activity) in an *in vitro* study; however, for many strains, there was a 1–2 log_{10} reduction in cfu/mL over 24 hours, indicating bactericidal activity.[5,26] Tigecycline also demonstrated bactericidal activity against some *E. coli* strains (0.8–1.7 log_{10} reduction in cfu/mL over 24 hours).[5,26]

Resistance

- Tigecycline (and other glycylcyclines) are thought to overcome ribosome-based tetracycline resistance through enhanced binding to the ribosome, and efflux-based tetracycline resistance through an inability to induce and/or be exported by tetracycline-specific efflux proteins.[2,30] Tigecycline is, however, a substrate for multidrug efflux systems (e.g. MexXY, AcrAB); overexpression of

these pumps is associated with reduced susceptibility to the drug in several species of Gram-negative bacteria (e.g. *E. coli*, *K. pneumoniae*, *Morganella morganii*, *Proteus* spp., *Providencia* spp. and *P. aeruginosa*[31-35]).

- Other resistance mechanisms, such as β-lactamases (including ESBLs), target site modifications, macrolide efflux pumps or enzyme target changes (e.g. gyrase/topoisomerase) do not affect tigecycline; cross-resistance with other (unspecified) antibiotics has not been observed.[6]

2. Pharmacokinetic Profile

The pharmacokinetics of tigecycline after single or multiple doses have been examined in adult volunteers,[36-40] in patients with cSSSIs,[41,42] and in patients with renal[38,43] or hepatic[6] impairment.

Throughout this section, the recommended dosage regimen for tigecycline refers to an initial loading dose of 100mg, followed by a maintenance dose of 50mg every 12 hours[6] (see section 5). All doses of tigecycline were given as an intravenous infusion over 30–60 minutes. Reported values for pharmacokinetic parameters are means (where known).

- Tigecycline displays linear pharmacokinetics.[36] When administered at the recommended dose (60-minute infusion) in 15 patients with cSSSIs,[41] the maximum serum concentration (C_{max}) at steady state was 0.633 μg/mL and the area under the serum concentration-time curve (AUC) from 0 to 12 hours (AUC_{12}) was 3.04 μg • h/mL. Steady-state was reached after approximately 3–4 days of repeated administration.[41]
- The US manufacturer's prescribing information presents pooled data from 103 healthy subjects without infection who participated in clinical pharmacology studies.[6] The tigecycline C_{max} at steady state was 0.87 and 0.63 μg/mL after 30- and 60-minute infusions of the recommended dose, respectively; the AUC from 0 to 24 hours was 4.7 μg • h/mL.
- Food has no effect on the pharmacokinetics of tigecycline.[36]
- At drug concentrations observed in clinical studies (0.1–1.0 μg/mL), tigecycline is ≈71–89% bound to plasma proteins *in vitro*.[6]
- Tigecycline has a large apparent volume of distribution at steady-state after administration of a single 100mg dose (568L; n = 224) or multiple doses (recommended regimen, 639L; n = 103).[6,39,44]
- Tigecycline penetrates well into tissues and body fluids.[6,39,44] The ratios of tigecycline in the gall bladder, lung, colon, bone and synovial fluid relative to tigecycline in the serum 4 hours after administration of a single 100mg dose in 54 patients undergoing elective surgery were 39, 8.6, 2.1, 0.35 and 0.58, respectively.[44] The relatively low concentration of tigecycline in bone (and synovial fluid) was possibly the result of difficulties encountered in extracting the drug from the bone samples for assay.[44]
- After administration of the recommended tigecycline dosage regimen to healthy volunteers (n = 33[6] and 10[39]), tigecycline was detected in alveolar[6] and epithelial cells[6] and cantharidin-induced blister fluid,[39] with respective AUC_{12} values 78-fold higher, 32% higher and 26% lower than those in the serum. Tigecycline at concentrations of 1 and 10 μg/mL was taken up by polymorphonuclear neutrophils, in which concentrations were ≈20- and ≈30-fold higher than extracellular concentrations after 1 hour, in an *in vitro* study.[45]
- Tigecycline is not metabolised extensively.[6] The most abundant metabolites observed are glucuronide metabolites of tigecycline and its epimer (M1 and M2) and the N-acetyl-9-aminominocycline (M6).[40]
- Tigecycline is primarily eliminated in the faeces, predominantly as unchanged drug. In healthy men administered a single 50mg dose of radiolabelled ^{14}C-tigecycline after receiving unlabelled tigecycline at the recommended dosage, 59% of the radioactive dose was recovered in the faeces; 33% was recovered in the urine.[40] Approximately 22% of the administered dose of tigecycline is excreted in the urine as unchanged parent compound;[6] ≈4% and ≈5% is excreted as glucuronide conjugates in the urine and faeces, respectively.[40]
- Tigecycline has a long serum half-life ($t_{1/2}$) after administration of a single 100mg dose (27.1 hours;

n = 224) or the recommended dosage (42.4 hours; n = 103). Systemic clearance values were similar after administration of a single 100mg dose (21.8 L/h) or the recommended dosage (23.8 L/h).[6]

- The pharmacokinetic disposition of a single intravenous dose of tigecycline 100mg did not differ significantly in healthy adult men (young or old), compared with healthy adult women (young or old),[37] nor was it altered significantly in patients with severe renal impairment (creatinine clearance <30 mL/min) or those with end-stage renal failure undergoing haemodialysis[43] (see section 5).
- The pharmacokinetics of a single (unspecified) dose of tigecycline were not altered in patients with mild (Child Pugh A) hepatic impairment, although systemic clearance was reduced by 25% and 55% in patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment, respectively; $t_{1/2}$ was prolonged by 23% and 43% (see section 5 for dosage adjustments).
- No significant drug interactions were noted during concomitant administration of tigecycline at the recommended dosage and oral digoxin 0.25mg in healthy men.[46]
- The pharmacokinetic profile of tigecycline administered at the recommended dosage was unaltered after a single dose of warfarin 25mg in healthy volunteers, whereas R-warfarin and S-warfarin AUC values were increased by 68% and 29%, respectively.[6] Although tigecycline had no influence on the effect of warfarin on the international normalised ratio, the US manufacturer recommends monitoring anticoagulation when these drugs are coadministered.[6]
- Based on the results of *in vitro* studies in human liver microsomes, tigecycline is not expected to alter the disposition of drugs metabolised by the cytochrome P450 (CYP) 1A2, 2C8, 2C9, 2C19, 2D6 or 3A4 isoforms.[6] Moreover, drugs that inhibit or induce these CYP isoforms are not expected to influence the pharmacokinetics of tigecycline.[6]

3. Therapeutic Efficacy

The clinical efficacy of tigecycline in hospitalised adults with cSSSIs or cIAIs has been evaluated in four randomised, double-blind, active-comparator-controlled, multinational, phase III trials[47-50] and two open-label, multicentre, phase II studies based in the US.[42,51] The following discussion, however, focuses only on the phase III trials, which consisted of two similarly designed, noninferiority comparisons of tigecycline monotherapy with vancomycin plus aztreonam combination therapy in patients with cSSSIs (Studies 300[47] and 305[48]) and two similarly designed, noninferiority comparisons of tigecycline monotherapy with imipenem/cilastatin broad-spectrum therapy in patients with cIAIs (Studies 301[50] and 306[49]). All agents were administered intravenously; tigecycline was given at the recommended dosage (see section 5).

All four trials have been published in full.[47-50] However, all of the data in this section are derived from integrated analyses of Studies 300/305[52,53] and 301/306,[54] which have been published in full[52,54] or as an abstract only.[53] Individual and integrated analyses of these studies have also been presented in the US manufacturer's prescribing information.[6]

The primary efficacy endpoint in Studies 300 and 305 in patients with cSSSIs was the clinical response at the test-of-cure (TOC) visit (12–92 days after treatment end) in the clinical-modified intent-to-treat (C-MITT; n = 1057) and clinically evaluable (CE; n = 833) populations[52] (pooled data) [see figure 1 for definitions of each co-primary population]. The primary efficacy endpoint in Studies 301 and 306 in patients with cIAIs was the clinical response at the TOC visit (12–42 days after treatment end) in the microbiological-modified intent-to-treat (M-MITT; n = 1262) and microbiologically evaluable (ME; n = 1025) populations[54] (pooled data) [see figure 2 for definitions of each co-primary population].

In these studies, clinical success (cure) was defined as resolution of signs and symptoms such that no further antibacterial therapy (or surgical or radiological intervention) was necessary.[52,54] Microbiological response was assessed at the level of the patient and the isolate;[52,54] bacterial eradication occurred when no pathogens were present in the

culture obtained from the original site of infection, or was presumed when clinical cure precluded the availability of a specimen for culture.[49,52,54]

Tigecycline was concluded to be no less effective than the active comparator if the lower limit of the two-sided 95% confidence interval for the between-group difference in clinical or microbiological response (tigecycline minus active comparator) was no less than −15%.[52,54] The confidence interval was corrected for continuity[52,54] and, in patients with cIAIs only, adjusted for disease severity.[54]

Complicated Skin and Skin Structure Infections

In Studies 300 and 305, patients aged ≥18 years with cSSSIs were randomised to treatment with tigecycline or vancomycin 1g plus aztreonam 2g (every 12 hours) for 5–14[6] (mean ≈8[52]) days. Deep soft tissue infection involving cellulitis (59%) and major abscesses (28%) were the most common baseline infection subdiagnoses (CE population).[52] *S. aureus* (MSSA, 47%; MRSA, 12%) was the most commonly isolated organism from the site of infection at baseline, while *E. coli* (10.9%) was the most frequently isolated Gram-negative aerobe (ME population).[52]

- Tigecycline was no less effective than vancomycin plus aztreonam in the treatment of cSSSIs, based on a combined noninferiority analysis of clinical cure rates in Studies 300 and 305.[52] The lower limits of the 95% confidence intervals for the between-group differences in clinical cure rates at the TOC visit were −7.1% (C-MITT population) and −6.8% (CE population) [both $p < 0.001$]. Individual and integrated clinical cure rates in these studies are shown in figure 1.
- In secondary analyses based on integrated data from Studies 300/305,[52] no significant differences between tigecycline- and vancomycin plus aztreonam-treated patients were seen when clinical cure rates at the TOC visit were stratified by the number of pretherapy isolates (monomicrobial vs polymicrobial; M-MITT and ME populations) or by the baseline infection subdiagnosis (CE population).
- Tigecycline was also noninferior to vancomycin plus aztreonam with respect to the microbiological eradication rate (ME population).[52] Pooled eradication rates at the TOC visit were 82.1% in tigecycline recipients versus 86.2% in vancomycin plus aztreonam recipients; the lower limit of the 95% confidence interval for the between-group difference was −10.6.[52]
- Pooled eradication rates at the TOC visit (ME population) for selected infecting pathogens were generally similar in tigecycline and vancomycin plus aztreonam recipients, as follows: MRSA, 78.1% (25/32) versus 75.8% (25/33); MSSA, 88.8% (119/134) versus 90.8% (109/120); *S. pyogenes*, 93.8% (30/32) versus 92.6% (25/27); *S. agalactiae*, 87.5% (7/8) versus 84.6% (11/13); *S. anginosus/*

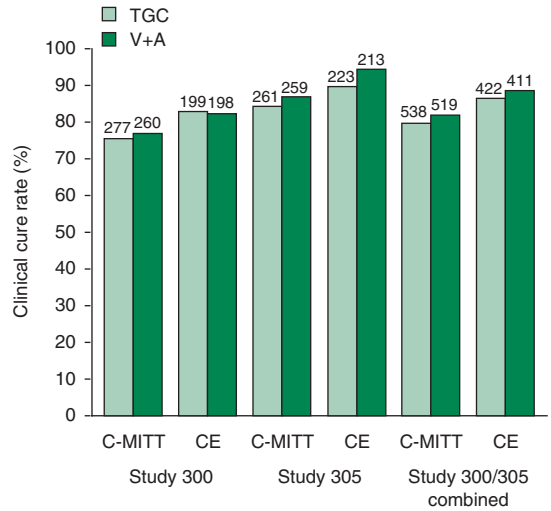


Fig. 1. Comparative efficacy of tigecycline (TGC) and vancomycin plus aztreonam (V+A) in complicated skin and skin structure infections (cSSSIs). Individual and integrated clinical cure rates at the test-of-cure visit (12–92 days after treatment end) in two randomised, double-blind, multinational trials (Studies 300 and 305) in hospitalised adult patients with cSSSIs who received intravenous TGC (100mg initially, followed by 50mg every 12 hours) or V+A (1g/2g every 12 hours) for 5–14 days.[6,52] All patients received at least one dose of study medication; individuals in the co-primary clinical-modified intent-to-treat (C-MITT) population satisfied severity criteria, while those in the co-primary clinically evaluable (CE) population satisfied severity and evaluability criteria. Clinical cure was defined as resolution of signs and symptoms such that no further antibacterial therapy (or surgical or radiological intervention) was necessary. Numbers above the bars are the total number of patients in each population.

intermedius/constellatus, 87.5% (14/16) versus 85.7% (6/7); *E. faecalis* (vancomycin-susceptible only), 87.5% (14/16) versus 91.7% (22/24); *E. coli*, 82.8% (24/29) versus 90.0% (27/30); and *B. fragilis*, 100.0% (8/8) versus 80.0% (4/5).[52]

- Another pooled analysis of Studies 300/305[53] indicated that the length of hospital stay, especially among patients with a causative Gram-negative pathogen, was significantly reduced by ≈1 day in tigecycline recipients, compared with vancomycin plus aztreonam recipients.

Complicated Intra-Abdominal Infections

In Studies 301[50] and 306,[49] patients aged ≥18 years with cIAIs were stratified by disease severity (APACHE II score ≤15 vs >15 to <31) and randomised to treatment with tigecycline or imipenem/cilastatin (200–500mg/200–500mg [adjusted according to bodyweight and creatinine clearance] every 6 hours) for 5–14 (mean ≈7–8) days. According to a combined analysis of these two studies,[54] complicated appendicitis (50%), complicated cholecystitis (14%), intra-abdominal abscess (10%) and intestinal perforation (10%) were the most common baseline infection subdiagnoses (M-MITT population), and *E. coli* (65%) and *Klebsiella* spp. (15%) were the most commonly isolated Gram-negative aerobes (ME population). Ineligible patients included those with suspected pancreatic abscess or infected necrotising pancreatitis.[54]

- Tigecycline was no less effective than imipenem/cilastatin in the treatment of cIAIs, based on a combined noninferiority analysis of clinical cure rates in Studies 301 and 306.[54] The lower limits of the 95% confidence intervals for the between-group differences in clinical cure rates at the TOC visit were −5.8% (M-MITT population) and −4.5% (ME population) [both $p < 0.0001$]. Individual and integrated clinical cure rates in these studies are shown in figure 2.
- In secondary analyses based on integrated data from Studies 301/306,[54] no significant differences between the tigecycline and imipenem/cilastatin groups were observed when clinical cure rates at the TOC visit were stratified by monomicrobial versus polymicrobial infection (M-MITT and ME populations) or by the baseline infection subdiagnosis (ME population).
- Tigecycline was also noninferior to imipenem/cilastatin with respect to the microbiological eradication rate (ME population).[54] Pooled eradication rates at the TOC visit were 86.1% in tigecycline recipients versus 86.2% in imipenem/cilastatin recipients; the lower limit of the 95% confidence interval for the between-group difference was −4.5 ($p < 0.0001$).[54] No significant differences between treatment groups were seen when eradication rates were stratified by monomicrobial versus polymicrobial infection.[54]

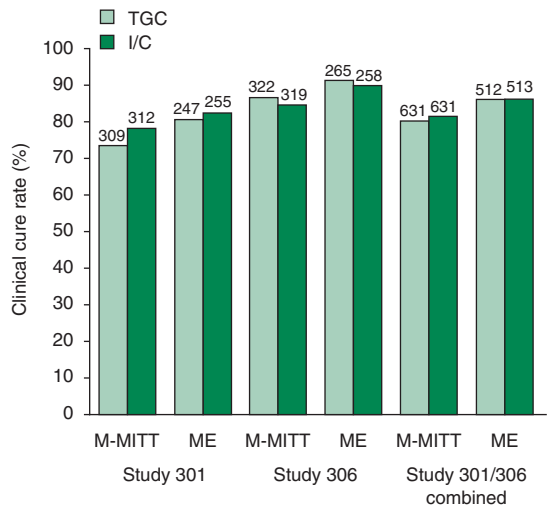


Fig. 2. Comparative efficacy of tigecycline (TGC) and imipenem/cilastatin (I/C) in complicated intra-abdominal infections (cIAIs). Individual and integrated clinical cure rates at the test-of-cure visit (12–42 days after treatment end) in two randomised, double-blind, multinational trials (Studies 301 and 306) in hospitalised adult patients with cIAIs who received intravenous TGC (100mg initially, followed by 50mg every 12 hours) or I/C (200–500mg/200–500mg [adjusted according to bodyweight and creatinine clearance] every 6 hours) for 5–14 days.[6,54] All patients received at least one dose of study medication; individuals in the co-primary microbiological-modified intent-to-treat (M-MITT) population satisfied severity criteria and had a baseline pathogen, while those in the co-primary microbiologically evaluable (ME) population satisfied severity and evaluability criteria, and had a baseline or susceptible pathogen. Clinical cure was defined as resolution of signs and symptoms such that no further antibacterial therapy (or surgical or radiological intervention) was necessary. Numbers above the bars are the total numbers of patients in each group.

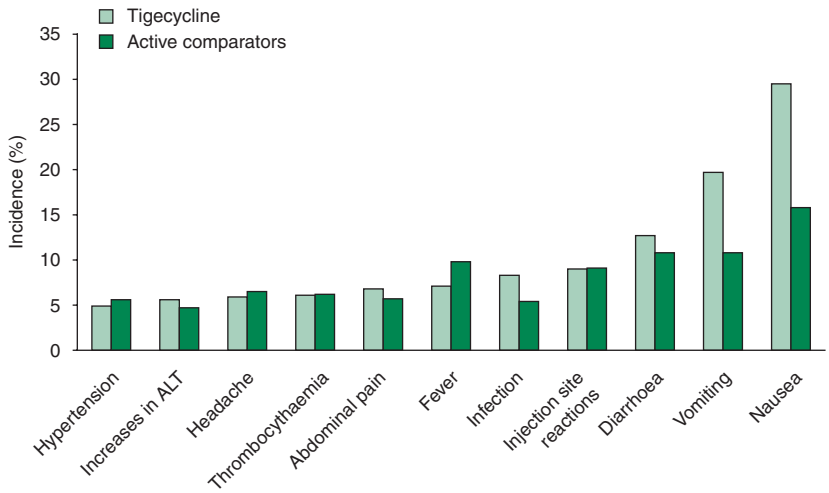


Fig. 3. Comparative tolerability profile of tigecycline. Pooled incidences of treatment-emergent adverse events, regardless of causality, affecting >5% of patients who received intravenous tigecycline (100mg initially, followed by 50mg every 12 hours; n = 1415) or an active comparator (vancomycin plus aztreonam, imipenem/cilastatin or linezolid; n = 1382) in phase III clinical studies.[6] Statistical comparisons were not reported.

● Pooled microbiological eradication rates at the TOC visit (ME population) for selected infecting pathogens were generally similar in tigecycline and imipenem/cilastatin recipients, as follows: *E. coli*, 86.2% (280/325) versus 87.1% (296/340); *E. faecalis* (vancomycin-susceptible only), 78.8% (26/33) versus 74.5% (35/47); MSSA, 92.9% (26/28) versus 91.7% (22/24); MRSA, 75.0% (3/4) versus 33.3% (1/3); *Clostridium perfringens*, 94.7% (18/19) versus 90.9% (20/22); *S. anginosus* group (includes *S. anginosus/intermedius/constellatus*), 86.6% (103/119) versus 75.9% (60/79); *B. fragilis*, 78.2% (68/87) versus 80.8% (59/73); *Citrobacter freundii*, 75.0% (12/16) versus 75.0% (3/4); *E. cloacae*, 87.5% (14/16) versus 94.1% (16/17); *K. oxytoca*, 95.0% (19/20) versus 89.5% (17/19); *K. pneumoniae*, 88.5% (46/52) versus 90.0% (54/60); *P. aeruginosa*, 84.6% (33/39) versus 86.1% (31/36); and *Peptostreptococcus micros*, 76.5% (13/17) versus 72.7% (8/11).[54]

4. Tolerability

The following tolerability profile of tigecycline is largely based on pooled adverse event data from phase III clinical studies (primarily the four pivotal trials discussed in section 3), which are presented in the US manufacturer's prescribing information.[6] This meta-analysis includes 1415 patients who received the recommended intravenous tigecycline dosage regimen (see section 5) and 1382 patients who received an active comparator (vancomycin plus aztreonam, imipenem/cilastatin or linezolid). It considers treatment-emergent adverse events reported during the period up to, and including, the TOC visit.[6] Combined adverse event data from Studies 300/305 (n = 1116; intent-to-treat population)[52] and Studies 301/306 (n = 1642; intent-to-treat population)[54] have also been published in full.

● Nausea, vomiting and diarrhoea were the most frequent treatment-emergent adverse events in patients receiving tigecycline or an active comparator in phase III clinical studies (figure 3). Episodes of nausea and vomiting generally occurred on the first or second day of treatment and, in the majority of cases, were mild-to-moderate in intensity.[6] Of the tigecycline recipients, 19.6%, 8.5% and 1.4% reported mild, moderate and severe nausea, respectively, while 12.3%, 6.3% and 1.1% reported mild, moderate and severe vomiting, respectively.[6]

● In the pooled analysis of phase III clinical trials, the study discontinuation rate as a result of treatment-emergent adverse events was similar in tige-

cycline recipients (5.0%), vancomycin plus aztreonam recipients (5.3%) and imipenem/cilastatin recipients (4.4%) [statistical analyses not reported].[6] The adverse events most commonly associated with discontinuation were nausea (1.3%) and vomiting (1.0%) in tigecycline recipients, rash (1.1%) in vancomycin plus aztreonam recipients, and nausea (1.0%) in imipenem/cilastatin recipients.[6]

- Whereas patients with cSSSIs treated with tigecycline were more likely than those treated with vancomycin plus aztreonam to experience digestive system adverse events (45.6% vs 20.5%; $p < 0.001$), including nausea (34.5% vs 8.2%; $p < 0.001$), vomiting (19.6% vs 3.6%; $p < 0.001$) and diarrhoea (8.5% vs 5.1%; $p = 0.032$), they were less likely to experience cardiovascular system adverse events (8.8% vs 14.7%; $p = 0.003$) and skin and appendage adverse events (10.6% vs 19.3%; $p < 0.001$).[52] Additionally, significantly fewer tigecycline than vancomycin plus aztreonam recipients had increases in serum AST (1.8% vs 5.1%; $p = 0.003$) or serum ALT (1.4% vs 6.2%; $p < 0.001$) levels.[52]
- Patients with cIAIs treated with tigecycline were more likely than those treated with imipenem/cilastatin to experience digestive system adverse events (44.4% vs 39.4%; $p = 0.04$), including nausea (24.4% vs 19.0%; $p = 0.01$) and vomiting (19.2% vs 14.3%; $p = 0.008$), but less likely to experience phlebitis (2.0% vs 4.0%; $p = 0.019$).[54]
- Tigecycline recipients had a numerically higher incidence of infection-related serious adverse events (6.7% vs 4.6%; statistical analysis not reported) and a significantly higher incidence of sepsis/septic shock (1.5% vs 0.5%; p-value not reported) relative to active comparator recipients in phase III clinical studies.[6] However, a causal relationship between treatment and sepsis/septic shock cannot be established.[6]
- Similarly, there was no significant difference in the mortality rate between patients receiving tigecycline and those receiving an active comparator in phase III studies in patients with cSSSIs or cIAIs (2.3% vs 1.6% [pooled data]).[6] Death was associated with higher comorbidity and/or greater severity of infection at baseline (data not reported); however, a causal relationship between treatment and mortality cannot be established.[6]

5. Dosage and Administration

In the US, tigecycline is approved for the treatment of adults with cSSSIs or cIAIs caused by susceptible strains of designated organisms. For cSSSIs, these pathogens are *E. coli*, *E. faecalis* (vancomycin-susceptible isolates only), MSSA, MRSA, *S. agalactiae*, *S. anginosus* group (includes *S. anginosus/intermedius/constellatus*), *S. pyogenes* and *B. fragilis*; for cIAIs, they are *C. freundii*, *E. cloacae*, *E. coli*, *K. oxytoca*, *K. pneumoniae*, *E. faecalis* (vancomycin-susceptible isolates only), MSSA, *S. anginosus* group (includes *S. anginosus*, *S. intermedius* and *S. constellatus*), *B. fragilis*, *B. thetaiotaomicron*, *B. uniformis*, *B. vulgatus*, *C. perfringens* and *P. micros*.

Tigecycline is administered as an intravenous infusion over 30–60 minutes. The approved dosage in patients with cSSSIs or cIAIs is 100mg initially, followed by a maintenance dose of 50mg every 12 hours; treatment should be continued for 5–14 days.[6] A reduced maintenance dose of 25mg is recommended in patients with severe hepatic impairment[6] (see section 2). No dosage adjustment is required in patients with mild-to-moderate hepatic impairment or in patients with renal impairment or undergoing haemodialysis.[6]

Local prescribing information should be consulted for other warnings and precautions, specific dosage recommendations in special patient populations and drug interactions.

6. Tigecycline: Current Status

Tigecycline demonstrates *in vitro* activity against a broad range of Gram-positive and -negative bacteria (including multidrug-resistant strains), as well as anaerobic organisms (section 1).

In four randomised, multinational, phase III studies, intravenously administered tigecycline monotherapy was noninferior to vancomycin plus aztreonam combination therapy in the treatment of hospitalised adult patients with cSSSIs and

imipenem/cilastatin broad-spectrum therapy in the treatment of hospitalised adult patients with cIAIs (section 3). In terms of type of adverse events, the tolerability profile of tigecycline was generally similar to that of comparators (section 4).

In June 2005, tigecycline was approved by the US FDA for the treatment of adult patients with cSSSIs or cIAIs caused by susceptible microorganisms;[55] it has also been approved in Brazil and Mexico.[56] Currently, it is being evaluated for approval by regulatory authorities in other regions/countries worldwide, including the EU, Canada, Australia and South Africa.[55]

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