Drugs 2008; 68 (18): 2633-2644
0012-6667/08/0018-2633/$53.45/0

Tigecycline
In Community-Acquired Pneumonia

Kate McKeage and *Gillian M. Keating*

Wolters Kluwer Health | Adis, Auckland, New Zealand, an editorial office of Wolters Kluwer Health, Conshohocken, Pennsylvania, USA

Contents

Abstract

▲ Tigecycline is a first-in-class glycylcycline, broad-spectrum, intravenous antibacterial developed to overcome the two major mechanisms of tetracycline resistance (ribosomal protection and efflux). The drug has been in use since 2005 for complicated intra-abdominal infections, and complicated skin and soft tissue structure infections, but is currently being assessed in the US for community-acquired pneumonia (CAP) in adults.

▲ *In vitro*, tigecycline had good activity against a range of Gram-positive, Gram-negative and atypical community-acquired respiratory tract pathogens implicated in CAP.

▲ Compared with other antibacterials, tigecycline has a prolonged post-antibiotic effect against key bacteria and a long serum elimination half-life in humans. The drug effectively penetrates lung tissue.

▲ The combined results of two well designed, phase III studies demonstrated that tigecycline 100 mg initially, followed by 50 mg every 12 hours for 7–14 days was not inferior to recommended dosages of levofloxacin in the treatment of hospitalized patients with CAP. Clinical cure rates were 89.7% versus 86.3% in the clinically evaluable population and 81.0% versus 79.7% in the clinical modified intent-to-treat population.

▲ Tigecycline was generally well tolerated in patients with CAP.

Features and properties of tigecycline (Tygacil®)	
Featured Indication	
Community-acquired pneumonia	
Mechanism of action	
Protein 30S ribosomal subunit inhibitor	
Dosage and administration	
Dosage in clinical trials	100 mg initially, followed by 50 mg every 12 h
Duration	7–14 d
Route	Intravenous infusion over 30–60 min
Pharmacokinetic Profile (100 mg initially, followed by 50 mg every 12 h administered over 30–60 min). Mean steady-state values in healthy volunteers	
Peak serum concentration	0.87 μg/mL (30-min infusion)
Area under the serum concentration-time curve from 0 to 24 h	4.7 μg • h/mL
Volume of distribution	500–700 L
Elimination half-life	42.4 h
Most common drug-related adverse events	
Nausea, vomiting	

Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality. Empirical antibacterial therapy is used initially until the causal microorganism is identified.[1] Recommended antibacterial agents for empirical use are contained in local treatment guidelines, which aim to rationalize agent selection based on the local prevalence and resistance patterns of the various causative pathogens and disease severity.[1] In hospitalized patients with CAP, who do not require treatment in an intensive care unit, a respiratory fluoroquinolone is recommended or a β-lactam (e.g. cefotaxime, ceftriaxone or amoxicillin/clavulanic-acid) administered in combination with a macrolide.[1]

Tigecycline (Tygacil®)[1] is a first-in-class glycylcycline antibacterial for intravenous use. The glycylcyclines are synthetic analogues of the tetracycline family that were developed to overcome mechanisms of tetracycline resistance and provide a treatment option for patients with difficult-to-treat bacterial infections.[2] Tigecycline has a broad spectrum of activity that encompasses numerous Gram-positive and -negative aerobes, atypical respiratory pathogens and anaerobic microorganisms.[2] Since 2005, the agent has been widely used for the treatment of complicated intra-abdominal infections (cIAIs) and complicated skin and soft tissue structure infections (cSSSIs), which were the focus of a previous review in *Drugs*.[3] More recently, an application for the approval of tigecycline in the treatment of CAP has been filed with the US FDA. This profile examines the *in vitro* antibacterial activity of tigecycline against bacteria commonly associated with CAP, and reviews the efficacy and tolerability of the agent in the management of hospitalized patients with CAP. All agents were given intravenously, unless stated otherwise.

Medical literature on the use of tigecycline in CAP was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles. Fully published data have been used where possible, but some recent abstract and/or poster reports have been included for completeness.

1. Antibacterial Activity

As with other glycylcyclines, the antibacterial effect of tigecycline results from inhibition of bacterial protein synthesis. The drug achieves this by binding to the bacterial 30S ribosomal subunit, where it blocks entry of amino-acyl transfer RNA molecules into the A-site of the ribosome, thereby preventing the incorporation of amino acid residues into elongating peptide chains.[4] Although the glycylcyclines and tetracyclines have a common binding site on the ribosome, tigecycline has a 5-fold stronger ribosome binding affinity than tetracycline.[4]

In Vitro Activity

The *in vitro* antibacterial activity of tigecycline was assessed using the minimum inhibitory concentration (MIC) required to inhibit 90% (MIC_{90}) of bacterial strains. MICs were determined by broth dilution techniques, performed according to the methods of the Clinical and Laboratory Standards Institute (CLSI).[5] A summary of the *in vitro* activity of tigecycline and levofloxacin against clinical isolates associated with CAP is shown in table I.

Tigecycline MIC breakpoints for various organisms have not yet been determined by the CLSI. As a result, proposed breakpoints are used: ≤0.5 μg/mL for *Staphlococcus aureus* and ≤2 μg/mL for *Klebsiella pneumoniae*.[6] One study assessed tigecycline susceptibility using the CLSI tetracycline breakpoint of ≤2 μg/mL for *Streptococcus pneumoniae* and for *Moraxella catarrhalis*,[7] and one study estimated a tigecycline susceptibility breakpoint of ≤2 μg/mL for *M. catarrhalis* and *Haemophilus influenzae*.[8] Breakpoints for tigecycline against the atypical organisms *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae* and *Legionella pneumophila* were not reported.

A recent study has shown that the presence of blood in media yields falsely elevated mutant pre-

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

vention concentrations for tigecycline, and media containing blood should not be used (reported in an abstract and poster).[9] A second study comparing the reproducibility of E-test with broth dilution techniques to evaluate tigecycline *in vitro* activity demonstrated similar profiles for most organisms with each technique, but for others, including *S. pneumoniae*, further analysis of the suitability of E-test was required.[10]

The *in vitro* activity summarized in this section is largely based on data from the ongoing TEST (Tigecycline Evaluation and Surveillance Trial) programme, which is available online, using data from the US for all years combined for organisms from respiratory sources.[11] TEST data are not available for the activity of tigecycline against some organisms, so other surveillance studies are used,[7,8,12] including one reported in an abstract.[13]

Gram-Positive Aerobes

- Tigecycline is very active against Gram-positive aerobes commonly associated with CAP, including *S. pneumoniae* and *S. aureus*. MIC_{90} values for these bacteria ranged from ≤0.03 to 0.5 μg/mL (table I).[7,8,11-13]
- The MIC_{90} value for tigecycline against *S. pneumoniae* was ≤0.12 μg/mL regardless of penicillin susceptibility (table I),[7,8,11,12] and the susceptibility rate was 98–100% when the estimated breakpoint of ≤2 μg/mL was used.[7,8] In contrast, levofloxacin

Table I. *In vitro* antibacterial activity of tigecycline and levofloxacin against common Gram-positive, Gram-negative and atypical community-acquired respiratory tract pathogens. Data[a] are from the TEST database for the US (all years)[11] and surveillance studies conducted worldwide (2000–4),[7,8] in the US (2006)[12] and in Greece (2006–7).[13,14] All tigecycline studies used broth dilution techniques

Species (no. of isolates)	Tigecycline MIC_{90} (μg/mL)	S (%)	Levofloxacin MIC_{90} (μg/mL)	S (%)	References
Gram-positive bacteria					
Staphylococcus aureus (7883)	0.25	99.9–100	64	56.4	11,13[b]
meticillin/oxacillin-susceptible (8442)	0.12–0.5	100	0.5–1	90.6–92.7	7,11,12
meticillin/oxacillin-resistant (8414)	0.25–0.5	99.9–100	>4–64	26.5–27.3	7,11,12
Streptococcus pneumoniae (6651)	0.12	98	1	98.9–99.2	8,11
penicillin-susceptible (1788)	≤0.03–0.12	100	1	98.9–99	7,12
penicillin-intermediate (430)	≤0.03–0.12	100	1	98	7,12
penicillin-resistant (401)	≤0.03–0.12	100	1	98.7–99.4	7,12
Gram-negative bacteria					
Haemophilus influenzae (7312)	0.5–1	100	0.03	100	8,11
β-lactamase negative (3398)	0.5–1	100	0.03	100	7,11
β-lactamase positive (1118)	0.5–1	100	0.03	100	7,11
Klebsiella pneumoniae (6302)	1–2	94.8–99	8	87.1	11,13[b]
Moraxella catarrhalis (640)	≤0.12–0.25	100			8,13[b]
β-lactamase negative (21)	0.25	100			7
β-lactamase positive (474)	0.25	100			7
Atypical Respiratory Pathogens					
Chlamydophila pneumoniae (10)	0.125				15
Legionella spp. (50)	0.5–8[c]				16
Mycoplasma pneumoniae (30)	0.25				17

a Includes the range of MIC_{90} values (μg/mL) and percentage of S. Susceptibility breakpoints for tigecycline were proposed[6] or specified in individual studies,[7,8] and for levofloxacin, were those determined by the CLSI:[5] ≤2 μg/mL for tigecycline and levofloxacin, except for *S. aureus*, for which the breakpoint for tigecycline was ≤0.5 μg/mL and levofloxacin was ≤1 μg/mL.

b Data reported in an abstract.

c Range of MIC_{90} values against a range of *Legionella* spp. including *L. pneumophilia*.

CLSI = Clinical and Laboratory Standards Institute; **MIC_{90}** = minimum drug concentration required to inhibit 90% of isolates; **S** = susceptible isolates.

MIC_{90} values for *S. pneumoniae* were 1.0 μg/mL regardless of penicillin susceptibility, and susceptibility rates ranged from 98.0% to 99.4%.[7,8,11,12]

- The MIC_{90} value for tigecycline against *S. aureus* was 0.25 μg/mL compared with 64 μg/mL for levofloxacin, and susceptibility rates were 99.9–100% versus 56.4% (table I).[11,13] Respective MIC_{90} values for meticillin/oxacillin-resistant *S. aureus* were generally the same as those for all *S. aureus* pathogens, and for meticillin/oxacillin-susceptible *S. aureus*, MIC_{90} values were 0.12–0.5 versus 0.5–1 μg/mL for levofloxacin.[7,11,12]

Gram-Negative Aerobes

- Tigecycline has good *in vitro* activity against common respiratory tract Gram-negative bacteria. Against *H. influenzae*, the MIC_{90} value of tigecycline was 0.5–1 μg/mL compared with 0.03 μg/mL for levofloxacin.[8,11] The susceptibility rates for both antibacterials against this organism were 100%[8,11] when an estimated breakpoint of ≤2 μg/mL was used for tigecycline.[8] β-Lactamase production had no effect on MIC values of either antibacterial agent against *H. influenzae* (table I).[7,11]
- Against *K. pneumoniae*, the MIC_{90} value of tigecycline was 1–2 μg/mL compared with 8 μg/mL for levofloxacin, with respective susceptibilities of 94.8–99% versus 87.1% (table I).[11,13]
- *M. catarrhalis* is highly susceptible to tigecycline, with MIC_{90} values of ≤0.12–0.25 μg/mL[8,13] and a susceptibility rate of 100% (table I).[8] β-Lactamase production had no effect on tigecycline MIC values against *M. catarrhalis*.[7]

Atypical Bacteria

- Tigecycline has good activity against the atypical organisms *C. pneumoniae* (MIC_{90} = 0.125 μg/mL)[15] and *M. pneumoniae* (MIC_{90} = 0.25 μg/mL).[17] The tigecycline MIC_{90} against a range of *Legionella* spp., including *L. pneumophila*, was 0.5–8.0 μg/mL (table I).[16]

Other Bacteria

- Tigecycline use appears to be associated with a low risk of developing *Clostridium difficile* infection. No *C. difficile* strains were isolated in a study in healthy volunteers (n = 13) who received intravenous tigecycline 100 mg on day 1 followed by 50 mg every 12 hours for 10 days.[18]

Bacteriostatic/Bactericidal Activity and Post-Antibiotic Effect

- Tigecycline generally demonstrated bacteriostatic activity (i.e. <3 $\log_{10}$ reduction in total bacterial count) against *Staphlococcus* spp. (including meticillin- and tetracycline-resistant *S. aureus*) and against one strain of *K. pneumoniae* (although regrowth was seen with another *K. pneumoniae* strain).[19] Bactericidal activity (i.e. ≥3 $\log_{10}$ reduction in total bacterial count) was seen against a penicillin-intermediate and -resistant *S. pneumoniae* isolate and against a glycopeptide-intermediate strain of *S. aureus*.[19]
- The *in vitro* post-antibiotic effect (PAE) of tigecycline after various bacteria were exposed to the antibacterial for 2 hours at 8 × MIC was consistently numerically greater than that of minocycline for all species tested.[20] Against various strains of *S. aureus*, including those carrying a tetracycline (K or M) resistance determinant, the PAE ranged from >3.0 to 4.1 hours with tigecycline versus 1.0 to 3.2 hours with minocycline.[20] In a mouse model, the PAE of tigecycline 3 mg/kg against *S. pneumoniae* was 8.9 hours.[21]

Resistance Issues

- Tigecycline appears to overcome the two major mechanisms of tetracycline resistance, ribosomal protection and active efflux of drug from inside the bacteria.[20] The chemical modification thought to be responsible for the ability of tigecycline to overcome these mechanisms of resistance is via steric hindrance created by a large substituent at position 9 of the tetracycline molecule, which restores activity against bacteria harbouring genes encoding efflux and/or ribosomal protection.[20]
- *In vitro* studies have demonstrated that tigecycline is active against bacterial strains harbouring all of the tetracycline resistance genes tested to date.[20] For example, the tetracycline-specific efflux transporters TetB, TetC and TetK did not take up tigecycline when present in low concentrations,

which may explain why tigecycline maintains antibacterial activity against these resistant strains.[22,23]

- However, in bacterial strains overexpressing the multidrug transporter genes *acr*AB and *acr*EF previously associated with tetracycline resistance, susceptibility to tigecycline was decreased, with MICs increasing 4-fold.[22] The antibacterial activity of tigecycline was reduced against *K. pneumoniae* in strains with increased expression of the *acr*AB multidrug efflux pump.[24]

- Tigecycline appears to have a relatively low propensity to develop resistance compared with other antibacterials.[25] A single-step analysis (reported in an abstract and poster) comparing the propensity of several antibacterials to select for resistance against 12 strains of *S. pneumoniae* demonstrated mutation frequencies for tigecycline of $<6.7 \times 10^{-9}$ to $<1.7 \times 10^{-10}$ at 2 and 8 × MIC, which were lower than or similar to those obtained with several comparators. For example, mutation frequencies for levofloxacin were 7.9×10^{-8} to $<1.0 \times 10^{-10}$ at 2 × MIC and $<3.7 \times 10^{-10}$ to $<1.0 \times 10^{-10}$ at 8 × MIC.[25]

- TEST data (reported in an abstract and poster) show that, apart from *H. influenzae*, there has not been a significant shift in tigecycline MIC values in any organism group over 4 years compared with pre-approval baseline values (2004–7) from a global perspective, even in strains resistant to other antibacterials including *S. pneumoniae* and meticillin-resistant *S. aureus*.[26] Tigecycline MIC_{90} values for *H. influenzae* increased from 0.25 μg/mL in 2004 to 1.0 μg/mL in 2007; monitoring is ongoing.[26]

In Vivo Activity

- Subcutaneous tigecycline 2 or 4 mg/kg/day completely protected mice in a model of *S. pneumoniae* pneumonia.[20] In addition, subcutaneous tigecycline reduced levels of bronchoalveolar lavage proinflammatory cytokines to a significantly ($p < 0.05$) greater extent than placebo in a murine model of *M. pneumoniae* pneumonia (reported in an abstract).[27]

2. Pharmacokinetic Profile

The pharmacokinetic properties of single and multiple doses of tigecycline in healthy volunteers have been presented previously.[6,28,29] This section presents a summary of data obtained from healthy volunteers who received the dosage regimen recommended in patients with cIAIs or cSSSIs: an initial intravenous loading dose of 100 mg, followed by maintenance intravenous doses of 50 mg every 12 hours, given over 30–60 minutes.

Serum Concentrations and Distribution

- The tigecycline mean maximum serum concentration (C_{max}) at steady state in healthy volunteers (n = 103) who received the recommended dosage regimen was 0.87 μg/mL after a 30-minute infusion and 0.63 μg/mL after a 60-minute infusion.[6] The mean area under the serum concentration-time curve (AUC) from 0 to 24 hours (AUC_{24}) was 4.7 μg • h/mL and the mean minimum serum concentration was 0.13 μg/mL.[6]
- The plasma protein binding of tigecycline *in vitro* at concentrations observed in clinical studies (0.1–1.0 μg/mL) ranged from ≈71% to 89%.[6]
- Tigecycline is extensively distributed into body tissues, with an average steady-state volume of distribution of 500–700 L (7–9 L/kg).[6]
- Tigecycline effectively penetrates lung tissue.[30] Following administration of the recommended dosage regimen of tigecycline to healthy volunteers (n = 30), the AUC_{12} in alveolar cells (134 μg • h/mL) and in epithelial lining fluid (2.28 μg • h/mL) was ≈78-fold and ≈1.3-fold higher than the AUC_{12} in serum. C_{max} in alveolar cells and in epithelial lining fluid was 15.2 and 0.37 μg/mL.[30]
- In an *in vitro* study, tigecycline achieved rapid intracellular concentrations in human polymorphonuclear neutrophils, with maximal penetration noted at 1 hour.[31] At tigecycline concentrations of 1 and 10 mg/L, intracellular drug concentrations were ≈20- and ≈30-fold higher than extracellular concentrations at 1 hour.[31]

Metabolism and Elimination

- Tigecycline undergoes minimal metabolism. Only small amounts (each ≤10% of the dose) of glucuronide metabolites, an *N*-acetyl metabolite and a tigecycline epimer, were present in healthy male volunteers receiving ^{14}C-labelled tigecycline.[29]
- The primary route of elimination is the excretion of unchanged tigecycline in the faeces, and secondary elimination is via renal excretion of unchanged drug.[29] Following administration of ^{14}C-tigecycline in healthy men, 59% of the dose was excreted in the faeces and 33% in the urine.[29]
- Tigecycline has a long serum elimination half-life ($t_{1/2}$). Following administration of a single 100 mg dose, the mean $t_{1/2}$ was 27.1 hours, and at steady state, it was 42.4 hours. At steady state, mean systemic clearance was 23.8 L/h.[6]

Special Patient Populations

- The pharmacokinetics of tigecycline were not altered to a clinically significant extent in patients with severe renal impairment (creatinine clearance <30 mL/min [<1.8 L/h]) or end-stage renal disease. Tigecycline is not removed by haemodialysis.[6]
- In patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment, the systemic clearance of tigecycline was reduced by 25% and 55%, and the $t_{1/2}$ was prolonged by 23% and 43%.[6] Dosage adjustment is required in patients with severe hepatic impairment (section 6), but not in patients with mild to moderate hepatic impairment.[6]
- The pharmacokinetics of tigecycline are not affected to a clinically significant extent by older age (≥65 years), gender or race, and dosage adjustments are not required based on these differences.[6]
- The pharmacokinetics of tigecycline have not been confirmed in patients aged <18 years.[6]

Potential Drug Interactions

- No clinically significant drug interactions were observed when tigecycline was coadministered with oral digoxin in healthy men.[6]
- If tigecycline is coadministered with warfarin, prothrombin time (or other anticoagulation test) should be monitored, as clearance of R- and S-warfarin is reduced, and C_{max} and AUC values are increased. Warfarin did not affect the pharmacokinetics of tigecycline.[6]
- Based on *in vitro* results, tigecycline is not expected to alter the metabolism of drugs metabolized by the cytochrome P450 (CYP) 1A2, 2C8, 2C9, 2C19, 2D6 or 3A4 isoforms.[6] Furthermore, tigecycline is not expected to be affected by drugs that inhibit or induce the activity of these CYP isoforms.

3. Pharmacodynamic/Pharmacokinetic Considerations

Currently, there are little data available to identify which pharmacodynamic/pharmacokinetic parameters are the best predictors of tigecycline efficacy in humans.[2] Animal studies suggest that the best predictor of efficacy with tigecycline against most organisms is percentage time above MIC, but the AUC : MIC ratio was also important in predicting activity against *S. pneumoniae*.[21] However, findings of this murine model cannot be extrapolated to humans.[2] A commonly held view is that the AUC : MIC ratio will best predict efficacy, based on the prolonged PAE of tigecycline against key bacteria (section 1) and relatively long $t_{1/2}$ value in humans (section 2).[2] In a recent analysis of data from phase III studies in patients (n = 68) with CAP (reported in an abstract), there was a trend for patients with an AUC_{24} : MIC ratio of <12.8 to have a longer time to fever resolution than patients with a greater ratio.[32] However, a target AUC_{24} : MIC ratio of 5–10 has been suggested, based on models with other tetracyclines.[33]

This section summarizes results from a prospective, nonblind study in 30 healthy volunteers who received a loading dose of tigecycline 100 mg followed by six 50 mg doses administered every 12 hours over 30 minutes.[30] Ratios for AUC_{24} : MIC_{90} and the percentage of time above MIC_{90} were calculated for intrapulmonary and serum tigecycline concentrations against common respiratory pathogens (*S. pneumoniae* [MIC_{90} =

0.03 μg/mL], *C. pneumoniae* [MIC_{90} = 0.125 μg/mL], *M. pneumoniae* [MIC_{90} = 0.25 μg/mL], *M. catarrhalis* [MIC_{90} = 0.12 μg/mL] and *H. influenzae* [MIC_{90} = 0.5 μg/mL]).[30] Results of a study, reported in an abstract, which used Monte Carlo simulation analyses to estimate the potential of tigecycline to attain the target AUC_{24} : MIC_{90} ratio against community-acquired (CA-MRSA) and hospital-acquired meticillin-resistant *S. aureus* (HR-MRSA) are also presented.[34]

- The study in healthy volunteers demonstrated that tigecycline concentrated in alveolar cells.[30] The tigecycline AUC_{24} : MIC_{90} ratio in alveolar cells was well above suggested targets (5–10 or >12.8) for all five organisms tested.[30] The AUC_{24} : MIC_{90} ratios were 4467 for *S. pneumoniae*, 1117 for *C. pneumoniae* and *M. catarrhalis*, 536 for *M. pneumoniae* and 268 for *H. influenzae*. Furthermore, the percentage of the dosing interval that the tigecycline concentration in alveolar macrophages was above the MIC_{90} was 100% for all five respiratory pathogens.[30]
- In epithelial lining fluid, AUC_{24} : MIC_{90} ratios ranged from 4.56 for *H. influenzae* to 76 for *S. pneumoniae*, and the percentage of the dosing interval that the tigecycline concentration was above the MIC_{90} ranged from 0% to 100%.[30]
- In serum, AUC_{24} : MIC_{90} ratios ranged from 3.46 for *H. influenzae* to 57.7 for *S. pneumoniae*, and the percentage of the dosing interval that the tigecycline concentration was above the MIC_{90} ranged from 0% to 100%.[30]
- A Monte Carlo simulation analysis predicted that tigecycline, at the recommended dosage, has a high probability of achieving bacterial eradication against CA-MRSA and HA-MRSA; tigecycline had a 91% probability of achieving the target AUC_{24} : MIC_{90} ratio (target not specified).[34]

4. Therapeutic Efficacy

The clinical efficacy of tigecycline in hospitalized adults with CAP (n = 859) has been compared with that of levofloxacin in two randomized, double-blind, multicentre, phase III, noninferiority studies; integrated results were recently published.[35] Tigecycline was compared with levofloxacin because levofloxacin is recommended for use in CAP and is commonly used in this patient population.[1]

Patients received intravenous tigecycline 100 mg initially, followed by 50 mg every 12 hours, or intravenous levofloxacin 500 mg every 24 hours in one study, or 500 mg every 12 or 24 hours (at the investigators discretion) in the other study.[35] It should be noted that the recommended levofloxacin dosage in adults with CAP is now 750 mg/day.[36] If patients showed predefined improvement in signs and symptoms after at least 3 days of treatment with either intravenous agent in one study, they were able to switch to oral levofloxacin.[35] There was no significant difference between tigecycline and levofloxacin recipients in the percentages of clinically evaluable patients who switched from intravenous therapy to oral levofloxacin (89.9% vs 87.8%) or in the median duration of oral therapy (3.9 vs 3.3 days).[35] The total duration of therapy in both trials was 7–14 (mean of ≈10) days and the test-of-cure (TOC) assessments occurred 7–23 days after administration of the final antibacterial dose.[35]

Eligible patients were aged >18 years and had been diagnosed with CAP that was severe enough to require hospitalization and intravenous antibacterials.[35] Other inclusion criteria included fever within the past 24 hours, chest radiograph showing new infiltrate within 48 hours before the first dose of study medication, and the presence of at least two symptoms consistent with CAP (e.g. cough, production of purulent sputum, elevated white blood cell count of >10 000 cells/mm^3, ausculatory findings of rales). Patients were excluded if they had been hospitalized within the past 14 days or resided at a long-term care facility.[35]

In the modified intent-to-treat (ITT) population (n = 846; i.e. randomized patients who received at least one dose of study drug), the mean age was 52 years and approximately 60% were male.[35] The proportion of patients with Fine Pneumonia Severity Index scores of I, II, III, IV or V was 21.9%, 31.3%, 27.0%, 19.3% and 0.6%, respectively. It is worthy of note that the severity of the total patient group was not particularly high; patients with Fine scores

of I, II and III are usually not hospitalized. The proportion of patients with CURB-65 (an estimated score based on confusion, urea >7 mmol/L, respiratory rate >30/min, low blood pressure [<90 mmHg systolic or <60 mmHg diastolic] and age >65 years) scores of 0, 1, 2, 3 or 4 was 34.2%, 36.8%, 20.9%, 7.2% and 0.9%, respectively.[35] Approximately 13% of patients in the modified ITT population had diabetes mellitus, ≈11% had chronic obstructive pulmonary disease, ≈7% had congestive heart failure and ≈30% were aged >65 years.[35]

The coprimary endpoints were clinical response at the TOC assessments in clinically evaluable (CE) patients (n = 574) and in the clinical modified ITT population (n = 797).[35] The clinical modified ITT population included all patients who received at least one dose of study drug and who met minimum disease requirements with clinical evidence of CAP, and the CE population included patients in the clinically modified ITT population who received no more than one dose of a non-once-daily antibacterial agent before the first dose of a study drug, had a TOC assessment of cure or failure (not intermediate), and remained blinded to treatment throughout the study. Microbiological responses were evaluated as secondary efficacy endpoints. Healthcare resource utilization was evaluated in the clinical modified ITT population.[35]

The clinical response was reported as a cure if CAP signs and symptoms had improved or resolved, there was an improvement or no worsening of chest x-ray and no additional antibacterial therapy was required.[35] A failure was defined as persistence or worsening of signs and symptoms of CAP. An indeterminate result was given to patients who were lost to follow-up, withdrew consent, or died within 2 days of the first dose (because of any reason except a treatment-related adverse event) or after 2 days not as a result of CAP.[35] Microbiological responses were determined from respiratory or blood specimen cultures and included eradication (all pathogens identified at study entry were eliminated), persistent (at least one pathogen identified at study entry persisted, or clinical response was a failure and there was no repeat microbiology data available), superinfection (a new isolate emerged during therapy at the site of infection) or indeterminate (no outcome assessment available).[35] The noninferiority of tigecycline to levofloxacin was established if the lower limit of the 2-sided 95% confidence interval for the between-group difference in the clinical and microbiological response rate was greater than or equal to −15%.[35]

Clinical Cure Rates

- In regard to clinical efficacy, tigecycline was not inferior to levofloxacin ($p < 0.001$).[35] In the CE population, the percentage of patients cured at the TOC visit was 89.7% with tigecycline and 86.3% with levofloxacin (absolute difference 3.4% [95% CI −2.2, 9.1]). In the clinical modified ITT population, the corresponding cure rates were 81.0% ver-

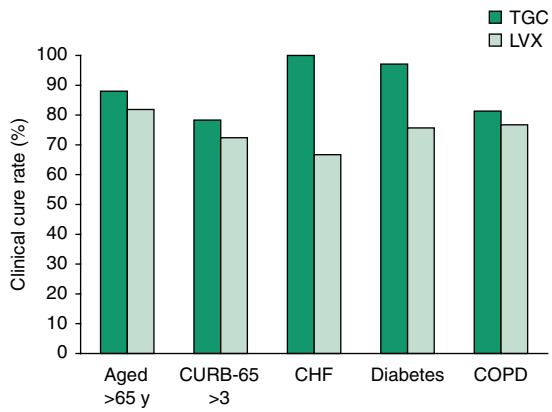

Fig. 1. Clinical cure rates based on demographic characteristics and risk factors. Results are for the combined clinically evaluable population (n = 574) in two randomized, double-blind, multicentre, phase III studies comparing intravenous tigecycline (TGC) 100 mg initially, followed by 50 mg every 12 hours, or intravenous levofloxacin (LVX) 500 mg every 24 hours in one study, or 500 mg every 12 or 24 hours (at the investigators discretion) in the other study for 7–14 days in patients with community-acquired pneumonia (some patients in one study switched to oral LVX after ≥3 days of treatment with either intravenous agent).[35] Test-of-cure assessment was performed 7–23 days after administration of the final dose. Clinical cure rates are illustrated for patients aged >65 years (83 TGC recipients and 94 LVX recipients); those with a CURB-65 score (estimated based on confusion, urea, respiratory rate, blood pressure and age >65 years) of >3 (23 and 29); and those with congestive heart failure (CHF; 22 and 21), diabetes mellitus (35 and 37) or chronic obstructive pulmonary disease (COPD; 32 and 30). There were no statistically significant differences in clinical cure rates between the two treatment groups.

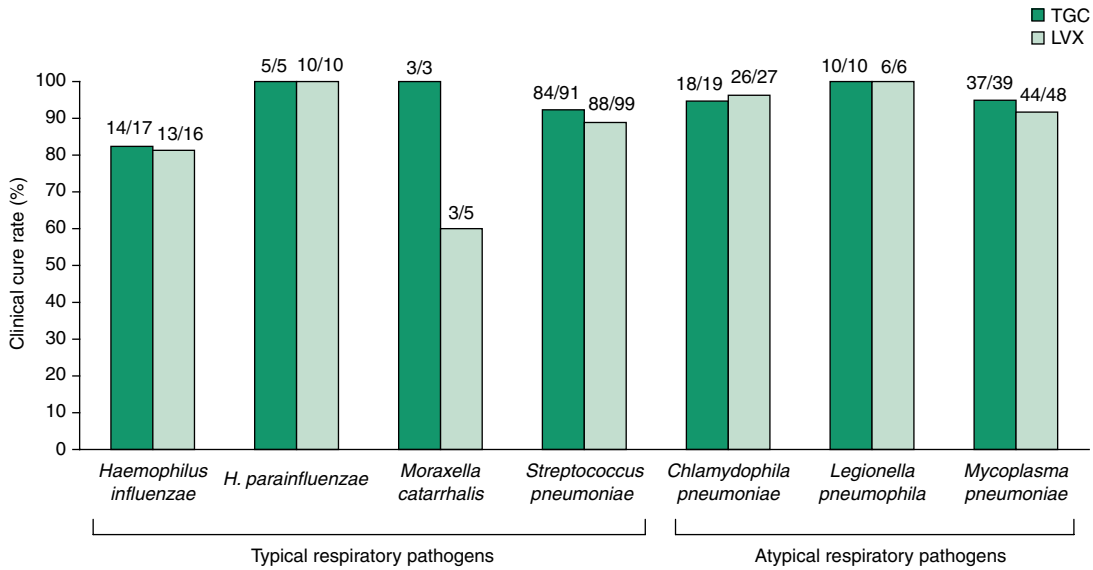

Fig. 2. Clinical cure rates based on respiratory pathogen. Results are for the microbiologically evaluable population (n = 345) in two randomized, double-blind, multicentre, phase III studies comparing intravenous tigecycline (TGC) 100 mg initially, followed by 50 mg every 12 hours, or intravenous levofloxacin (LVX) 500 mg every 24 hours in one study, or 500 mg every 12 or 24 hours (at the investigators discretion) in the other study for 7–14 days in patients with community-acquired pneumonia (some patients in one study switched to oral LVX after ≥3 days of treatment with either intravenous agent).[35] Test-of-cure assessment was performed 7–23 days after administration of the final dose. Numbers above the bars indicate the number of patients achieving a cure and the total number of patients in each subgroup. There were no statistically significant differences in clinical cure rates between the two treatment groups.

sus 79.7% (absolute difference 1.3% [95% CI −4.5, 7.1]).[35]

- Results of subgroup analyses based on demographic characteristics and risk factors were generally similar to those of the primary analysis; tigecycline was no less effective than levofloxacin in all subgroups evaluated.[35] Results are illustrated in figure 1.
- The rate of clinical cure in 40 microbiologically evaluable patients with *S. pneumoniae* bacteraemia was 90.9% with tigecycline (20/22 patients) and 72.2% (13/18 patients) with levofloxacin.[35]
- The clinical cure rates in subgroups categorized by respiratory pathogen were not significantly different between tigecycline and levofloxacin recipients in the microbiologically evaluable population.[35] Results are illustrated in figure 2.

Microbiological Response Rates

- There was no significant difference in microbiological response between tigecycline and levofloxacin treatment groups; eradication was primarily presumed based on clinical response (data not reported).[35]

Healthcare Resource Utilization

- In terms of healthcare resource utilization, there was no significant difference between tigecycline and levofloxacin recipients in the mean length of hospital stay during primary hospitalization (9.8 vs 9.8 days) or in the mean duration of study antibacterial therapy (9.8 vs 10.0 days), including the mean duration of intravenous (4.6 vs 4.3 days) and, following the switch from either treatment group, oral (5.2 vs 5.5 days) therapy.[35]
- Following discharge, there were no significant differences between tigecycline and levofloxacin treatment groups in the rates of rehospitalization, admission to intensive care, admission to emergency room care, use of home healthcare, or nursing home admission.[35] However, significantly fewer patients in the tigecycline group than in the levofloxacin

group required concomitant antibacterial treatment at or after discharge from primary hospitalization (5.6% vs 11.7%; p = 0.002).

5. Tolerability

The tolerability of tigecycline has been reviewed previously.[3] This section focuses on tolerability data from the integrated results of the two well designed studies detailed in section 4 that compared tigecycline with levofloxacin in patients with CAP.[35]

- In phase III clinical trials, tigecycline was generally well tolerated.[35] However, significantly more tigecycline-treated patients than levofloxacin-treated patients experienced drug-related adverse events (47.9% vs 37.4%; p < 0.01) in the modified ITT population (n = 846).[35] The comparative incidence of drug-related adverse events is illustrated in figure 3.
- Tigecycline was associated with a significantly higher incidence of nausea and vomiting than levofloxacin, whereas levofloxacin was associated with a significantly higher incidence of elevated serum ALT and AST levels than tigecycline (figure 3).[35]
- The proportion of patients who experienced a serious adverse event (9.9% vs 10.9%) or who discontinued therapy due to an adverse event (6.1% vs 8.1%) was not significantly different among tigecycline or levofloxacin recipients.[35] The proportion of deaths in each group was 2.8% and 2.6%, respectively, and none were considered to be related to study medication.
- In general, there were no significant differences between groups receiving tigecycline or levofloxacin in mean changes from baseline in laboratory measurements, vital signs and ECG recordings.[35]

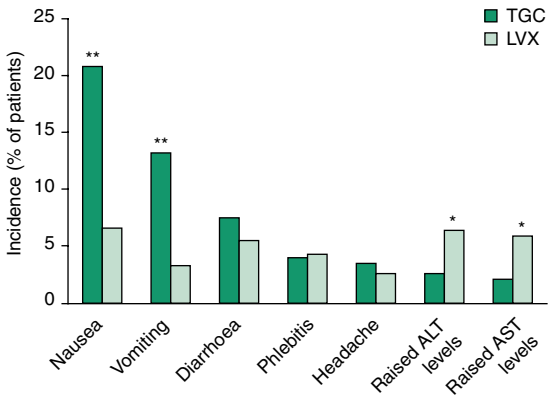

Fig. 3. Comparative tolerability of tigecycline (TGC) with levofloxacin (LVX). Pooled incidence of drug-related adverse events reported in two randomized, double-blind, multicentre, phase III studies comparing intravenous TGC 100 mg initially, followed by 50 mg every 12 hours, or intravenous LVX 500 mg every 24 hours in one study, or 500 mg every 12 or 24 hours (at the investigators discretion) in the other study for 7–14 days in patients with community-acquired pneumonia (some patients in one study switched to oral LVX after ≥3 days of treatment with either intravenous agent).[35] Results are for the modified intent-to-treat population (n = 846). * p < 0.01, ** p < 0.001 vs comparator.

6. Dosage and Administration

In clinical trials of patients with CAP, the tigecycline dosage comprised an initial intravenous dose of 100 mg, followed by 50 mg every 12 hours (each infusion given over 30–60 minutes) for a duration of 7–14 days (mean of about 10 days).[35] No dosage adjustment is required in patients with mild to moderate hepatic impairment, but in patients with severe hepatic impairment, the maintenance dosage should be reduced to 25 mg every 12 hours (section 2).[6] Local prescribing information should be consulted for information regarding other specific patient populations, contraindications, warnings and precautions.

7. Tigecycline: Current Status in Community-Acquired Pneumonia

An application for the approval of tigecycline in the treatment of CAP has been filed with the FDA.

In clinical trials in patients hospitalized with CAP, tigecycline demonstrated noninferiority to levofloxacin in terms of clinical cure rates and was generally well tolerated.

Acknowledgements and Disclosure

The manuscript was reviewed by: **H.M. Lode**, Research Centre for Medical Studies, Charité Universitätsmedizin Berlin, Berlin, Germany; **L.A. Mandell**, Division of Infectious Diseases, McMaster University, Hamilton, Ontario, Canada.

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

References

1. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007 Mar; 44 Suppl. 2: S27-72
2. Zhanel GG, Karlowsky JA, Rubinstein E, et al. Tigecycline: a novel glycylcycline antibiotic. Expert Rev Anti Infect Ther 2006; 4 (1): 9-25
3. Frampton JE, Curran MP. Tigecycline. Drugs 2005; 65 (18): 2623-35
4. Bergeron J, Ammirati M, Danely D, et al. Glycylcyclines bind to the high-affinity tetracycline ribosomal binding site and evade Tet(M)- and Tet(O)-mediated ribosomal protection. Antimicrob Agents Chemother 1996; 40 (9): 2226-8
5. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial suscepibility testing; eighteenth informational supplement. Wayne (PA): Clinical and Laboratory Standards Institute, 2008 Jan
6. Tygacil® (tigecycline) for injection. US prescribing information. Philadelphia (PA): Wyeth Pharmaceuticals Inc, 2007
7. Fritsche TR, Kirby JT, Jones RN. *In vitro* activity of tigecycline (GAR-936) tested against 11,859 recent clinical isolates associated with community-acquired respiratory tract and Gram-positive cutaneous infections. Diagn Microbiol Infect Dis 2004; 49 (3): 201-9
8. Fritsche TR, Sader HS, Stilwell MG, et al. Antimicrobial activity of tigecycline tested against organisms causing community-acquired respiratory tract infection and nosocomial pneumonia. Diagn Microbiol Infect Dis 2005; 52 (3): 187-93
9. Hesje C, Borsos S, Blondeau J. The impact of blood in media on the determination of mutant prevention concentration testing of tigecycline against clinical isolates of *Streptococcus pneumoniae* [abstract no. P605 plus poster]. 18th European Congress of Clinical Microbiology and Infectious Diseases; 2008 Apr 19-22; Barcelona
10. Pillar CM, Draghi DC, Dowzicky MJ, et al. In vitro activity of tigecycline against Gram-positive and Gram-negative pathogens as evaluated by broth microdilution and E-test. J Clin Microbiol 2008 Sep; 46 (9): 2862-7
11. T.E.S.T. Tigecycline Evaluation and Surveillance Trial [online]. Available from URL: http://www.testsurveillance.com [Accessed 2008 Nov 4]
12. Gales AC, Sader HS, Fritsche TR. Tigecycline activity tested against 11808 bacterial pathogens recently collected from US medical centers. Diagn Microbiol Infect Dis 2008 Apr; 60 (4): 421-7
13. Papaparaskevas J, Tsakris A, Tzouvelekis L, et al. The *in vitro* activity of tigecycline against 2,423 clinical isolates: comparison of the EUCAST and the FDA approved breakpoints [abstract no. P687]. 18th European Congress of Clinical Microbiology and Infectious Diseases; 2008 Apr 19-22; Barcelona
14. Jones RN, Fritsche TR, Sader HS, et al. Activity of garenoxacin, an investigational des-F(6)-quinolone, tested against pathogens from community-acquired respiratory tract infections, including those with elevated or resistant-level floroquinolone MIC values. Diagn Microbiol Infect Dis 2007; 58: 9-17
15. Roblin PM, Hammerschlag MR. *In vitro* activity of GAR-936 against *Chlamydia pneumoniae* and *Chlamydi trachomatis*. Int J Antimicrob Agents 2000; 16: 61-3
16. Edelstein PH, Weiss WJ, Edelstein MAC. Activities of tigecycline (GAR-936) against *Legionella pneumophila in vitro* and guinea pigs with *L. pneumophila* pneumonia. Antimicrob Agents Chemother 2003; 47 (2): 533-40
17. Kenny GE, Cartwright FD. Susceptibilities of *Mycoplasma hominis*, *M. pneumoniae*, and *Ureaplasma urealyticum* to GAR-936, dalforpristin, dirithromycin, evernimicin, gatifloxacin, linezolid, moxifloxacin, quinupristin-dalopristin, and telithromycin compared to their susceptibilites to reference macrolides, tetracyclines, and quinolones. Antimicrob Agents Chemother 2001; 45 (9): 2604-8
18. Nord CE, Sillerström E, Wahlund E. Effect of tigecycline on normal oropharyngeal and intestinal microflora. Antimicrob Agents Chemother 2006 Oct; 50 (10): 3375-80
19. Petersen PJ, Jones CH, Bradford PA. *In vitro* antibacterial activities of tigecycline and comparative agents by time-kill kinetic studies in fresh Mueller-Hinton broth. Diagn Microbiol Infect Dis 2007 Nov; 59 (3): 347-9
20. Projan SJ. Preclinical pharmacology of GAR-936, a novel glycylcycline antibacterial agent. Pharmacotherapy 2000; 20 (9 Pt 2): 219-3S
21. van Ogtrop ML, Andes D, Stamstad TJ, et al. *In vivo* pharmacodymic activites of two glycylcyclines (GAR-936 and WAY-152,288) against various Gram-positive and Gram-negative bacteria. Anitmicrob Agents Chemother 2000 Apr; 44: 943-9
22. Hirata T, Saito A, Nishino K, et al. Effects of efflux transporter genes on susceptibility of *Escherichia coli* to tigecycline (GAR-936). Antimicrob Agents Chemother 2004; 48 (6): 2179-84
23. Pankey GA. Tigecycline. J Antimicrob Chemother 2005; 56: 470-80
24. Ruzin A, Visalli MA, Keeney D, et al. Influence of transcriptional activator RamA on expression of multidrug efflux pump *Acr*AB and tigecycline susceptibility in *Klebsiella pneumoniae*. Antimicrob Agents Chemother 2005; 49 (3): 1017-22
25. Ednie LM, Kosowska-Shick K, Appelbaum PC. Comparative ability of tigecycline to select for resistant pneumococcal mutants by single-step methodology [abstract no. E297 plus poster]. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2007 Sep 17-20; Chicago (IL)
26. Bouchillon S, Johnson B, Hackel M, et al. A global perspective of antimicrobial *in vitro* activity from the T.E.S.T. program: annual analysis from 2004-2007 [abstract no. P676 plus poster]. 18th European Congress of Clinical Microbiology and Infectious Diseases; 2008 Apr 19-22; Barcelona
27. Salvatore CM, Katz-Gaynor K, McCracken GH, et al. Tigecycline therapy significantly reduces inflammatory pulmonary cytokines and chemokines in a murine model of *Mycoplasma pneumoniae* pneumonia [abstract no. B401]. 46th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2006 Sep 27-30; San Francisco (CA)
28. Muralidharan G, Micalizzi M, Speth J, et al. Pharmacokinetics of tigecycline after single and multiple doses in healthy subjects. Antimicrob Agents Chemother 2005; 49 (1): 220-9
29. Hoffmann M, DeMaio W, Jordan RA, et al. Metabolism, excretion, and pharmacokinetics of 14C tigecycline, a first-in-class

glycylcycline antibiotic, after intravenous infusion to healthy male subjects. Drug Metab Dispos 2007 Sep; 35 (9): 1543-53
30. Conte JE, Golden JA, Kelly MG, et al. Steady-state serum and intrapulmonary pharmacokinetics and pharmacodynamics of tigecycline. Int J Antimicrob Agents 2005 Jun 1; 25 (6): 523-9
31. Ong CT, Babalola CP, Nightingale CH, et al. Penetration, efflux and intracellular activity of tigecycline in human polymorphonuclear neutrophils (PMNs). J Antimicrob Chemother 2005 Sep; 56: 498-501
32. Rubino CM, Bhavnani S, Forrest A, et al. Pharmacokinetic-pharmacodynamic analysis for efficacy of tigecycline in patients with hospital- or community-acquired pneumonia [abstract no. A-588]. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2007 Sep 17-20; Chicago (IL)
33. Stein GE, Craig WA. Tigecycline: a critical analysis. Clin Infect Dis 2006; 43 (4): 518-24
34. Noreddin AM, Salem AH, Haynes VM, et al. Pharmacodynamic profiling of dalbavancin, daptomycin, tigecycline, linezolid and vancomycin in the treatment of community acquired and hospital acquired methicillin resistant *Staphylococcus aureus* (CA-MRSA and HA-MRSA): Monte Carolo simulation analysis [abstract no. 451]. 45th Annual Meeting of the Infectious Diseases Society of America; 2007 Oct 4-7; San Diego (CA)
35. Tanaseanu C, Bergallo C, Teglia O, et al. Integrated results of 2 phase 3 studies comparing tigecycline and levofloxacin in community-acquired pneumonia. Diagn Microbiol Infect Dis 2008 Jul; 61 (3): 329-38
36. Levaquin® (levofloxacin). US prescribing information. Raritan (NJ): Ortho-McNeil-Janssen Pharmaceuticals, Inc. 2008 Sep

Correspondence: *Kate McKeage*, Wolters Kluwer Health | Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand. E-mail: demail@adis.co.nz