

Tigecycline: The Next New Wonder Drug?

By Jaipriya Parkhani, Pharm.D.

Microbial resistance to current antibiotics is increasing while the progression of new agents to fight the war against bacterial infections is decreasing.^{1,2} Once rare, multi-drug resistant organisms are now seen more and more frequently. Tigecycline (Tygacil®) is the first drug in a new generation of tetracyclines, the *glycylcyclines*, and the first tetracycline derivative to be introduced in over 30 years.³ Initial research on the glycylcyclines was started in the early 1990s. Tigecycline has FDA approval (as of June 2005) for the treatment of complicated skin and skin structure infections and complicated intra-abdominal infections in patients 18 years and older (see Table I). Although the clinical significance is yet unknown, *in vitro* data demonstrates tigecycline activity against a broad spectrum of bacteria, including multi-drug resistant organisms (see Table I). This article will review the pharmacology of tigecycline and summarize the literature supporting its use for complicated infections, as well as discuss implications for its use and the clinical limits of this new “wonder drug.”

Table I: Spectrum of Tigecycline Activity

Organisms Listed by Indication		
Complicated Skin and Skin Structure Infections	Complicated Intra-Abdominal Infections	
<i>B. fragilis</i> <i>E. faecalis</i> (vancomycin susceptible isolates only) <i>E. coli</i> <i>S. aureus</i> (MSSA and MRSA) <i>S. agalactiae</i> <i>S. anginosus</i> group <i>S. pyogenes</i>	<i>B. fragilis</i> <i>B. thetaiotaomicron</i> <i>B. uniformis</i> <i>B. vulgatus</i> <i>C. freundii</i> <i>C. perfringens</i> <i>E. cloacae</i> <i>E. coli</i>	<i>E. faecalis</i> (vancomycin susceptible isolates only) <i>K. oxytoca</i> <i>K. pneumoniae</i> <i>P. micros</i> <i>S. anginosus</i> group
Additional Organisms Showing <i>In Vitro</i> Susceptibility		
<i>A. baumannii</i> <i>B. distasonis</i> <i>B. ovatus</i> <i>C. koseri</i> <i>E. aerogenes</i> <i>E. avium</i> <i>E. casseliflavus</i> <i>E. faecalis</i> and <i>E. faecium</i> (vancomycin susceptible and resistant isolates)	<i>E. gallinarum</i> <i>L. monocytogenes</i> <i>M. abscessus</i> <i>M. chelonae</i> <i>M. fortuitum</i> <i>P. multocida</i> <i>Peptostreptococcus</i> spp. <i>Prevotella</i> spp. <i>Porphyromonas</i> spp.	<i>S. epidermidis</i> (methicillin susceptible and resistant isolates) <i>S. haemolyticus</i> <i>S. maltophilia</i> <i>S. marcescens</i>

Like other tetracyclines, tigecycline inhibits bacterial protein translation by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the receptor (A) site of the ribosome, thus preventing the integration of amino acids into extending microbial peptide chains and thereby preventing bacterial growth. Thus, tigecycline, like other tetracyclines, is considered a bacteriostatic agent. Tigecycline’s structure is modified from minocycline with a glycylamido moiety at the 9-position of the D-ring. This structural modification allows tigecycline to overcome the two major forms of bacterial resistance to tetracyclines: active Tet (A-E, K) efflux pumps and ribosomal protection such as that mediated by Tet (M).³ Tet (M) can dislodge older tetracyclines

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Concurrent with FDA approval of tigecycline, IV minocycline was withdrawn from the U.S. market by the manufacturer (Wyeth), making tigecycline the *de facto* replacement.

from the ribosome. The glycylicyclines may bind more tightly to ribosomes compared to older tetracyclines and Tet (M) may be unable to disrupt this tight binding.^{4,5} Alternatively, perhaps glycylicyclines bind to the ribosome in such a manner that Tet (M) is unable to interact with the ribosome.^{4,5} How long this overcoming of bacterial resistance will last remains to be seen, as *in vitro* selected mutations of Tet (A) have enabled efflux of glycylicyclines. Additionally, five instances of emerging resistance were noted during Phase 3 trials, involving four organisms (*A. baumannii*, *E. cloacae*, *K. pneumoniae*, *M. morgani*). The apparent mechanism of this resistance was associated with up-regulation of chromosomally mediated efflux pumps.³ Furthermore, tigecycline has been shown to be active against extended-spectrum beta-lactamases (ESBLs), mutant plasmid-born enzymes, seen in 10–15% of hospital isolates of *E. coli* and *Klebsiella* spp.^{1,2,6,7}

Organism (# tested / % of total)	Cumulative % inhibited (mcg/mL)						
	≤0.12	0.25	0.5	1	2	4	8
<i>Acinetobacter</i> spp. (223/2.4%)	11	21	35	65	93	>99	100
Beta-hemolytic Strep (177/1.9%)	97	100					
<i>B. fragilis</i>	–	–	–	50	–	90	–
Coag Negative Staph (1181/13%)	47	77	97	100			
<i>Enterobacter</i> spp. (405/4.4%)	2	25	77	90	96	>99	100
Enterococci (1245/13.7%)	66	92	>99	>99	100		
<i>Enterococcus</i> VanA phenotype (179/1.9%)	76	97	100				
<i>Enterococcus</i> VanB phenotype (23/0.25%)	74	100					
<i>E. coli</i> (721/7.9%)	49	90	>99	100			
<i>Klebsiella</i> spp. (582/6.4%)	1	36	78	92	98	100	
<i>P. aeruginosa</i> (765/8.4%)	–	<1	1	2	5	21	64
<i>Proteus mirabilis</i>	–	–	–	–	–	50	90
<i>Proteus vulgaris</i>	–	–	–	–	–	90	–
<i>Serratia</i> spp. (168/1.8%)	–	1	13	80	94	97	100
<i>S. aureus</i> MSSA (1649/18.1%)	61	89	>99	100			
<i>S. aureus</i> MRSA (1272/14%)	52	86	99	100			
<i>S. pneumoniae</i> (141/1.5%)	96	100					
<i>S. maltophilia</i> (131/1.4%)	1	8	36	69	90	97	100

Tigecycline is not clinically useful against *Pseudomonas* or *Proteus* spp.

C _{max} (30 min. infusion)	0.87 mcg/mL
C _{max} (60 min. infusion)	0.63 mcg/mL
AUC _{0-24h}	4.7 mcg • h/mL
t _{1/2}	42.4 h
CL	23.8 L/h
CL renal	51 mL/min
Vd	639 L
Protein Binding	71% - 89%

activity against *Proteus mirabilis* and *P. vulgaris*.⁷ Additionally, *B. fragilis* has an MIC₅₀ of 1mcg/mL and MIC₉₀ of 4mcg/mL (range 0.015–32mcg/mL)¹, making the MICs higher than the achievable blood concentrations; however, the efficacy of tigecycline against *B. fragilis* may be partially explained by concentration of the drug in key tissues (e.g., colon tigecycline concentrations are 2.1 times that of serum).⁸

Pertinent pharmacokinetic information for tigecycline is summarized in Table III. Standard tigecycline dosing is 100mg IV as an initial dose, followed by 50mg every 12 hours, with an infusion time of 30–60 minutes and a treatment duration of 5–14 days. The large volume of distribution of tigecycline at steady-state indicates extensive tissue distribution. Tigecycline is not extensively metabolized nor does it appear to inhibit CYP450 isoforms. Elimination of the drug is 59% biliary/fecal and 33% urine. Dosage adjustment is not necessary in patients with renal impairment or mild-to-moderate hepatic impairment. Patients with severe hepatic disease should receive an initial tigecycline dose of 100mg followed by a reduced maintenance dose of 25mg every 12 hours.

The most common adverse effects associated with tigecycline use among the 1415 patients treated in Phase 3 clinical trials were mild-to-moderate nausea and vomiting. Overall incidence of nausea was 29.5% while the incidence of vomiting was 19.7%.

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Tigecycline is considered a pregnancy category D drug. Animal studies illustrate that tigecycline crosses the placenta and distributes to fetal tissue. Animal studies also demonstrate decreased fetal weights, delays in ossification, and fetal loss with tigecycline. As with all tetracyclines, administration of tigecycline during the second or third trimester could potentially lead to staining of fetal primary dentition.

To date, a total of two papers summarizing the results of four Phase 3 clinical trials of tigecycline for complicated skin and skin structure (2 trials) and complicated intra-abdominal infections (2 trials) have been published.^{9,10} The first of these papers compared the use of IV tigecycline to IV vancomycin/aztreonam for the treatment of complicated skin and skin structure infections (cSSSI).⁹ Both cSSSI studies were randomized, double-blind and active controlled, as well as multinational and multicentered. The primary endpoint was clinical response at the test-of-cure visit 12–42 days after the last dose of study medication, which was given for 5–14 days. The treatment arms were: tigecycline 100mg initially followed by 50mg every 12 hours with placebo; or sequential vancomycin at a dose of 1g every 12 hours followed by aztreonam 2g every 12 hours. Of the 1057 patients (538 tigecycline vs. 519 vancomycin/aztreonam), 79.7% treated with tigecycline and 81.9% treated with vancomycin/aztreonam had clinical cure ($p=0.4183$). As indicated by the non-significant p-value, tigecycline was shown to be non-inferior to the combination treatment of vancomycin/aztreonam for complicated skin and skin structure infections. The predominant pathogens identified in these trials were *S. aureus* (primarily MSSA with a small number of MRSA) and *Streptococcus* spp. Currently, cefazolin is typically considered first-line therapy for cSSSI, if resistance is not suspected, and vancomycin monotherapy is another reasonable choice for the treatment of serious infections due to beta-lactam-resistant Gram-positive organisms.

The second paper reported the results of the use of tigecycline for complicated intra-abdominal infections (cIAI).¹⁰ Again, the results of the two randomized, double-blind, active-control, multicentered trials looked at a primary endpoint of clinical response at the test-of-cure visit 12–42 days after the last dose of study medication. Patients were randomized to receive either tigecycline 100mg loading dose followed by 50mg every 12 hours or imipenem-cilastatin 500mg every 6 hours for a treatment duration of 5–14 days. Of the 1601 patients treated (801 tigecycline vs. 800 imipenem-cilastatin) 79.8% treated with tigecycline and 82% treated with imipenem-cilastatin had clinical cure ($p=0.2851$). As indicated by the non-significant p-value, tigecycline was shown to be non-inferior to imipenem-cilastatin for complicated intra-abdominal infections. In clinical practice, piperacillin-tazobactam and carbapenems are typical monotherapy options for cIAI; however, combination regimens such as metronidazole with upper generation cephalosporins, ciprofloxacin, or aztreonam are often used. Although it is fair to compare tigecycline to imipenem-cilastatin for cIAI, other studies demonstrating tigecycline effectiveness compared to standard combination treatment options are warranted.

Clinical trials show that tigecycline is a successful option for cSSSI and cIAI; however, given the climate of increasing bacterial resistance, it is wiser to reserve it for life-threatening infections caused by multi-drug resistant organisms. As mentioned above, many reasonable therapeutic alternatives are available for non-multidrug resistant cSSSI and cIAIs.

UW Medicine formulary broad-spectrum antibiotics arranged by cost are summarized in Table IV at http://depts.washington.edu/druginfo/DTT/2006_V35_Files/V35N2_TableIV.pdf. Tigecycline therapy is comparable in cost to imipenem therapy. Though tigecycline can be used for MRSA, less costly formulary drugs are available and equally effective. Treatment with tigecycline is monitored by the HMC AARM team for use restricted to resistant organisms.

With increasing bacterial resistance, the need for new drugs, such as tigecycline, is expanding. Tigecycline would be most beneficial in the realm of multi-drug resistant bacteria,

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Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form(s), Strength(s), & Cost [‡]	Therapeutic Classification	Use	Usual Adult Starting Dose*
Gadobenate dimeglumine (MultiHance)	Injection: 529mg/mL (5, 10, 15, and 20mL)	Diagnostic agent	Magnetic resonance imaging of the CNS	Refer to product labeling.

* Refer to product labeling for full prescribing information. ‡ Contact pharmacy for information on drug costs.

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as it is active against Gram-positive, Gram-negative, atypicals, and resistant strains of common pathogens such as MRSA, ESBL-producing *E. coli* and *Klebsiella* spp., VRE, and multi-drug resistant *Acinetobacter*. Tigecycline is not active against *Proteus* or *Pseudomonas* spp. A potential future use for tigecycline is the treatment of nosocomial pneumonia where *Pseudomonas* is not suspected. Likewise, the ultimate role for tigecycline may be expanded as resistance patterns change and as more complete clinical evidence regarding the drug emerges.

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