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REVIEW

Review of Tigecycline: Focus on Clinical Utilization

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Abstract: This paper reviews the antimicrobial profile and available clinical data for the first member of the glycylcycline class, tigecycline. Emerging multi-drug resistance among gram-positive and gram-negative pathogens continues to limit the antibiotic armamentarium. Tigecycline, a derivative of minocycline, may provide a therapeutic option in select patients, given its broad spectrum of activity, including multi-drug resistant (MDR) strains. A search of Medline and EmBase of articles through April 2010 and references of select citations was conducted. Several randomized controlled studies have resulted in the approval of tigecycline in the treatment of skin and skin structure infections, complicated intra-abdominal infections, and community acquired pneumonia. Several other studies and single-center observations have demonstrated select efficacy in specific populations including ventilator-associated pneumonia, bacteremia, and other infections secondary to MDR pathogens. These data, along with pharmacokinetic and safety issues, are reviewed to offer insight into appropriate patient selection for tigecycline therapy.

Keywords: tigecycline, skin and soft tissue infections, intra-abdominal infections, pneumonia, bacteremia

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Introduction

In this era of progressive antimicrobial resistance, the utility and role for antimicrobials, both old and new, are quickly evolving. The Infectious Diseases Society of America (IDSA) has recently published a third installment to a series which began as a call to action for antimicrobial drug development. The work, originally entitled, "Bad Bugs, No Drugs," now in its updated form as "Bad Bugs, Need Drugs," is a plea to federal funding agencies, the Food and Drug Administration, and the pharmaceutical industry, among others, to jointly work to foster in a new period of novel antimicrobial discovery.[1–3] The landscape of resistance is far reaching among most gram-positive and gram-negative bacteria. Rates of methicillin resistance among *Staphylococcus aureus* and vancomycin resistance in Enterococcal species continue to rise.[4,5] Resistance among Enterobacteriaceae in the form of AmpC-, KPC-, and other ESBL-producing strains often creates a treatment dilemma for clinicians, as activity of extended spectrum beta-lactams and carbapenems, once potent, is now becoming more limited.[6,7] Several non-lactose fermenting gram-negative rods, including *Acinetobacter* species, are often carrying multi-drug resistance (MDR) to nearly all available antimicrobial classes.[6,7] Beyond resistance, accounting for host factors such as renal and hepatic disease, significant co-morbidities, drug-drug interactions, and medication allergies, further limits the antibiotic armamentarium.

A derivative of minocycline, tigecycline, the first member of the glycylcycline class of antibiotics, was introduced to the market in 2005.[8] The tetracycline class of antibiotics has existed for nearly 60 years. Unlike its predecessors, tigecycline possesses broad-spectrum activity secondary to its unique structural modifications. Coverage includes gram-positive aerobes: *Staphylococcus aureus* (including tetracycline and methicillin-resistant strains), Streptococcus species, and Enterococcal species (including vancomycin resistant strains); gram-negative aerobes: most Enterobacteriaceae (including MDR strains) and *Acinetobacter baumanii*; and anaerobic bacteria including *Clostridium difficile*.[8–10] Tigecycline, a parenteral-only compound, has been approved in the United States for the treatment of complicated skin and skin structure infections (cSSSI), complicated intra-abdominal infections (cIAI), and community-acquired pneumonia (CAP).[8] Because of its unique spectrum of activity, clinical use of tigecycline is observed in infections secondary to MDR pathogens, often in the intensive care unit setting.[9,11,12] This review outlines the pharmacology and pharmacokinetic profile of tigecycline, safety and tolerability data, and a presentation of published clinical data in the areas of cSSSI, cIAI, and CAP. More recent data on bacteremia and utilization in infections secondary to MDR organisms are also highlighted.

We conducted a Medline search for articles published through April 2010 using the MeSH terms "tigecycline" and "glycylcycline". An additional search of international pharmaceutical abstracts and EmBase was conducted using similar search methods. Reporting of *in vitro* activity studies was limited to pertinent representatives of key concepts. Reference lists from retrieved articles were also searched for additional relevant citations. Unpublished data, including meeting abstracts, were not detailed in this review.

Mechanism of Action

Tigecycline, a synthetic derivative of minocycline, is a novel antimicrobial with expanded broad spectrum activity from a new class of compounds, the glycylcyclines. Tigecycline exhibits bacteriostatic activity through reversible binding to 30S ribosomal subunit and inhibition of protein synthesis and translation in bacteria. This inhibition prevents incorporation of amino acid residues into elongating peptide chains.[8,13–15] Structural modifications to minocycline in position 9 (Fig. 1) and stronger binding affinity enhance the activity and decrease the potential for resistance of tigecycline compared to tetracycline and minocycline.[13–16]

Pharmacokinetics

The pharmacokinetic properties of tigecycline are summarized in Table 1.[10,16] Tigecycline is parenterally administered and exhibits linear pharmacokinetics after a single dose in the range of 12.5 to 300 milligrams (mg) and multiple doses of 25 to 100 mg every 12 hours.[1,16] After IV administration, tigecycline is rapidly distributed into the tissues. The *in vitro* plasma protein binding ranges from 71% to 89% (0.1–1.0 mcg/mL).[1,16,17] The unbound fraction decreases as the concentrations of tigecycline increase (29% at concentrations of 0.1 vs. 11% at

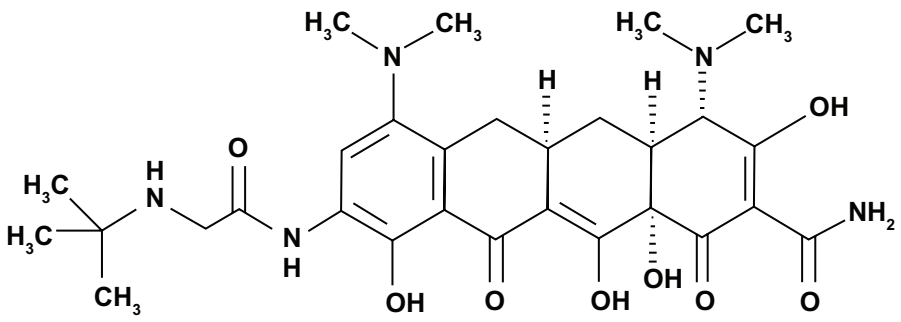

Figure 1 Structure of tigecycline.
Reproduced with permission from Livermore D, 2005.[63]

concentrations of 1.0 mcg/mL).[16] The volume of distribution averages 500 to 700 L (7–10 L/kg) at steady-state suggesting extensive tigecycline distribution beyond plasma volume into tissues as shown in Figure 2. Food does not significantly affect the pharmacokinetics of tigecycline, although it mayimprove tolerability of the drug.[8,16–21]

Penetration of tigecycline into epithelial lining fluid and alveolar cells has been studied. A loading dose of tigecycline 100 mg followed by 50 mg every 12 hours in healthy volunteers demonstrated a C_{max} of 0.37 mcg/ml, AUC 2.28 mcg.hr/ml, and half life of 39.1 hours in epithelial lining fluid and 15.2 mcg/ml, 134 mcg.hr/ml, and 23.7 hours in alveolar cells respectively.[17] After a 100-mg loading dose followed by 50 mg every 12 hours demonstrated a mean penetration of tigecycline in blister fluid of 74% of that of serum.[22]

Tigecycline undergoes no significant metabolism in the liver. *In vitro* studies using human liver microsomes, liver slices and hepatocytes led to the formation of only trace amounts of tigecycline metabolites.[8] The primary route of elimination of tigecycline is biliary excretion (59%) of unchanged tigecycline and its metabolites with glucuronidation and renal elimination as secondary routes.[23] Tigecycline does not affect the cytochrome P450 (CYP450) enzyme family nor does tigecycline alter the metabolism of drugs metabolized by the CYP450 enzymes.[24,25] No clinically relevant drug interactions were noted. Anticoagulation tests should be monitored if tigecycline is co-administered with warfarin; however, no dosage adjustment of either agent is necessary.[26,27] The effects of age and sex on the pharmacokinetics are negligible and dosage adjustment is not necessary.[25]

Table 1. Serum pharmacokinetic parameters of tigecycline.[8,16,20,21]

Dose (mg)	C_{max} (mcg/ml)	AUC_{ss} (mcg.hr/ml)	$t_{1/2}$ (hrs)	Clearance (L/hr/kg)	V_{ss} (L/kg)
25	0.3	1.5	49.3	0.2	8.6
50	0.6	3.0	36.9	0.2	7.2
100	1.2	5.0	66.5	0.2	9.1

Adapted with permission from Rose W, et al 2006.[10]
Notes: Doses were administered every 12 hours for 10 days in healthy male volunteers.
Abbreviations: AUC_{ss}, area under the concentration-time curve at steady state; C_{max}, maximum serum concentration; $t_{1/2}$, half-life; V_{ss}, steady state volume of distribution.

Pharmacokinetics in special populations

Hepatic impairment

The single dose pharmacokinetics of tigecycline are not altered in patients with mild hepatic impairment (Child Pugh A). However, the pharmacokinetic disposition of tigecycline is altered in patients with moderate to severe hepatic impairment. Systemic clearance is reduced by 25% and half-life prolonged by 23% in patients with moderate hepatic impairment (Child Pugh B) while systemic clearance is reduced by 55% and half-life prolonged by 43% in patients with severe hepatic impairment (Child Pugh C) warranting dosage adjustments in patients with severe hepatic impairment.[8] The recommended dosage in patients with severe hepatic impairment is a loading dose of 100 mg followed by 25 mg every 12 hours.[8]

Renal impairment

The pharmacokinetic profile of tigecycline is not significantly altered in renally impaired patients, and tigecycline is not appreciably removed by hemodialysis.

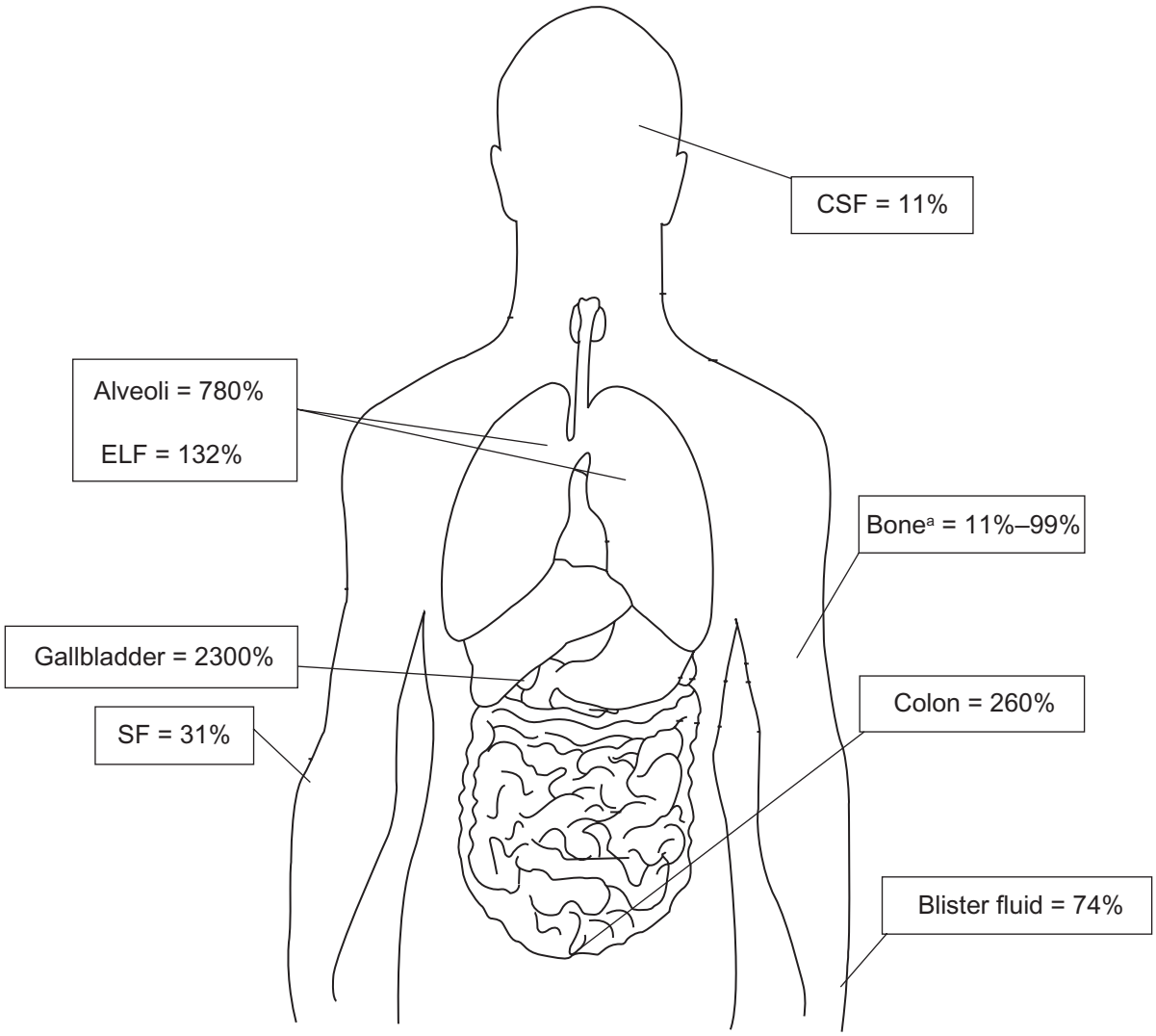

Figure 2. Tigecycline distribution into body compartments.[8,17,20,21]
Notes: Data presented as percentage (%) of serum AUC_{0-24}; SF = synovial fluid.
[a]Considerable variation in bone penetration depending on model and technique used. Recent methodology suggests higher percentage of penetration.

No dosage adjustment is necessary in patients with renal impairment or those undergoing hemodialysis.[8,19]

Obesity

The pharmacokinetics of tigecycline in obese patients has not been thoroughly investigated. Tigecycline clearance increases proportionally with body weight, while the C_{max}, C_{min}, and AUC are reduced.[17,20,29,30] Dose adjustments may be warranted in morbid obesity, although specific recommendations cannot be made with available data.

Others

There are no significant differences in pharmacokinetics between elderly and young subjects; men and women; women; and among black, white, Asian, and Hispanic subjects. No dosage adjustment are necessitated by age, sex, or race.[25] Tigecycline is indicated for patients 18 years of age or older and should be avoided in pediatrics, specifically those adolescents less than 8 years of age.[8]

Clinical Studies

Skin and skin structure infections

Tigecycline is approved for the treatment of complicated skin and skin structure infections (cSSSI) in hospitalized patients secondary to multiple pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA) at a dose of 100 mg load and 50 mg twice daily.[8] In an open-label study, the

Tigecycline 200 study group demonstrated increased efficacy in the 100 mg load, followed by 50 mg twice daily dosing regimen when compared to 25 mg twice daily group.[31] The primary endpoints of clinical cure and microbiological eradication rates were both higher in the 50 mg group which supported further study at this dose. Two randomized controlled trials comparing tigecycline to the combination of vancomycin plus aztreonam were conducted in over 1100 patients in each treatment arm.[32,33] Pooled analysis of the two studies was conducted by the sponsoring company.[34] A total of 422 and 411 patients who received either tigecycline or vancomycin plus aztreonam respectively were included in the clinically evaluable population. Standard diagnosis of cSSSI were considered in the inclusion criteria, however patients with suspected osteomyelitis or necrotizing fasciitis were excluded. Patients were approximately 48 years of age, predominantly Caucasian males with a mean weight of nearly 82 kilograms. In general patients were relatively healthy, with 20% carrying a diagnosis of diabetes mellitus and 7% with peripheral vascular disease. The studies were designed to demonstrate non-inferiority of tigecycline to the vancomycin plus aztreonam treatment arm. Overall cure rates for the clinically evaluable population were 86.5% and 88.6% respectively for the tigecycline and vancomycin plus aztreonam arms. In the subset of patients with concurrent bacteremia, cure rates were similar again, 82.6% (n = 23) versus 87.5% (n = 24). There was no difference in the treatment groups when looking at infection type or pathogen, including MRSA, although the overall cure rate was appreciably lower in this subset of patients (~77%).[32–34] These results were further supported in a randomized study in hospitalized patients with infections secondary to either MRSA or vancomycin-resistant *Enterococci*. Clinical cure rates were similar in the subset of patients with cSSSI in the tigecycline (86.4%, 51/59) and vancomycin (86.9%, 20/23) arms.[35] A phase III clinical trial has recently been completed comparing tigecycline to ertapenem for the treatment of diabetic foot infections (DFI), however full results have not been published and will not be discussed in this review.[36]

Complicated intra-abdominal infections

Results of two randomized, controlled trials supported the initial approval of tigecycline at the same dosing schedule for complicated intra-abdominal infections (cIAI) secondary to gram-negative, gram-positive, and anaerobic pathogens.[8,37,38] Tigecycline was compared to imipenem-cilastatin in hospitalized patients with cIAI in over 1,600 randomized patients in a pooled analysis.[39] Inclusion criteria were that of standard cIAI to include such infections as appendicitis, cholecystitis, and peritonitis. Patients with underlying hepatic disease or significant renal disease (clearance <40 ml/min/1.73 m^2) were excluded, as well as those with a pancreatic abscess or necrotizing pancreatitis. Six-hundred thirty one patients were evaluable in each treatment arm and the majority of patients were Caucasian males. There were very few seriously ill patients, as the population had a mean APACHE II score of 6. Overall cure rates were very good, and comparable in each arm at 86.7% and 87.1% respectively. The majority of patients (~50%) carried a diagnosis of complicated appendicitis. There was no difference between the groups in cure rates of any subset of infection types. Patients with concomitant bacteremia had approximately 80% cure rates in each arm. Microbiological eradication was also similar among all pathogens, including *P. aeruginosa* isolates.[37–39] Towfigh and colleagues conducted a multi-center, randomized open-label study comparing tigecycline to ceftriaxone plus metronidazole for cIAI.[40] Inclusion and exclusion criteria was similar to previously mentioned studies. Nearly 200 patients in each arm were clinically evaluable for analysis. Overall cure rates were appreciably lower in this study compared to previously published studies (tigecycline: 70.4% versus ceftriaxone plus metronidazole: 74.3%); however, there was no difference between the treatment arms. When stratified by infection type, pathogen, and severity of illness (APACHE II score), there was no significant difference between the treatment arms.[40] Tigecycline is recommended (A-1 rating) in the IDSA guidelines for cIAI in patients with mild to moderate disease without risk of Pseudomonal infections.[41]

Community-acquired pneumonia

Tigecycline was recently approved for treatment of community-acquired pneumonia (CAP) in response to data from two randomized controlled trials.[8,42,43] Bergallo and colleagues conducted the first of two company-sponsored studies comparing standard dose

tigecycline to levofloxacin 500 mg daily.[42] Immunocompromised patients or those requiring admittance to the ICU were excluded from the study. Over 400 patients were randomized, and 294 were clinically evaluable (tigecycline: n = 138; levofloxacin: n = 156) for analysis. Patients were 1:1 male to female, and the mean age was approximately 55 years. Nearly 15% of patients had diabetes mellitus and COPD. Of the clinically evaluable patients, cure rates were comparable at 90.6% and 87.2% for the tigecycline and levofloxacin groups respectively. The intention to treat analysis resulted in cure rates of 78% in both arms. Microbiological eradication was similar for all pathogens isolated. All secondary clinical and laboratory outcomes were similar, although approximately 4.5% of patients required concomitant antibiotic therapy in the levofloxacin arm. There was also no difference based on presence of comorbidities or pneumonia severity index (PSI) score. A small number of patients were also bacteremic and there was no difference in cure rates among these patients (tigecycline: 90.9% vs. levofloxacin: 76.9%).[42] A second randomized controlled trial with very similar inclusion criteria comparing the same two agents, enrolled over 400 patients. In the levofloxacin arm, twice daily administration was allowed at the discretion of the investigator, although it was not discussed in the results. Approximately 150 patients in each arm were clinically evaluable. The majority of patients had a PSI score of II or III. No difference was found in the primary endpoint of clinical cure between the two arms, 88.9% and 85.3%. Subset analyses by PSI and CURB-65 score showed no difference in the treatment arms. There was a small population of patients with concurrent bacteremia, and no difference was detected.[43] Tigecycline also carries *in vitro* activity against *Legionella pneumophila*.[44] Pooled data of limited patients (n = 10) suggest good clinical efficacy as well.[42,43] A single case report in an immunocompromised patient also supports these results.[44]

Ventilator-associated pneumonia

Due to its *in vitro* activity against MDR gram-negative organisms, including *Acinetobacter baumanii* and ESBL-producing Enterobacteriaceae, tigecycline may be an option in select patients.[7,9,11,46,47] Hospital-acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP) secondary to these pathogens is becoming increasingly problematic.[6,7] Several reports suggest tigecycline is seeing increased utilization in these serious infections as both empiric and targeted therapy.[48–51] A single center study in the mid-western US reported clinical success in 15 of 19 patients with documented VAP treated with tigecycline. Of the 4 failures reported, 2 had increasing MIC values during therapy and 1 was concurrently bacteremic.[50] The Latin American Tigecycline Use Registry was a larger cohort of 117 patients with documented VAP from multiple centers. Clinical success was reported in 63% of patients, all of which received standard dosing of tigecycline. Success was not different in those with prior antibiotic therapy or those receiving tigecycline monotherapy. An APACHE II score >15 was a negative predictor of clinical success.[48]

Bacteremia

Concern arises among some clinicians in using tigecycline in patients with bacteremia due to its bacteriostatic properties and large volume distribution leading to low serum concentrations.[19–20,52] A pooled analysis of 8 Phase III clinical trials of enrolled patients with secondary bacteremia was published detailing clinical cure rates of tigecycline versus comparators.[53] Overall, 91 patients in the tigecycline arm and 79 patients in the comparator arm were included in the analysis. All patients had secondary bacteremia with the primary infection site being cIAI (42.9%), CAP (31.9%), or cSSSI (25.3%) in the tigecycline arm. Overall clinical cure was 81.3% compared to 78.5% in the tigecycline versus comparator arm respectively (P = 0.702). Cure rates were significantly lower as expected in the ITT population, although no differences were noted between groups. No factors (demographics, severity of illness, primary infection) were found to be significant predictors of clinical outcomes including analysis by causative pathogen. Small numbers of patients with MRSA or VRE make it difficult to establish sound conclusions in these patients.[35,53]

In cases of bacteremia associated with an indwelling central venous catheter, there is limited data to support the use of local instillation of tigecycline in an antibiotic lock solution.[54,55]

Safety

Tigecycline should be used with caution in patients with known hypersensitivity to tetracycline-class

antibiotics as it may produce similar adverse effects. Nausea, vomiting, and gastrointestinal upset are the most commonly reported adverse events in patients receiving tigecycline as demonstrated in several safety and efficacy studies.[16,30–34,39,46] Nausea and vomiting are more likely to occur in young women (<50 years).[25] The nausea and vomiting due to tigecycline is mild to moderate occurring within 1–2 days of initiating tigecycline therapy, typically associated with the higher loading dose.[34,39] Gastrointestinal adverse events are improved when tigecycline is administered with food.[16,30] Prolongation of the infusion periods does not appear to have a role and the value of antiemetic agents is not well-established.[16] Table 2 displays other treatment-emergent adverse events of tigecycline.

Increases in transaminases, prothrombin time, and total bilirubin concentration have been observed in patients treated with tigecycline.[8] Tigecycline may cause fetal harm when administered to a pregnant woman. Permanent discoloration of the teeth may occur with the use of tigecycline during tooth development. *Clostridium difficile*-associated diarrhea has been reported and may range in severity.[8]

Tigecycline should be used cautiously in bacteremia and endocarditis even when responsible pathogens are susceptible as evident by laboratory MICs. Tigecycline has a large volume of distribution with subsequent low serum concentrations and demonstrates bacteriostatic action.[19,20,52,56] Break-through bacteremia including Enterococcus species, despite susceptible tigecycline MICs may occur secondary to low serum concentrations.[8] Clinicians should use tigecycline monotherapy cautiously in bacteremia.

Like any other antimicrobial agent, tigecycline may result in overgrowth of non-susceptible organisms. While tigecycline has a broad-spectrum *in vitro* activity against several gram-positive and gram-negative organisms, *Pseudomonas aeruginosa* is intrinsically resistant and some species of *Proteus* have reduced susceptibility. The superinfection rate observed during tigecycline therapy is increasing. A retrospective observational study of 51 patients treated with tigecycline for nosocomial infections due to multidrug MDR microorganisms evaluated the superinfection rate. The superinfection rate during tigecycline treatment was 23.5% (12 of 51). *Pseudomonas aeruginosa* was the most frequent pathogen responsible for the superinfections.[58]

Table 2. Incidence of treatment-emergent adverse events of tigecycline in clinical studies.[34,39]

Percentage	Adverse event
≥10%	Nausea
	Vomiting
	Diarrhea
≥5%–10%	Abdominal pain
	Headache
	Fever
≥3%–5%	ALT increase
	AST increase
	Hyperbilirubinemia
	Dizziness
	Rash
	Anemia
	Phlebitis

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotrasnferase.

Place in Therapy

Tigecycline has demonstrated to be non-inferior to standard therapies in the treatment of hospitalized patients with SSSI, cIAI, and CAP. Due to its pharmacokinetic properties, including excellent tissue penetration, tigecycline is an option where the nidus for the infection is within the tissues. Treatment guidelines from the IDSA for IAI include tigecycline as an option in community-acquired disease.[41] Tygecycline's broad spectrum of activity makes it a good parenteral option in polymicrobial infections, except when likely pathogens are *Pseudomonas* or *Proteus* species. Patients with a significant beta-lactam hypersensitivity may also be good candidates for tigecycline therapy. Limited data suggest tigecycline may be an option in refractory *C. difficile* infections.[59,60] Although caution should be employed in cases of secondary bacteremia, clinicians should consider the source of the bacteremia when making the antimicrobial selection. Tigecycline has also demonstrated potent antimicrobial activity against ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*. It constitutes one of the few potentially active agents against multi-drug resistant organisms (MDRO) including carbapenem-resistant *Acinetobacter baumannii*.[9,11,61,62] At this point, clinical outcomes data are too limited to support its use in ICU sepsis, including bacteremia or VAP, except potentially in cases of MDRO, as mentioned previously, with limited treatment options.

Conclusions

Tigecycline is the first available drug in a new class of antibiotics, the glycylcyclines, indicated for the treatment of SSSI, IAI, and CAP. Available only in parenteral form, tigecycline is recommended at loading dose of 100 mg with a 50 mg twice daily maintenance dose. There is no adjustment in renal disease; however in moderate to severe hepatic insufficiency, the maintenance dose should be reduced to 25 mg twice daily. Future research as a once-daily administration may result in added utilization to include outpatient therapy. Gastrointestinal adverse effects, specifically nausea and vomiting, are common with this agent and may require anti-emetic therapy, especially with the initial loading dose. Tigecycline has broad-spectrum activity against susceptible and commonly encountered resistant strains of gram-negative pathogens (excluding *Proteus* and *Pseudomonas* species), gram-positive aerobes, anaerobes, and atypicals. The presence of mechanisms that confer resistance to other antimicrobial agents does not influence the antimicrobial activity of tigecycline against most pathogens. Drug-drug interactions are not of clinical concern. Tigecycline presents a viable option in patients with mixed or polymicrobial infections and those with documented beta-lactam hypersensitivity, especially in those with a tissue nidus for infection. Risk-benefit should be weighed by the clinician before using this agent in the presence of bacteremia or sepsis in acutely-ill patients due to its relatively sub-inhibitory serum concentrations experienced shortly after the dose is administered. Tigecycline does present a therapeutic option in MDR infections, such as *Acinetobacter baumanii*, with otherwise limited treatment options.

Disclosures

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