Role of Tigecycline for the Treatment of Urinary Tract Infections

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Abstract

Objective: To review and critically analyze the literature for the use of tigecycline for the treatment of urinary tract infections (UTIs). **Data Sources:** A search of the MEDLINE database was performed (2004 to July 2013). Search terms included tigecycline, Tygacil, pyelonephritis, cystitis, and urinary tract infections in addition to a manual search of references from the articles retrieved. **Study Selection and Data Exaction:** All studies of humans, English-language articles, clinical studies, observational studies, and case reports were evaluated. **Data Synthesis:** Fourteen cases of tigecycline use for UTIs were identified. No clinical trials were identified via the search of the MEDLINE database. Twelve of the 14 cases described positive clinical outcomes with use of tigecycline for the treatment of UTI. Microbiological clearance was evaluable in 11 patients, of which 9 patients achieved documented microbiological clearance. None of the patients had mortality attributable to the use of tigecycline for the UTI. Two of the 14 cases reported had patients with subsequent cultures growing tigecycline-resistant organisms. **Conclusion:** Case reports have documented clinical improvement/success with the use of tigecycline for the treatment of UTIs. However, use of tigecycline for the treatment of UTIs remains controversial because of limited data and the lack of randomized control trials demonstrating efficacy. Tigecycline should be avoided for the treatment of UTIs when well-established options such as aminoglycosides and β -lactams are available. When alternative options are nonexistent, tigecycline can be considered.

Keywords

tigecycline, urinary tract infections

Background

Urinary tract infections (UTIs) are among the most common causes of infection.¹ Uncomplicated UTI generally involves young, healthy, nonpregnant women, whereas complicated UTI can involve any age group, typically in patients with either functional or structural abnormality of the urinary tract.¹ UTIs associated with symptoms require treatment whereas asymptomatic infection frequently does not.¹ Important factors when considering pharmacotherapy is the ability to achieve appropriate concentrations in the urine at least to the level of minimum inhibitory concentration (MIC) at the site of infection. Therefore, agents that have poor urinary concentrations may not be suitable for the treatment of UTI.²

Tigecycline Overview

Tigecycline is a glycylcycline derived from minocycline, which overcomes mechanisms of resistance that may preclude the use of tetracyclines.^{3,4} This is achieved by the addition of a *tert*-butyl-glycylamido group to the C-9 position of minocycline, which enables tigecycline to overcome efflux pump and

ribosomal protection that can affect tetracyclines.⁴ It is a broad spectrum antibiotic that demonstrates activity against gram-positive, gram-negative, anaerobic, and atypical bacteria including methicillin-resistant *Staphylococcus aureus*, extended spectrum beta lactamase (ESBL), and carbapenemase-producing enterobacteriaceae and *Acinetobacter baumannii*. Currently, tigecycline has US Food and Drug Administration indication for the treatment of community-acquired bacterial pneumonia, complicated intra-abdominal infections, and complicated skin and skin structure infections.⁵ It is not indicated for the treatment of UTI although it has been used off label for treatment (Table 1).^{6–15} In a retrospective cohort study by Satlin et al, the microbiological clearance was compared between aminoglycosides, polymyxin, tigecycline, and an untreated cohort in patients with bacteriuria caused by carbapenem-resistant *Klebsiella pneumoniae* (CKRP).¹⁶ In

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this study, tigecycline demonstrated inferior microbiologic clearance rate as compared with the aminoglycosides and the polymyxin cohort and similar clearance rates to the untreated cohort. Although tigecycline has activity against many bacteria including multidrug-resistant strains and limited side effects, there are pharmacokinetic concerns with using tigecycline for UTI as only 22% of the total dose is excreted unchanged.⁵ As a result, there is existing controversy regarding the efficacy of tigecycline for this treatment population.¹⁶

Literature Review

A MEDLINE search of the literature published from 2004 to July 2013 utilizing the terms tigecycline, Tygacil, pyelonephritis, cystitis, and urinary tract infections was performed in addition to a manual search of references from the articles retrieved. The search included clinical trials and case reports. Fourteen cases were identified that described the experience of tigecycline for treatment of complicated UTI and included patients with urosepsis and prostatitis.⁶⁻¹⁵ No clinical trials were identified.

A 63-year-old male patient with complicated UTI and probable prostatitis was successfully treated with tigecycline.⁶ He had been treated with 10 days of doxycycline for ESBL-producing *Escherichia coli*. Despite doxycycline therapy, symptoms continued and ESBL *E coli* was recovered from the cultures again. His primary care provider eventually contacted Infectious Disease Service for management assistance because of continued symptoms. The patient was advised to go to the hospital for initiation of ertapenem. On admission, the patient confirmed a history of fever to 103°F with associated rigors. Physical exam revealed a mildly tender and enlarged prostate in addition to suprapubic tenderness. Laboratory studies on admission included a urine culture growing >100 000 colony forming unit (cfu)/mL ESBL-producing *E coli* with associated pyuria, and prostate-specific antigen (PSA) of 13.36 ng/mL. During the first dose of ertapenem, the patient developed a swollen right eye and diffuse urticaria. After the risks and benefits were considered, the clinician decided to start the patient on tigecycline. Fourteen days of therapy was prescribed, and the patient eventually became asymptomatic. On physical exam his prostate was smaller and nontender. Laboratory studies revealed no pyuria on urinalysis, negative urine cultures, and PSA of 6.23 ng/mL. One month after completion of tigecycline therapy, a repeat urine culture grew ESBL *E coli*. It was decided not to give the patient any further treatment, because he was asymptomatic and remained so for at least 5 months without receipt of further antimicrobials.

Geerlings et al reported 2 cases of intravenous tigecycline used for the treatment of UTI.⁷ The first patient was a 44-year-old man with pyelonephritis caused by recurrent ESBL *E coli* due to suspected chronic prostatitis. Meropenem was used for the treatment of the initial 2 UTIs;

however, within 4 weeks there was recurrence. Instead of continued usage of a carbapenem, tigecycline for 6 weeks was initiated. Another case involved a 66-year-old female with recurrent UTIs caused by ESBL *E coli* because of infected renal cysts. This patient was treated with tigecycline for 6 weeks due to reported allergies to β -lactam antibiotic, which included carbapenems. Both patients had not developed a new UTI 5 months (patient 1) and 4 months (patient 2) after treatment.

Bates et al described a case of an 86-year-old man with obstructive urosepsis and was given empiric treatment with 1 dose of ceftriaxone followed by piperacillin-tazobactam therapy.⁸ Gram-negative bacilli with 100 000 cfu/mL were seen on preliminary urine cultures, and a gram stain of blood cultures also revealed gram-negative bacilli. As a result of the concern regarding the possibility that *E coli* was an ESBL-producing strain, piperacillin-tazobactam was discontinued and meropenem was started and later changed to ertapenem. Cultures were subsequently finalized and determined to be ESBL-producing *E coli*. After several days of carbapenem therapy, the patient developed a rash on multiple areas including but not limited to the palms, arms, and feet, which was characterized as a painful, and pruritic erythematous macular rash. Carbapenem therapy was suspected to be the culprit, so ertapenem was changed to tigecycline. While on tigecycline, the patient had no documentation of episodes of dysuria, urinary urgency, or increased urinary frequency; however, a repeat urine culture yielded >100 000 cfu/mL of ESBL-producing *E coli* although the blood cultures were negative. A diagnosis of chronic prostatitis was considered as a result of the patient's persistent bacteriuria, and a prolonged course of tigecycline was thought to be necessary. On day 25 of therapy, tigecycline was discontinued. Repeat urine culture yielded 10 000 to 100 000 cfu/mL of ESBL-producing *E coli*; however, no further treatment was recommended because the patient was asymptomatic. The patient was later discharged but readmitted with flank pain and urine culture again yielding 100 000 cfu/mL of ESBL-producing *E coli*. As a result of the presence of persistent bacteriuria, tigecycline was administered for an additional 6 weeks. After the tigecycline course was completed, the patient did not report any urinary tract symptoms and was discharged home. The patient was readmitted at another date for shortness of breath secondary to heart failure. Cultures of the urine yielded >100 000 cfu/mL of ESBL-producing *E coli*, and urinary analysis revealed 30 white blood cells per high power field. Tigecycline was initiated because of the patient's history; however, after 5 days of therapy, it was discontinued because the patient was asymptomatic and colonization by ESBL-producing *E coli* was thought to be likely. Although the patient had become asymptomatic multiple times during treatment with tigecycline, microbiological clearance never achieved.

Table 1. Tigecycline Use for Treatment of Complicated Urinary Tract Infections: Case Reports.

Reference	Patient; Primary Diagnosis	Organism	Tigecycline Dose/Duration	Microbiological Clearance	Clinical Cure/Improvement	Outcome (Comments)
Drekonja and Johnson (2011) ⁶	63-year-old man; complicated UTI	ESBL <i>E coli</i>	100 mg once, 50 mg IV q12h; 2 weeks	Yes	Yes	Alive (on a repeat urine culture 1 month after completion of therapy, ESBL <i>E coli</i> grew again; however, the patient was not treated because he was asymptomatic without receipt of subsequent antimicrobials during a 5-month follow-up period)
Geerlings et al (2010) ⁷	44-year-old male; recurrent pyelonephritis with possible prostatitis	ESBL <i>E coli</i>	NR; 6 weeks	NR	Yes	Alive (no new UTI during follow-up period of 5 months)
	66-year-old female; recurrent, complicated UTI	ESBL <i>E coli</i>	NR; 6 weeks	NR	Yes	Alive (no new UTI during follow-up period of 4 months)
Bates et al (2012) ⁸	86-year-old man; urosepsis, prostatitis	ESBL <i>E coli</i>	100 mg once, 50 mg IV q12h; multiple courses	No	Yes	Alive (after multiple recurrences of UTI, the patient eventually became asymptomatic although microbiologic clearance was not achieved)
Reid et al (2007) ⁹	53-year-old female; complicated UTI	<i>A baumannii</i> , vancomycin-resistant <i>Enterococcus</i>	100 mg once, 50 mg IV q12h, 2 weeks	Yes	Yes	Alive (although patient had microbiological clearance of <i>A baumannii</i> and vancomycin-resistant enterococcus, <i>A baumannii</i> was cultured again in a subsequent urine culture during the same admission)
Tsai et al (2012) ¹⁰	70-year-old female; complicated UTI	Carbapenem-resistant <i>E coli</i>	100 mg daily; 7 days	Yes	Yes	Alive (2 weeks after completion of tigecycline, the patient had a UTI caused by tigecycline-resistant <i>K pneumoniae</i>)
Krueger et al (2008) ¹¹	25-year-old female; urosepsis	ESBL <i>E coli</i>	NR; 13 days	NA	Yes	Alive (clinically improved and discharged from hospital)
Cunha et al (2007) ¹²	Elderly male; complicated UTI	Carbapenem-resistant <i>K pneumoniae</i> , <i>E aerogenes</i>	200 mg IV 24h; 14 days	Yes	Yes	Alive (urinary tract infection resolved and no further infections documented during hospital stay)
Gallagher and Rouse (2008) ¹³	63-year-old; complicated UTI	<i>A baumannii</i>	100 once, 50 mg IV q12h; 4 days	Yes	Yes	Alive
	49-year-old; complicated UTI	<i>A baumannii</i>	100 once, 50 mg IV q12h; 13 days	Yes	Yes	Alive
	63-year-old; complicated UTI	<i>A baumannii</i>	100 once, 50 mg IV q12h; 12 days	Yes	Yes	Alive
Anthony et al (2008) ¹⁴	54-year-old female; complicated UTI	<i>A baumannii</i>	100 mg once, 50 mg IV q12h; 17 days	Yes	Yes	Alive
	64-year-old male; complicated urinary tract infection	ESBL <i>K pneumoniae</i>	100 mg once, 50 mg IV q12h; 11 days	Yes	No	Expired (unrelated to UTI)
Kuo et al (2011) ¹⁵	76-year-old male; complicated UTI	<i>A baumannii</i>	100 mg once, 50 mg IV q12h; 12 days	No	No	Alive

Abbreviations: ESBL, extended spectrum beta-lactamase; NA, not applicable; NR, not reported; UTI, urinary tract infection.

Another case report described a 53-year-old woman who was admitted from a skilled nursing facility for fever and mental status changes.⁹ UTI and pneumonia were the suspected causes. Urine cultures grew multidrug-resistant *A baumannii* and vancomycin-resistant *Enterococcus* (VRE) while sputum cultures yielded normal flora. The urine isolate of *A baumannii* was resistant to imipenem-cilastatin, piperacillin-tazobactam, and levofloxacin. Therapy with tigecycline was initiated for 14 days with clearance of *A baumannii* and VRE from the urine and resolution of fever. However, the patient's hospital course was complicated and tigecycline had to be restarted secondary to respiratory failure requiring mechanical ventilation and positive sputum cultures that grew *A baumannii* susceptible to tigecycline with MIC of 2 µg/mL. During day 5, after re-initiation of tigecycline, urine cultures were performed and revealed *A baumannii* with a tigecycline MIC of 24 µg/mL. Although urine cultures were completed, it is unclear whether the patient had UTI; however, it is important to note the rapid development of *A baumannii* resistance that may develop after exposure to tigecycline.

Tsai et al reported a case of a 70-year-old acutely ill female who complained of a 3-day history of dysuria and suprapubic discomfort due to complicated UTI.¹⁰ Urinary cultures revealed >100 000 cfu/mL of carbapenem-resistant *E coli*. Tigecycline was started for 7 days. The patient had been asymptomatic for 2 weeks after the completion of therapy. However, after 2 weeks, the patient presented again, with signs and symptoms of UTI. Unlike the previous episode, the UTI was caused by *Klebsiella pneumoniae* that was resistant to tigecycline (MIC of 8 µg/mL). The organism was susceptible to cefazolin and the patient was prescribed cephalexin for 10 days, and a repeat urine culture was negative for tigecycline resistant *K pneumoniae*.

High-dose tigecycline regimen of 200 mg IV q24 hours was administered to an elderly male hospitalized due to hospital-acquired UTI caused by CRKP and MDR *Enterobacter aerogenes*.¹¹ The patient had a documented fever but no complaints of dysuria. After 5 days of treatment, microbiological clearance of the *K pneumoniae* was achieved. For *E aerogenes*, microbiological clearance was achieved after 12 days. Overall no side effects were noted with this high-dose daily regimen that was given for 14 days.

Krueger et al described a case of a 25-year-old female with urosepsis admitted to the ICU. Piperacillin-tazobactam was initiated for treatment of the patient's urosepsis.¹¹ The patient's condition deteriorated rapidly, and the patient was intubated 1 day after she was admitted in the intensive care unit (ICU) due to septic shock and respiratory failure. Piperacillin-tazobactam was discontinued and antibiotic therapy was changed to cefotaxime and amikacin. Urine cultures that were obtained in the 1 day following ICU admission identified *E coli* with susceptibility pending. The

patient was transferred to a tertiary care hospital for further treatment. She was admitted to the ICU and was started on meropenem. One day after admission to the tertiary hospital's ICU, a report from the transferring hospital was sent that identified the *E coli* strain isolated from the patient's urine culture was an ESBL-producing *E coli* strain resistant to piperacillin-tazobactam, trimethoprim-sulfamethoxazole, and fluoroquinolones. The pathogen was susceptible to amikacin, imipenem, and intermediately susceptible to gentamicin and tobramycin. The patient's condition improved and she was weaned from a respirator and extubated. Meropenem was stopped after completion of 16 days of therapy. The patient became tachycardiac (140/bpm) and developed a fever (102°F) 1 day after stopping meropenem. Meropenem was restarted again. However, because the patient continued to have fevers, meropenem was switched to tigecycline. Within a day after initiation of tigecycline, the fevers subsided. The patient's clinical condition improved and was transferred out of the ICU and eventually discharged from the hospital. The total course of tigecycline therapy was 13 days.

There were several case series that reported outcomes of UTI treated with tigecycline published although they were not solely focused on tigecycline for that indication.¹³⁻¹⁵ Overall in these 3 reports, 5 cases of tigecycline for treatment of *A baumannii* UTI were identified and 1 case of UTI caused by *K pneumoniae*.¹³⁻¹⁵ In the case series by Gallagher and Rouse, positive clinical and microbiological outcomes were described for the 3 patients reported using tigecycline for the treatment of UTI.¹³ In the case series by Anthony et al, 2 UTIs were reported that were caused by *A baumannii* and ESBL-producing *K pneumoniae*, respectively.¹⁴ For the case of UTI caused by *A baumannii*, tigecycline was prescribed with documented positive clinical and microbiological responses.¹⁴ For the ESBL *K pneumoniae* UTI, although microbiological response was documented the patient did not have a positive clinical response.¹⁴ Lastly and unlike the prior cases of *A baumannii* UTIs described previously, the case series by Kuo et al reported 1 patient who received tigecycline and failed to achieve a positive clinical response or microbiological eradication.¹⁵

Discussion

The case reports described demonstrated mostly successful use of tigecycline for the treatment of complicated UTIs in a predominantly elderly population. Two of the cases were complicated by prostatitis. The most frequently targeted pathogens were ESBL or carbapenemase-producing enterobacteriaceae reported in 8 of 14 patients followed by *A baumannii* in 6 of 14 patients (1 patient was co-infected with vancomycin-resistant enterococcus). Reasons for initiation of tigecycline, when provided, were for treatment of highly resistant gram-negative bacteria (including carbapenems),

medication allergies, or inadequate therapeutic response to previous therapy.

Although pharmacokinetic studies have demonstrated poor tigecycline excretion into the urine, some have estimated that the concentrations achieved will be approximately 7 to 11 µg/mL and is expected to be adequate for the treatment of UTI.¹⁷ However, this estimation has not been validated in a pharmacokinetic study. Data published have demonstrated mixed results. Outcomes from a retrospective cohort study did not demonstrate that tigecycline achieved better microbiologic clearance rates compared with an untreated cohort.¹⁶ This contrasts with the case reports where the majority of patients achieved microbiological clearance and positive clinical outcomes.⁶⁻¹⁵ A possible explanation and concern could be that positive results observed are attributed to publication bias, a phenomenon whereby positive findings are more likely to be published and negative findings rejected, while the negative results from the retrospective cohort study has intrinsic limitations due to its study design.¹⁸

With increasing bacterial resistance, clinicians are often challenged with limited treatment options particularly for the treatment of UTI caused by CKRP and other multidrug-resistant pathogens. Aminoglycosides and polymyxins may be potential treatment options for β-lactams and fluoroquinolones resistant pathogens. Tigecycline may be attractive to clinicians because of its relatively favorable adverse effect profile. This however must be counterbalanced with potential collateral damage caused by overexposing patients to tigecycline, leading to subsequent development of resistance to one of the current last-line therapies for multi-drug-resistant gram-negative infections. This is best exemplified in 2 of the cases described previously, where subsequent tigecycline-resistant organisms were cultured following completion of therapy. Data remain limited on the potential efficacy or lack thereof for treatment of UTI.

Summary

Available literature for the use of tigecycline in UTI shows a clinical response or improvement in 12 of the 14 cases reported and microbiological clearance in 9 of 11 cases. No cases of mortality attributable to tigecycline use were reported. Based on the current available literature, use of tigecycline for the treatment of UTI remains controversial because of a lack of randomized control trials. In addition, contrasting data from a retrospective cohort study and published case reports show a clear need for additional data researching the efficacy of tigecycline for UTI. Thus, tigecycline should be avoided for the treatment of UTI when well-established options such as fluoroquinolones, aminoglycosides, and β-lactams are available. Tigecycline can be considered when alternative options are not available.

Declaration of Conflicting Interests

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