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CASE REPORT

Tigecycline for the Treatment of Severe and Severe Complicated *Clostridium difficile* Infection

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ABSTRACT

Introduction: *Clostridium difficile* infection (CDI) is a common cause of nosocomial diarrhea. Metronidazole and vancomycin are the primary treatment options for CDI, but increasing rates of antimicrobial resistance and severe, refractory disease have prompted the need for alternative agents. Tigecycline has previously demonstrated favorable in vitro activity against *C. difficile* isolates, but clinical data on its use in the treatment of CDI are severely lacking. The objective of this study was to describe our experience using tigecycline in the treatment of severe and severe complicated CDI.

Methods: This was a retrospective case series of hospitalized patients with severe and severe complicated CDI who were treated with tigecycline. Disease severity assessments were determined according to current practice guidelines. Diagnosis of toxigenic CDI was confirmed by polymerase chain reaction and patients were excluded if they received tigecycline for <48 h. Data were collected by review of the electronic medical record. The primary outcome was clinical cure. Secondary outcomes were sustained response, hospital mortality, and 28-day all-cause mortality.

Results: A total of 7 cases of severe and complicated CDI were reviewed. Intravenous tigecycline administered as a 100-mg loading dose followed by 50 mg twice daily resulted in clinical cure in 85.7% ($n = 6/7$) of cases. The majority of patients ($n = 4/5$) were treated with the novel triple therapy combination of

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tigecycline, vancomycin, and metronidazole and resulted in clinical cure in 80% ($n = 4/5$) cases. Sustained response at 28 days was 100% among evaluable cases ($n = 5/5$). Hospital mortality did not occur in any patients, and 28-day all-cause mortality was 28.6% ($n = 2/7$). ***Conclusion***: Tigecycline appears to be a reasonable addition to the therapeutic regimen in the treatment of severe or complicated CDI, including cases that are refractory to standard therapy. A prospective clinical trial confirming these observational findings is warranted.

Keywords: *Clostridium difficile*; Combination drug therapy; Tigecycline

INTRODUCTION

Clostridium difficile infection (CDI) is the most common cause of nosocomial diarrhea in adults [1, 2]. The clinical manifestations of CDI range from mild diarrhea to fulminant colitis and severe sepsis, which may be life threatening [2, 3]. Metronidazole and vancomycin have been mainstays in CDI treatment guidelines for several decades, but increasing rates of refractory disease have necessitated the consideration of alternative therapies [1, 4]. According to a recent United States Centers for Disease Control and Prevention (CDC) report, *C. difficile* is one of only three pathogens to be classified as an "urgent" threat to public health due to increasing rates of antimicrobial resistance [5]. Moreover, the emergence of the hypervirulent NAP1/BI/PCR ribotype 027 strain has been associated with severe, recurrent disease that is often non-responsive to standard therapy [6].

Metronidazole and vancomycin are still recommended for the initial management of CDI; however, there are no consensus guidelines for the treatment of CDI that is refractory to these agents [1]. Tigecycline is a broad spectrum glycylcycline antibiotic that is approved for use in the United States for the treatment of complicated skin and soft tissue infections, intra-abdominal infections, and community-acquired pneumonia [7]. Multiple studies have demonstrated the favorable in vitro activity of tigecycline against *C. difficile* isolates [8–10]. Additionally, tigecycline has demonstrated a low minimum inhibitory concentration (MIC) among multidrug-resistant *C. difficile* isolates (mean MIC_{90} 0.25 mg/L; range ≤0.06–2 mg/L) relative to its achieved fecal concentrations at standard doses (mean concentration 6.0 mg/kg; range 3.0–14.1 mg/kg) [8, 10, 11]. Tigecycline is excreted into the gastrointestinal tract with limited disruption of intestinal flora, making it an ideal candidate for the treatment of CDI [9, 12, 13].

Despite the favorable in vitro activity profile of tigecycline against *C. difficile*, there is limited clinical data describing its use in the management of CDI. There are limited case reports of the use of tigecycline for the treatment of CDI described in the literature [14–17]. Therefore, the objective of this study was to detail our experience using tigecycline for the treatment of CDI.

METHODS

Patients

This was a retrospective case series of hospitalized patients at the University of Kansas Hospital, a tertiary care academic medical center. All adult patients who were treated with tigecycline for CDI from January 2007 through July 2013 were eligible for inclusion in this study. Diagnosis of CDI was

confirmed by the presence of diarrhea with ≥3 unformed stools for 2 consecutive days plus detection of toxigenic *C. difficile* in the stool by polymerase chain reaction (PCR). Patients who received tigecycline for less than 48 h were excluded from analysis. Clinical data were collected by retrospective review of the electronic medical record using a standardized data collection form. Variables collected included: patient demographics, comorbidities, laboratory data, microbiological data, vital signs, antimicrobial treatment data, and preceding antimicrobial treatment information. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008. Due to the retrospective nature of this study, a waiver of informed consent was obtained and approved by the University of Kansas Medical Center human subjects committee.

Disease Severity Assessments

All cases were classified according to CDI disease severity upon detection of *C. difficile* toxin and initiation of tigecycline therapy according to current practice guidelines [1]. Severe disease was defined as a white blood cell (WBC) count of >15,000/μL or a rise in serum creatinine 150% of the premorbid level [1]. Severe complicated disease was defined as the presence of: (i) *C. difficile* sepsis; (ii) ileus; or (iii) toxic megacolon [1]. *Clostridium difficile* sepsis was defined as confirmed CDI plus the presence of at least two of the following systemic inflammatory response syndrome (SIRS) criteria: (i) temperature >38 °C or <36 °C; (ii) heart rate >90 beats per minute; (iii) respiratory rate >20 breaths per minute or $PaCO_2$ <32 mmHg; or (iv) WBC >12,000/μL or <4,000/μL or >10% bands [18]. Additionally, an ATLAS score was computed for each patient as described by Miller et al. [19]. ATLAS is a validated scoring system used to predict response to antibiotic treatment against CDI [19]. In general, the higher the ATLAS score, the lower the observed clinical cure rate [19]. To estimate individual comorbidity burden, the Charlson comorbidity index (CCI) was computed for each patient [20].

Outcome Measures

The primary outcome of this study was clinical cure, defined by the resolution of the following signs and symptoms of CDI maintained for the subsequent duration of tigecycline therapy without further addition of an anti-CDI agent: (i) diarrhea (≥3 unformed stools for 2 consecutive days); (ii) fever >37.5 °C; (iii) WBC count >12,000/μL; and (iv) abdominal pain. Clinical failure was defined as persistence of CDI symptoms or the need for additional anti-CDI therapy due to perceived failure of tigecycline therapy. Secondary outcomes included sustained response, hospital mortality, and 28-day all-cause mortality. Sustained response was defined as clinical cure without subsequent recurrence in 28 days following treatment with tigecycline. Data were also collected on side effects attributed to tigecycline use by a treating physician.

RESULTS

A total of 251 hospitalized patients who received tigecycline between January 2007 and July 2013 at our institution were screened for inclusion in this study. Of these patients, nine were treated with tigecycline for CDI. Two

patients were excluded due to <48 h of treatment with tigecycline. In both of these cases, alternative agents for CDI were used according to the decision of a treating physician. A total of seven patients met study criteria and were included in the final analysis.

Case Reports

Case 1 occurred in a 64-year-old female who was admitted for community onset CDI. This patient had multiple risk factors for CDI, including recent antibiotic use (meropenem and vancomycin for pneumonia, and levofloxacin for chronic leukopenia) and immunosuppression. She was initially leukopenic secondary to end-stage liver disease awaiting transplantation with mild CDI (WBC 600/μL, serum creatinine 138% relative to baseline). She was treated with intravenous metronidazole 500 mg three times daily for CDI starting on hospital day 1. On hospital day 2, follow-up PCR for toxigenic *C. difficile* remained positive. Her early hospital course was unremarkable; however, she developed ileus, nausea, and vomiting on hospital day 4 and her CDI had progressed from mild to a severe complicated case. The patient was transferred to the intensive care unit (ICU) and oral vancomycin 125 mg four times daily was added to the regimen. On hospital day 6, the patient's ileus remained unresolved, her serum creatinine level increased to 188% of the premorbid level and she developed severe abdominal pain. Due to the concerns for limited effectiveness of oral vancomycin in the setting of ileus, intravenous tigecycline was added to the regimen on hospital day 6 as a 100-mg loading dose followed by 50-mg doses twice daily. This patient was treated with a combination of intravenous tigecycline, oral vancomycin, and intravenous metronidazole for 10 days. No side effects of tigecycline therapy were noted in the electronic medical record. Follow-up PCR for toxigenic *C. difficile* was negative at the end of treatment. This patient was at high risk of recurrence due to her chronic antibiotic use and pancytopenia. Therefore, she was discharged to a long-term care facility where she completed a 30-day vancomycin taper. She had no subsequent recurrence of CDI on record.

Case 2 occurred in a 46-year-old male who was admitted to the ICU with severe diarrhea and septic shock requiring 13 L fluid resuscitation and vasopressors. The patient presented with severe leukocytosis (WBC 35,400/μL) and renal impairment (serum creatinine increased 166% of the premorbid level). This patient had a number of risk factors for CDI, including admission from a long-term care facility and multiple prior antibiotic use (see Table 1 for full listing). He was treated initially with oral metronidazole 500 mg three times daily. Oral metronidazole was switched to intravenous and oral vancomycin 125 mg four times daily was added on hospital day 2 upon detection of toxigenic *C. difficile*. At this point, the patient was intubated due to decreasing respiratory function and pulmonary edema. He also had other symptoms of severe complicated CDI, included nausea and vomiting, abdominal pain, colonic wall thickening, and ascites. Oral vancomycin was changed to rectal vancomycin 500 mg four times daily on hospital day 3 due to the development of paralytic ileus. This regimen continued through hospital day 7, with fever, ileus, and abdominal pain resolving. On hospital day 8, the patient again developed diarrhea with abdominal pain and persisting leukocytosis (WBC 24,300/μL). Due to these non-resolving symptoms and the severity of the patient's condition, intravenous tigecycline was added on hospital day 8 as a

Table 1 Summary of patient characteristics, risk factors, antimicrobial treatment, and clinical outcomes by case of *Clostridium difficile* infection

Case	Sex (age)	CCI	Disease severity	ATLAS	Preceding antibiotics (within 3 mo)	Setting of CDI onset	Treatment regimen	TIG duration (days)	Clinical cure	Sustained response	VAN taper	Hospital mortality	28-day mortality
1	F (64)	7	Severe complicated	5	LVX, VAN, MEM	Community	TIG + VAN + MTZ	10	Yes	Yes	Yes	No	No
2	M (46)	2	Severe complicated	5	TZP, VAN, LVX, TOB, ERY, FEP, MTZ, LZD, CFZ	LTC facility	TIG + VAN + MTZ	8	Yes	Yes	Yes	No	No
3	M (38)	4	Severe complicated	3	TZP, SAM	Hospital	TIG + VAN	8	Yes	Yes	No	No	No
4	F (80)	13	Severe complicated	6	VAN, LVX, TZP	Community	TIG + VAN + MTZ	6	Yes	Yes	Yes	No	No
5	M (68)	6	Severe complicated	6	TMP-SMX, LVX, LZD, FEP	Hospital	TIG + VAN + MTZ	21	Yes	–[a]	No	No	Yes
6	F (84)	9	Severe complicated	8	TMP-SMX	LTC facility	TIG + VAN + MTZ	3	No	–[b]	No	No	Yes
7	F (73)	8	Severe	5	TZP, LVX, VAN	Hospital	TIG + MTZ	4	Yes	Yes	No	No	No

CCI Charlson comorbidity index, *CDI Clostridium difficile* infection, *CFZ* cefazolin, *ERY* erythromycin, *FEP* cefepime, *LTC* long-term care, *LVX* levofloxacin, *LZD* linezolid, *MEM* meropenem, *MTZ* metronidazole, *SAM* ampicillin–sulbactam, *SCr* serum creatinine, *TIG* tigecycline, *TOB* tobramcycin, *TZP* piperacillin–tazobactam, *TMP–SMX* trimethoprim–sulfamethoxazole, *VAN* vancomycin

[a] Unevaluable due to patient death within 28 days of follow-up after clinical cure

[b] Unevaluable due to clinical failure

100-mg loading dose followed by 50 mg twice daily. Clinical cure was achieved after 8 days of treatment with tigecycline, rectal vancomycin, and intravenous metronidazole. Due to the high risk of recurrence, the patient completed a vancomycin taper upon discharge to a long-term care facility. There was no documented recurrence of CDI on record.

Case 3 occurred in a 38-year-old male who was initially admitted due to acute hypoxic respiratory failure and necrotizing pancreatitis. For this infection, he was treated with piperacillin–tazobactam, which was switched to ampicillin–sulbactam after 10 days by the consulting infectious diseases specialist. On hospital day 25, the patient started developing copious diarrhea (>15 loose stools per day), fever (38.4 °C), and leukocytosis (WBC 13,500/μL) consistent with *C. difficile* sepsis and severe complicated CDI. The patient's serum creatinine levels increased 143% relative to baseline. Upon confirmation of CDI on hospital day 26, intravenous metronidazole 500 mg three times daily was initiated. Tigecycline was added on hospital day 27 for dual coverage of enterococcal pancreatitis and *C. difficile*. Oral vancomycin 250 mg four times daily was also added at this time and metronidazole was discontinued by decision of the treating physician. Fever and leukocytosis subsided and diarrhea improved on 8 days of combination therapy with tigecycline and oral vancomycin. There was no recurrence of CDI on record.

Case 4 occurred in an 80-year-old female who was admitted due to increasing fatigue and copious diarrhea consistent with community onset CDI. Her risk factors for CDI included advanced age and recent antibiotic use (vancomycin, levofloxacin, and piperacillin–tazobactam). This patient's initial severity of illness was mild (WBC 9,100/μL, serum creatinine 116% of the premorbid level) and she was treated with oral metronidazole 500 mg three times daily beginning on hospital day 1. After 3 days of metronidazole treatment, her abdominal pain had improved, but the diarrhea persisted and her WBC began trending upward (16,500/μL). On hospital day 4, the patient developed septic shock secondary to CDI. As her CDI had progressed to a severe complicated case, intravenous tigecycline and vancomycin 250 mg four times daily were added. Tigecycline was given as a 100-mg loading dose followed by 50 mg twice daily. The patient was treated successfully with 6 days of triple therapy with tigecycline, vancomycin, and metronidazole. Due to the high risk of CDI recurrence in this patient, a vancomycin taper was completed. The patient was discharged to home and had no CDI recurrence within 28 days of follow-up.

Case 5 occurred in a 68-year-old male who was admitted to the hospital for febrile neutropenia secondary to pre-B cell acute lymphoblastic leukemia. This patient had multiple risk factors for CDI, including advanced age, hematologic malignancy, multiple prior antibiotic use (trimethoprim–sulfamethoxazole, levofloxacin, linezolid, and cefepime), prior chemotherapy use, and hospitalization. On hospital day 6, the patient developed acute respiratory distress and severe sepsis (4/4 SIRS criteria). On hospital day 7, the patient developed diarrhea and *C. difficile* toxin was detected. This case was classified as severe complicated CDI and treated initially with two days of intravenous metronidazole 500 mg three times daily and oral vancomycin 125 mg four times daily. On hospital day 9, tigecycline was added due to persisting diarrhea (>800 mL liquid stool) and fever (38.2 °C). The patient's fever resolved on hospital day 11, diarrhea resolved on hospital day 14, and clinical cure was achieved. Triple therapy with tigecycline,

vancomycin, and metronidazole was continued for a total of 21 days due to concerns for recurrence in the context of the patient's pancytopenia. At this time, the patient was switched to palliative care due to underlying cancer with a poor overall prognosis. He tolerated treatment with tigecycline well and no side effects were reported. The patient was discharged home to hospice with no further CDI treatment. Sustained response was unevaluable due to death within 28 days of tigecycline completion.

Case 6 occurred in an 84-year-old female admitted from a nursing home with altered mental status, leukocytosis (WBC 19,300/μL), and acute kidney failure (serum creatinine increased 497% relative to baseline). The patient was admitted to the ICU with severe complicated CDI with septic shock. Intravenous metronidazole 500 mg three times daily and oral vancomycin 125 mg four times daily were started on hospital day 1. The patient's diarrhea and leukocytosis persisted (WBC 41,200/μL) and intravenous tigecycline was added on hospital day 7 as a 100-mg loading dose followed by 50 mg twice daily. She was treated with combination tigecycline, vancomycin, and metronidazole for 3 days. The patient's diarrhea resolved and her WBC decreased yet remained elevated (WBC 33,600/μL). Tigecycline was discontinued per the family's decision to switch her to oral antibiotics for discharge to hospice. This patient was classified as clinical failure due to non-resolving leukocytosis and sustained response was unevaluable due to the lack of clinical cure. No side effects associated with tigecycline use were noted in the electronic medical record.

Case 7 occurred in a 73-year-old female who was initially admitted due to pneumonia and acute kidney injury. The patient was treated empirically with vancomycin, levofloxacin, and piperacillin-tazobactam. On hospital day 3, the patient developed copious diarrhea, nausea, leukocytosis (WBC 20,000/μL) and serum creatinine increased 151% of the premorbid level. *Clostridium difficile* toxin was detected and oral metronidazole 500 mg three times daily was initiated. Tigecycline was added on hospital day 5 based on recommendations by the consulting infectious diseases specialist. Tigecycline was initiated instead of vancomycin due to the additional coverage of the patient's concomitant vancomycin-resistant enterococcal urinary tract infection. The patient was successfully treated with 4 days of combination therapy with tigecycline and metronidazole with resolution of all CDI symptoms. No side effects attributed to tigecycline use were noted, and she had no documented CDI recurrence on record.

DISCUSSION

In this case series, we describe the successful use of tigecycline combination therapy for the treatment of severe and severe complicated CDI. A summary of patient characteristics, selected risk factors, antimicrobial treatments, and clinical outcomes is presented in Table 1. The majority of patients [85.7% ($n = 6/7$)] were classified as having severe complicated CDI upon initiation of tigecycline therapy. In all of the included cases, tigecycline was administered intravenously as a 100-mg loading dose, followed by 50 mg twice daily for the subsequent duration of treatment. The length of tigecycline therapy varied considerably (range 3–21 days; median, 8 days; interquartile range 4–11 days). The majority of cases [71.4% ($n = 5/7$)] featured triple therapy with tigecycline, vancomycin, and metronidazole, which has yet to be reported in the peer-

reviewed literature. This combination demonstrated a clinical cure rate of 80% ($n = 4/5$). Overall, tigecycline combination therapy resulted in clinical cure in 85.7% ($n = 6/7$) of cases with no observed hospital mortality. In general, the ATLAS scoring system seemed to correlate well with clinical success, with the only clinical failure observed in the patient with the highest score. In this case, tigecycline was discontinued prior to resolution of symptoms due the patient's poor overall prognosis and decision to switch to palliative care, not perceived treatment failure.

Oral vancomycin at a dose of 125 mg given 4 times per day is preferred for the treatment of severe CDI [1]. Unfortunately, in cases of severe complicated CDI where gut motility is impaired, the efficacy of oral vancomycin is questionable [1]. In these instances, addition of rectal vancomycin or intravenous metronidazole is recommended, although the delivery of rectal vancomycin may be insufficient and adds the risk for colonic perforation [1]. There are currently no other alternatives to these agents in severe and severe complicated CDI mentioned in the current guidelines [1]. Recent evidence indicates fidaxomicin is non-inferior to vancomycin in the treatment of severe CDI [21]. None of the patients included in this study received fidaxomicin; however, only 2 of the 7 cases (case 5 and 6) occurred after the introduction of fidaxomicin to the market. At the time of these cases, data on the effectiveness of fidaxomicin in severe CDI had not been widely disseminated, which may explain why this agent was not used. Of note, fidaxomicin is only available in oral formulation, which prevents its use in cases where intravenous treatment is required.

Based on the data presented in this case series, combination therapy with tigecycline appears to be a reasonable alternative in the treatment of severe and severe complicated CDI, including cases that are unresponsive to standard therapy. While it is difficult to attribute the high clinical cure rate observed in these cases solely to the addition of tigecycline, all of the patients had unresolved symptoms and met criteria for severe or severe complicated CDI upon tigecycline initiation. Several published case reports have also described the successful use of tigecycline for CDI, either as monotherapy or in combination with other agents [15–17, 22]. In contrast, there has been one published failure of tigecycline to treat severe CDI [23]. To our knowledge, there is no in vitro data on tigecycline combinations against *C. difficile* isolates, but tigecycline alone exhibits potent activity [8, 10]. Results from a recent study also suggest that tigecycline can prevent *C. difficile* sporulation [24].

Sustained response was observed in 100% ($n = 5/5$) of evaluable cases. Because the majority of evaluable cases [60% ($n = 3/5$)] featured maintenance treatment with tapered vancomycin, it is difficult to interpret this finding. Nonetheless, the limited disruption of intestinal microflora demonstrated by tigecycline in gut models suggests that increased recurrence with the addition of tigecycline is unlikely [9, 12, 13, 25]. Fidaxomicin also does not significantly alter the intestinal microbiota and as a result decreases the risk of CDI recurrence in comparison to vancomycin [21]. Whether tigecycline monotherapy can also significantly reduce the risk of CDI recurrence compared to standard therapies deserves future study. All of the included cases were in patients with no previous CDI detected. Therefore, we cannot draw any conclusions on the usefulness of tigecycline in treating recurrent CDI.

The present investigation has a number of limitations. First, this was a retrospective of case series and is limited by the lack of a comparison group. In 2 of the patients (cases 3 and 4), vancomycin and tigecycline were initiated on the same day, making any potential added benefit from tigecycline difficult to determine. In another case (case 7), tigecycline was added after only 1 day of treatment with metronidazole. Therefore, it is unclear if the infection would have resolved without the addition of tigecycline. Finally, *C. difficile* strain typing and susceptibility testing is not routinely performed at our institution and this potentially informative data were not available for any of the included cases.

Perhaps the greatest strength of this study was the ability to capture cases of severe and fulminant CDI, which are usually excluded from clinical trials and experimental studies. Observed 28-day mortality was only 28.6% ($n = 2/7$), which we consider to be low relative to the severity of illness observed. Mortality in severe fulminant CDI is as high as 90% overall and 75% post-colectomy [1, 3]. The basis for the substantially lower mortality rate in the present study is unclear. Tigecycline is a derivative of minocycline, which has well-established anti-inflammatory properties and has been shown to inhibit secretion of phospholipase A_2 [26, 27]. Phospholipase A_2 is released by fibroblasts in response to *C. difficile* toxin B and is known to play a role in shock and organ failure in sepsis [28]. Additionally, inhibition of phospholipase A_2 release has been shown to reduce mortality in septic rat models [28]. Although there is currently no data on the ability of tigecycline to inhibit *C. difficile* toxin-mediated colitis and phospholipase secretion, it is a hypothesis that warrants further exploration. None of the patients with fulminant disease were considered clinically stable enough to undergo colectomy. Therefore, tigecycline combination therapy may be an alternative for patients in which surgery is deemed too risky.

CONCLUSION

In summary, we describe the clinical cure of severe and severe complicated CDI in six of seven patients treated with tigecycline combination therapy. Tigecycline combination therapy appears to be an acceptable option for the treatment of CDI, including cases of fulminant disease that is refractory to other treatments. Further research is needed to better characterize the role of tigecycline in the treatment of CDI. In particular, in vitro data on the activity of tigecycline combinations against clinical *C. difficile* isolates (including hypervirulent strains) and replication of our findings in a prospective clinical trial are warranted.

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Conflict of interest. Nicholas S. Britt, Molly E. Steed, Emily M. Potter, and Lisa A. Clough declare that they have no conflict of interest.

Compliance with ethics guidelines. All procedures followed were in accordance with

the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008. Due to the retrospective nature of this study, a waiver of informed consent was obtained and approved by the University of Kansas Medical Center human subjects committee.

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