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Brief Communication



# Does Tigecycline Have a Place in Therapy for Rickettsial Infection of the Central Nervous System?

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## ABSTRACT

This brief report documents the safety and efficacy of high-dose tigecycline as a salvage-therapy in in a case series of five patients with serious central nervous system (CNS) rocky mountain spotted fever (RMSF). These severily ill patients were unable to take any oral drug therapy, parenteral doxycycline was unavailable and absorption of oral doxycycline was a concern in these critically ill patients. As far as we know, we report the successfull use of tigecycline for the treatment of rickettsial meningitis for the first time in Italy. We suggest more studies on tigecycline in severe CNS infections from *Rickettsia* species and multi-drug resistant bacteria, especially the use of tigecycline at higher than standard doses in these life-threathening infectious diseases.

**Keywords:** Tigecycline; *Rickettsia*; Rickettsiosis; *Rickettsia rickettsii*; Rocky mountain spotted fever

## INTRODUCTION

*Rickettsia* is a group of vector-borne organisms that cause acute febrile illnesses that continue to be a major health problem in tropical and temperate parts of the world. Patients present with febrile exanthems and visceral involvement. Rickettsial infection may present as meningitis and should be included in the differential diagnosis in endemic countries. Meningoencephalitis due to Rocky Mountain Spotted Fever (RMSF) may be a life-threatening infection, and high morbidity and mortality make early recognition and empiric treatment critical [1]. Rickettsial encephalitis, is characterised by confusion and obtundation due to increased intracranial pressure and has been associated with a worse prognosis. In general, rickettsial meningitis behaves like a viral meningitis but responds to doxycycline instead of symptomatic therapy with the dosing and length of therapy dependent on the specific causative organism. When affected individuals are experiencing nausea or vomiting, or are seriously ill, medications may be administered by infusion intravenously (iv). However, in Italy, where RMSF is endemic, iv doxycycline is not available. Another tetracycline-like parenteral antibiotic, tigecycline, is available in Italy, but its effectiveness against *R.rickettsii* is unknown. Tigecycline showed in vitro susceptibility to *Coxiella* species, *Rickettsia* species, and multidrug-resistant *Neisseria gonorrhoeae* strains. The aim of this retrospective study was to evaluate the safety and the efficacy of tigecycline in a case series of patients with RMSF of the

**Ethics statement**
The institutional review board (IRB) authorized the collection of data, after the acquisition of informed consent was obtained by all participants in this study. Data were collected between January 1,2016 and December 31, 2020 in medical records.

**Conflict of Interest**
No conflict of interest.

**Author Contributions**
Conceptualization: AM. Data curation: SG. Formal analysis: SG, VV. Investigation: SG, VV, MVM. Methodology: AM, FU. Project administration: AM, FU. Resources: AM, FU. Software: AM, FU. Supervision: AM, FU. Validation: AM, FU. Writing - original draft: AM. Writing - review & editing: AM.

central nervous system (CNS). This brief report documented the safety and efficacy of high dose tigecycline as a salvage-therapy in serious CNS rickettsial infections.

## CASE SERIES

Herein, we report a case series of five (3 males, 2 females; the mean ages were 67.64 ± 9.26 years) patients with RMSF of the CNS (**Table 1**). Data were collected between January 1, 2016 and December 31, 2020 in medical records. Five of 22 patients with RMSF presented with meningitis and/or encephalitis syndromes. Charlson comorbidity index was 4.40 ± 2.05, APACHE II score was 15 ± 4.95. Comorbidities included: diabetes mellitus (3), chronic obstructive pulmonary disease (3), chronic heart failure (2). In the years before symptom onset or diagnosis, no patient received an organ transplant. No patient removed a tick from their body. At the time of diagnosis, no patient was immunocompromised due to medical condition (s) or treatment (s) (such as one of the following: chemotherapy for current illness, human immunodeficiency virus (HIV), anti-rejection drugs post-transplant, corticosteroids >14 days, rheumatoid arthritis with use of immunomodulatory). No patient donated blood in the 30 days prior to symptom onset and no patient was blood donor identified during an investigation into a transfusion-associated infection. The diagnosis of rickettsial meningitis was based on clinical features and on cerebral spinal fluid (CSF) findings. Focal neurologic signs were rare; CSF profiles were similar to those of viral meningitis. Neurological features were typically non-focal, with headache, neck stiffness, photophobia, confusion and reduction in conscious level. One patient had cerebellitis. Other major organ involvement (renal, liver, or lungs) occurred in all five patients. Three patients were immediately intubated and placed on mechanical ventilation; initial laboratory investigations showed severe acidosis. Chest radiography, head computer tomography and magnetic resonance imaging were normal. The finding of abnormalities on electroencephalogram (EEG) during the course of aseptic meningitis was considered to be indicative of parenchymal brain involvement. CSF examination showed a slight pleocytosis, the protein content was raised, and glucose was normal. CSF and blood cultures were negative. Investigation for herpesvirus, enterovirus, arbovirus, *Borrelia* and *Mycobacterium tuberculosis* were negative. Serological blood studies including HIV, venereal disease research laboratory, *Mycoplasma, Brucella* and *Bartonella* excluded acute infection. The diagnosis was confirmed by serology (immunofluorescence assay) that showed a seroconversion, with an eightfold increase of IgG antibodies for *R. rickettsii* in 2 weeks (with titres of 128 and 1,024, respectively). Tigecycline was administered at a high dose (100 mg every 12 hours, after a 200 mg loading dose) for a median treatment duration of 7.5 days, with progressive improvement in all patients. Thirty-day crude mortality, defined as the incidence of deaths from any cause within the approximately 30-day follow-up duration, was chosen as the primary outcome variable for defining antimicrobial effectiveness All patients evolved favourably with remission of symptoms, and they hadn't sequelae. There were no patients requiring tigecycline discontinuation or dose reduction because of adverse events. The defervescence mean time was 3.94 days (± 0.96 SD). Treatment was completed with use of 5 - 10 days of oral doxycycline as patients were able to take the tablets orally. Tigecycline was well tolerated at a higher than standard dose. High-dose tigecycline was not associated with 30-day crude mortality, adverse drug reactions or abnormal laboratory measures.

**Table 1.** Epidemiologic and clinical characteristics of the patients with rocky mountain spotted fever-related meningo-encephalitis treated with tigecycline

| | |
|---|---|
| Number of laboratory-confirmed cases | 5 |
| Sex, Patient age (years), Race | 3 males, 2 females; the mean ages were 67.64 ± 9.26 years, caucasic |
| Life in endemic area, Contact with dog's ticks | 100%, 40% |
| Onset between May and October | 70% |
| Clinical Criteria | |
| Fever higher than 39°C | 100% |
| Eschar "Tache noire" | 40% |
| Maculopapular or purpuric eruption | 100% |
| Headache | 100% |
| Myalgia | 100% |
| Altered sensorium | 100% |
| Signs of meningial irritation | 100% |
| Did the patient experience any severe complications in the clinical course of this illness? | 100% |
| Acute respiratory distress syndrome (ARDS) | No |
| Disseminated intravascular coagulation (DIC) | No |
| Meningitis/encephalitis | 100% |
| Unspecific Biological Criteria | |
| Increased inflammatory indices (C-reactive protein, procalcitonin) | 100% |
| Leukocyte count <4 × $10^9$ cells/L, Neutrophils >70% | 60%, 70% |
| Normochromic normocytic anemia (Hemoglobin levels <110 g/L) | 80% |
| Platelet count <150 × $10^9$ cells/L, Platelet count <100 × $10^9$ cells/L | 100%, 60% |
| Alanine aminotransferase levels >40 U/L | 60% |
| Bacteriological Criteria | |
| Isolation of *Rickettsia rickettsii* from blood and/or cerebrospinal fluid | Not available |
| Detection of *Rickettsia rickettsii* in skin biopsy using immunofluorescence assays | Not available |
| Serological Criteria (Immunofluorescence) | |
| Serum with IgG >1 : 128 and IgM >1 : 64 | 100% |
| 4-fold increase in titer in a double serum sample within 2 weeks | 100% |
| Cerebrospinal fluid examination | Slight pleocytosis, a raised protein content, and a normal glucose value |
| Did the patient die from this illness or complications of this illness? | There was no mortality in our study |

## DISCUSSION

Treatment of rickettsial meningitis may be challenging, as the antimicrobial options are restricted [2]. A tetracycline should be regarded as the drug of choice due to its high efficacy, low toxicity, and oral doxycycline represents the most effective drug, but during severe life-threatening disease, iv therapy may be recommended [2]. Unfortunately, iv formulations of doxycycline are not always available, therefore it would be necessary to determine some new alternative parenteral agents. However, the Centers for Disease Control and Prevention did not definitively recommend alternative therapy should doxycycline be entirely unavailable [3]. In Italy, where RMSF is endemic, iv doxycycline is not available for use. Tigecycline, another tetracycline-like parenteral antibiotic, is available in Italy, but its effectiveness against *R. rickettsii* is unknown. Tigecycline, a tetracycline derivative, belongs to a novel class of antibiotics known as the glycylcyclines, developed in response to the emergence of resistant organisms. They are structurally related to tetracyclines and, like the classic tetracyclines, act through inhibition of protein translation in bacteria. *In vitro* and *in vivo* studies have shown that tigecycline possesses broad-spectrum antibacterial activity. In addition, the intracellular penetration of tigecycline and its high capability to remain accumulated inside may play a critical role in inhibiting the intracellular multiplication of bacteria, thus tigecycline can be used to treat intracellular bacteria [4].

Tigecycline is widely used to treat complicated intra-abdominal infections, skin-structure infections and community-acquired pneumonia with a good safety and tolerability profile. Different studies provide information regarding the use of tigecycline in various clinical


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conditions, however clinical experience in patients with meningitis is very limited. Despite its high efficacy against multi-drug-resistant (MDR) pathogens, tigecycline is currently not recommended in cases of meningeal infections, based on data showing modest penetration to the CSF [5-7]. Tigecycline weakly penetrates CSF and the CSF-to-serum concentration ratio ranged from 0.106 - 0.066 [6] to 0.242 - 0.049 [5] and 0.302 0.185 [7] in previous studies.

Tigecycline usually displays good antibacterial activity against resistant gram-negative and gram-positive bacteria, as do many antimicrobial drugs according to synergy, but due to the lack of penetration to the CNS, their serum concentration in the CSF is only 11% [5-7]. Despite the low concentrations reached by tigecycline in CSF compared to minimum inhibitory concentration, some reports describe a positive evolution of the therapy of CNS infections from multidrug-resistant organisms with tigecycline (**Table 2**) [8]. It could be hypothesized a drug accumulation in polymorphonuclear cells and then be delivered to the site of infection in higher than anticipated concentrations, or the presence of minor sub-inhibitory effects [7].

Although penetration into the CNS is minimal (around 11%), intraventricular therapy (IVT) with tigecycline could be of help in managing and could be considered in patients with post-neurosurgical CNS infections from MDR bacteria (**Table 3**) [9-13]. The use of multi-route [continuous ventricular irrigation (CVI), and intraventricular administration (IVT)] of tigecycline is effective and should be considered in managing lifethreatening MDR intraventricular infections. The use of multi-route (CVI and IVT) tigecycline and IVT colistin for MDR/XDR ventriculitis is effective, and those treatment options should be considered as a valuable therapy in managing these life-threatening intraventricular infections [11, 13].

In a rabbit model of penicillin-resistant pneumococcal meningitis, a single dose of tigecycline showed adequate CSF penetration, and it was found to be effective in reducing colony counts in CSF in combination with vancomycin [14].

Tigecycline resulted effective against *R. rickettsii* in cell culture and in an animal model of RMSF [15], it possesses enhanced in vitro activity against *C. burnetii* [16] and against *Rickettsia japonica* [17], and it sufficiently suppressed the activity of *Orientia tsutsugamushi in vitro* [18].

Patients with scrub typhus–induced acute kidney injury and renal transplantation-derived infection due to *Ehrlichia chaffeensis* effectively treated with tigecycline were retrospectively identified (**Supplementary Table 1**) [19, 20]. To the best of our knowledge, this is the first report of tigecycline therapy for CNS infections caused by *R. rickettsii*. In Italy the formulation of doxycilin for intravenous use is not available, furthermore our patients with CNS rickettsiosis were not being able to take doxycycline by mouth in the acute phase of illness. Although the number of patients presented in our report is limited, we underline the safely and efficay use of tigecycline as a salvage-therapy in patients with CNS rickettsiosis (**Supplementary Table 2**). Physicians should be aware of the possibility of using high dose tigecycline for the early treatment of CNS infection due to RMSF, in patients who cannot take oral doxycyclin, should intravenous doxycycline be entirely unavailable, in cases in which parentheral therapy is needed.


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**Table 2.** Characteristics of patients previously reported with CNS infection treated with intravenous tygecycline

| Characteristic | Patient 1 (Ray L, et al) | Patient 2 (Jaspan HB, et al) | Patient 3 (Emiroglu M, et al) | Patient 4 (Dandache P, et al) | Patient 5 (Guo W, et al) | Patient 6 (Tutuncu EE, et al) | Patient 7 (Tutuncu EE, et al) | Patient 8 (Wadi JA, et al) | Patient 9 (Gordon NC, et al) | Patient 10 (Shrestha GS, et al) | Patient 11 (De Pascale G, et al) | Patient 12 (Kooli I, et al) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age, y/sex | 38y/F | 21-month/F | 5-month/M | 42y/M | 57y/M | 48y/M | 52y/M | 26y/M | 44y/F | 75y/M | 42y/M | 24y/M |
| Country | USA | USA | Turkey | USA | China | Turkey | Turkey | Jordan | UK | Nepal | Italy | Tunisia |
| Underlying disease (s) | Middle cerebral artery strokes | Leukemia, peripheral blood stem cell transplant, muromonab | Ventriculoperitoneal shunt was placed for posthemorrhagic hydrocephalus | Sickle cell disease | Severe traumatic brain injury | T6 vertebral fracture. | L2 - L3 lumbar disk herniation | Multiple injuries to the head, face and extremities | Acoustic neuroma, post-resection CSF leak | Frontal contusion, subdural Hematoma, EVD | Ependymoma 4th ventricle, CSF leak, EVD | Pilocytic astrocytoma |
| Primary infection | Postoperative cerebritis | Meningitis | Ventriculo-peritoneal shunt meningitis | Meningitis | Ventriculitis | Post-neurosurgical meningitis | Post-neurosurgical meningitis | Post-neurosurgical meningitis | Post-neurosurgical meningitis | EVD-associated ventriculitis | Post-neurosurgical meningitis | Post-neurosurgical ventriculitis |
| Organism (s) | MRAB | Vancomycin-resistant Enterococcus fecium (VRE) | MDRKP | MDRKP | MRAB | MRAB | MRAB | MDR *Acinetobacter* sp. | *Acinetobacter* sp. | MRAB | MRAB | MDRAB |
| Tigecycline MIC (mg/L) | 0.75 (CSF) | 0.125 (CSF) | ≤0.5 μg/mL (CSF – E-Test) | 1.0 mg/L (E-test) | ≤1 μg/mL (CSF) | 0.38 μg/ml (CSF) by Etest (AB Biodisk, Solna, Sweden) | 0.38 μg/ml (CSF) by Etest (AB Biodisk) | NA | 2 mg/L | NA | NA | 3.2 mg/L by Etest |
| Tigecycline concentrations (mg/L) | 0.035 – 0.048 (CSF); 0.097 – 0.566 (Serum) | <0.05(CSF) | NA | 0.33 – 0.14 (Serum); 0.12 <0.10 (CSF) | NA | NA | NA | NA | NA | NA | NA | NR |
| Side effects | None | Mildly elevated hepatic transaminases (Drug-drug interactions) | None | None | None | None | None | None | None | Renal dysfunction (CST) | None | None |
| TGC | Tygecicline | Daptomycin (IVT) + Tigecycline | Meropenem (60 days) + Tygecycline | Tygecicline, at twice the daily dose (100 mg every 12 hours) | Polimixin (IVT, IV) + tygecicline iv | IV, 50 mg/q12h | IV, 50 mg/q12 | Tigecycline monotherapy. | Tigecicline | IV, 50 mg/q12h | IV, 50 mg/q12h (check please) | IV, 50 mg/q12h |
| LOT (Days) | 18 days | 14 days | 20 days | ≍ 21 days | NA | ≍ 21 days | ≍ 21 days | NA | 34 days | 14 days | NA | IV, 21 days |
| Co-administered antibiotics | NA | DAP (IVT) | MEM, 60 days | Polimixin (IVT, IV) | NA | Netilmicin IV, (400 mg/q24h),MEM IV, (2g/q8h) | Netilmicin IV, (400 mg/q24h),MEM IV, (2g/q8h) | NA | MEM, 5 days | CST IV, 2 million IU/q8h IVT, 0.2 million IU/q24h | CST IV, 2 million IU/q6h ITH, 150,000 IU/q24h | Colimycin, IV (9 MIU/day) |
| Days to CSF sterilization | 12 | 2 | 6 | 3 | 5 | 21 | 21 | 12 | NA | 7 | 20 | 23 |
| Outcome | Failed to achieve clinical response | Improved | Improved | Improved | Improved | Improved | Improved | Improved | Improved | Improved | Improved | Improved |

CNS, central nervous system; F, female; M, male; CSF, cerebrospinal fluid; EVD, external ventricular drainage; MRAB, multidrug-resistant *Acinetobacter baumannii*; MDRKP, multi-drug resistant *Klebsiella pneumoniae*; MDR, multi drug resistant; MIC:mean inhibitory concentration; NA, not available; CST, colistin; TGC, tygecycline; IVT, intraventricular therapy; IV, intravenous; LOT, length of treatment; DAP, daptomycin; MEM, meropenem.



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**Table 3.** Characteristics of adults previously reported with CNS infection treated with intraventricular tygecycline

| Characteristic | Patient 1 (Lauretti L, et al) | Patient 2 (Fang JQ, et al) | Patient 3 (Long W, et al) | Patient 54 (Tsolaki V, et al) | Patient 5 (Tsolaki V, et al) | Patient 6 (Tsolaki V, et al) | Patient 7 (Wu Y, et al) |
|---|---|---|---|---|---|---|---|
| Age, y/sex | 22y/M | 50y/M | 55y/M | 55y/F | 50y/M | 48y/M | 67y/M |
| Country | Italy | China | India | Greece | Greece | Greece | China |
| Underlying disease (s) | A giant pituitary adenoma, post-resection CSF leak | Craniocerebral injury | Intracerebellar hemorrhage, CSF leak, hydrocephalus, EVD | Aneurysmal subarachnoid hemorrhage | Intraventricular mass resection, cerebral edema, EVD | Cerebellum spontaneous hemorrage, EVD | Cerebral haemorrhage, EVD |
| Primary infection | Post-neurosurgical meningitis | Post-neurosurgical meningitis | Post-neurosurgical ventriculitis | Post-neurosurgical VM | Post-neurosurgical VM | Post-neurosurgical VM | Post-neurosurgical meningitis |
| Organism (s) | | XDRAB | MDRAB | MDRAB | MDRAB | MDRKP | MDRKP |
| Tigecycline MIC (mg/L) | 2 μg/ml | 2 | 16 μg/mL | 2 μg/ml | 1 μg/ml | NR | |
| Tigecycline concentrations (mg/L) | NR | NR | NR | NR | NR | NR | The trough concentrations of tigecycline in CSF for the three different dosages of tigecycline IV - ICV combined administration were 0.313, 1.290 and 2.886 mg/L for 40 mg IV/10 mg ICV, 45 mg IV/5 mg ICV and 50 mg, IV/1 mg ICV tigecycline, respectively |
| Side effects | Chemical ventriculitis, Myelitis (CST) | None | None | None | None | None | None |
| TGC, IV/CVI/IVT | IV, 100 mg/q12h IVT, 2 mg/(q24h - q12h) | IV, 100 mg/q12h IVT, (3 - 4) mg/q12h | IV, 100 mg/q12h, CVI, 10 mg/q12h, IVT, 2 mg/q12h | IV, 100 mg q12, IVT, 4 mg/dl | IV, NR<br>IVT | IV, NR<br>IVT | IV, 45 mg q12h, /40mg q12h<br>IVT, 1 mg q12h, 5mg q12h, 10 mg q12h |
| LOT (Days) | IVT, 45 days; 1 month from the restart of the IVT | IV, 14 days; ITV, 14 days | IV, 14 days, CVI, 14 days, IVT, 3 days | IV TGC, 14 days<br>IVT TGC, 15 days<br>IVT CST, 22 days | IV TGC, 15 days<br>IVT TGC, 15 days<br>IVT CST, 30 days | IV TGC, 9 days<br>IVT TGC, 9 days<br>IVT CST, 11 days | NR |
| Co-administered antibiotics | CST IVT, 120,000/q12h<br>Meropenem IV, 2 g/q8h<br>Vancomycin IV, 1 g/q12h | Cefoperazone-sulbactam IV, 3 g/q12h | Cefoperazone-sulbactam IV, (2 g/q8h) | IVT CST 250 x 103 IU qd | CST 250 x 103 IU qd | CST 125 x 103 IU qd | TMP/SMX 480 mg q12h per os |
| Outcome | Improved | Improved | Improved | Improved | Improved | Improved | Improved |
| Days to CSF sterilization | 75 | 14 | 12 | 4 days of IVT COL - TGC | 5 days of IVT | 3 days of IVT | 42nd day with IVT TGC 10 mg (gradually escalating dose) |

CNS, central nervous system; M, male; F, female; CSF, cerebrospinal fluid; EVD, external ventricular device; VM, ventriculitis and meningitis; XDRAB, extensive drug resistant *Acinetobacter baumannii*; MDRAB, multidrug-resistant *Acinetobacter baumannii*; MDRKP, multi-drug resistant *Klebsiella pneumoniae*; NR, not reported; IV, intravenous; IVT, intra-ventricular therapy; CVI, continuous ventricular irrigation; LOT, length of treatment; TGC, tygecicline; TMP/SMX, trimethoprim-sulfamethoxazole; COL, colimycin.

## SUPPLEMENTARY MATERIALS

### Supplementary Table 1

Characteristics of patients previously reported with intracellular infections treated with tygecycline

**Click here to view**

### Supplementary Table 2

Clinical data and outcome of 5 patients with CNS rickettsiosis treated with tigecycline

**Click here to view**


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