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BRIEF REPORT

Tigecycline as a Second-Line Agent for Legionnaires' Disease in Severely Ill Patients

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Treatment of Legionnaires' disease in severely ill or immunosuppressed patients presents a clinical challenge. Tigecycline (TG) achieves high concentrations intracellularly and has been shown to be effective against *L. pneumophila* in animal and cell models. We report our experience using TG as second-line therapy. Clinical response was seen in most patients after switching to TG alone or as a combination therapy.

Keywords. Legionnaires' disease; tigecycline.

Mortality due to Legionnaires' disease, the severe form of community-acquired or nosocomial pneumonia caused by *Legionella pneumophila*, decreased from 34% in 1980 to 3.1% in 2010. Yet, 20–25% of patients hospitalized with Legionnaire's require invasive mechanical ventilation, and hospital mortality among these patients remains at 35% [1–3]. The intracellular residence of the pathogen impacts antibiotic efficacy [4]. Currently, azithromycin or levofloxacin are considered the mainstay for Legionnaire's treatment. In the subgroup of patients with high–severity of illness scores and/or a high degree of immunosuppression, treatment of Legionnaire's still presents a clinical challenge. In these patients who are unresponsive to standard monotherapy, the addition of potentially active antibiotics is often considered [5].

Tigecycline, a minocycline derivative, achieves high concentrations intracellularly and has been shown to be active in vitro and in animal models against *L. pneumophila* [6, 7]. It has also been described as an alternative therapy for other clinically difficult pneumonias such as *Stenotrophomonas maltophilia* pneumonia [8]. We report our experience using tigecycline as second-line therapy for severely ill patients with Legionnaire's disease.

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CASE PRESENTATION

We performed a single-center, retrospective chart review at the New York University Langone Medical Center, a 726-bed tertiary care academic teaching hospital. The study was approved by the New York University School of Medicine Institutional Review Board. Hospitalized patients admitted between January 2008 and February 2016 who received tigecycline during their hospital stay were screened for study inclusion by review of electronic health records. Inclusion criteria were (1) age 18 years or older, (2) positive *Legionella* urinary antigen (classified as proven Legionnaire's), and (3) treatment with tigecycline for Legionnaire's disease. Patients were excluded if they received treatment for Legionnaire's for <24 hours, or if they received <24 hours of tigecycline. Data collected included baseline demographics, past medical history, microbiologic and radiographic data, hospital and intensive care unit length of stay, duration of treatment, concomitant antibiotics, days of mechanical ventilation, white blood cell count, and vital sign trend. The primary outcome measure was clinical improvement, defined as defervescence, decrease in leukocytosis, and decreased FiO_2 requirement. Additional outcomes measured include case fatality (early or late), disposition, time to change in white blood cell count, time to defervescence, and final outcome. Early case fatality was defined as fatality secondary to Legionnaire's, with progression of disease; late case fatality was defined as fatality during the same admission, but after improvement of Legionnaire's symptoms or transition to comfort care or hospice unrelated to the Legionnaire's disease process.

A total of 8 of 10 fulfilled inclusion criteria. Two cases were excluded due to receipt of tigecycline for <24 hours. Baseline characteristics, disease severity, treatment course, and outcomes are outlined in Table 1. Patients were evenly distributed by gender, with a median age of 81 years (range, 53–90 years), and all 8 had high burden of disease at baseline, with ≥2 comorbidities. Two of 8 were immunosuppressed secondary to medication effect on admission—decitabine 37 mg 2 weeks prior to admission for treatment of acute myeloid leukemia in 1 patient and infusion chemotherapy for breast cancer administered 3 days prior to admission in another. Included cases were severely ill, with either class IV or class V Pneumonia Severity Index scores.

All patients were initially treated with the standard of care (azithromycin or levofloxacin) for a median of 3 days (range, 1–8 days). No patients were found who did not receive standard therapy prior to tigecycline being added. The decision to add or switch to tigecycline as a second-line agent was made due to worsening clinical status, particularly hemodynamic and respiratory parameters in all 8 patients. At the time of addition or switch to tigecycline, median Sequential Organ Failure Assessment score was 6 (range, 1–9) and 5 of 8 (62.5%) patients

Table 1. Patient Characteristics, Disease Severity, and Outcomes

Case	Age (Sex)	Comorbidities	Immunosuppressed (Y/N)	PSI Score on Admission	Level of Care (Mechanical Ventilation– Y/N)	Pressors Required (Y/N)	Initial Regimen prior to TG Initiation (Duration in Days)	Reason for Switch to TG	SOFA at TG Switch	Treatment Regimen After TG Initiated (Total Duration in Days)	Time to Defervescence after TG Initiation, Y/N, (Days)	Decrease in WBC After TG Initiation, Y/N, (Days)	Early Case Fatality (Y/N)	Late Case Fatality (Y/N)	Clinical Response (Y/N)	Clinical Improvement After TG Initiation (Y/N)	Final Outcome
1	88 (M)	Infiltrative CHF, arrhythmia, hypothyroidism, malignancy	N	223	ICU (Y)	Y	AZ (2)	Worsening SS and RS	6	TG (4), LVX (8)	n/a	N (n/a)	Y	n/a	N	N	Expired
2	84 (M)	BPH, kidney stones	N	154	ICU (N)	N	AZ (1), LVX (1)	Worsening SS, RS leukocytosis, persistent fevers	6	TG (10), LVX (19)	Y (2)	Y (4)	N	N	Y	Y	Discharged to subacute rehab
3	64 (M)	HTN, HIV	N	149	ICU (Y)	Y	AZ (5), LVX (7)	Worsening SS, RR, persistent fevers	9	TG (8), LVX (7)	Y (5)	Y (3)	Y	n/a	N	N	Expired
4	53 (F)	Asthma, Kikuchi syndrome, Sjogren's syndrome	N	123	Gen Med (N)	N	AZ (2)	Worsening RS, persistent fevers	1	TG (6), LVX (20)	Y (1)	Y (1)	N	N	Y	Y	Discharged home
5	85 (M)	Arrhythmia, valve disease, HTN	N	146	ICU (N)	N	AZ (3), LVX (2)	Worsening RS	5	TG (17), LVX (21)	n/a	Y (15)	N	N	Y	Y	Discharged to rehab
6	61 (F)	Breast cancer in remission, depression, anxiety	N	141	ICU (Y)	Y	AZ (5), LVX (3)	Worsening RS, multi-organ failure, QTc prolongation	9	TG (5), LVX (5)	n/a	Y (2)	Y	n/a	N	N	Expired
7	90 (F)	CHF, arrhythmia, HTN, HLD	N	110	Gen Med (N)	N	AZ (3)	Multi-organ failure, worsening RS, and leukocytosis	4	TG (5), AZ (6)	n/a	N (n/a)	N	Y	Y	Y	Improvement in pneumonia, eventual discharge to hospice
8	77 (F)	HTN, malignancy, HLD	Y	137	Gen Med (N)	N	AZ (8)	SS, worsening RS	4	TG (14)	n/a	N (n/a)	N	N	Y	Y	Discharged to rehab

Abbreviations: AZ, azithromycin; BPH, benign prostatic hyperplasia; CHF, congestive heart failure; F, female; Gen Med, general medicine; HIV, human immunodeficiency virus; HLD, hyperlipidemia; HTN, hypertension; ICU, intensive care unit; LVX, levofloxacin; M, male; MS, mental status; N, no; PSI, Pneumonia Severity Index; RS, respiratory status (increased FiO_2 requirement, respiratory distress); SOFA, Sequential Organ Failure Assessment; SS, septic shock; TG, tigecycline; WBC, white blood cell; Y, yes;

required admission to the intensive care unit, with 3 of 8 (37.5%) requiring mechanical ventilation.

Three patients were febrile at the time of initiation of tigecycline, all of which responded with defervescence, with a median time of 2 days (range, 1–5 days). A decrease in leukocytosis was seen in 5 of 8 (62.5%) of patients; of those with no change in leukocytosis, 1 was neutropenic throughout the course of illness. Tigecycline was used for a median of 7 days (range, 4–17 days), in combination with levofloxacin in 6 patients and in combination with azithromycin in 1 patient; the remaining patient was treated with tigecycline monotherapy. Overall, following initiation of tigecycline, 5 of 8 (62.5%) improved clinically and 3 of 8 (37.5%) experienced no clinical improvement. Of the 5 patients requiring an intensive care unit level of care, the median duration of intensive care stay was 11 days (range, 1–13 days), and of the 3 patients requiring mechanical ventilation, the median duration of mechanical ventilation was 10 days (range, 1–13 days). The median duration of hospitalization was 13 days (range, 8–27 days). Three patients (37.5%) experienced early case fatality, with progressively worsening respiratory status or sepsis and ultimate demise—these are the same patients described as having no clinical improvement after initiation of tigecycline. There was 1 additional patient (12.5%) who was discharged to hospice at the end of hospitalization secondary to end-stage heart failure.

DISCUSSION

Our findings suggest that tigecycline is a potential second-line agent for treatment of patients with severe Legionnaire's responding poorly to conventional firstline agents such as levofloxacin and azithromycin. In the described population, with multiple comorbidities and severe illness on admission, improvement was seen in most patients. In those who did not have clinical improvement, 1 defervesced and 2 had a decrease in leukocytosis despite worsening of clinical status.

Tigecycline is among several agents studied for treatment of Legionnaire's disease, including macrolides, fluoroquinolones, rifampin, and tetracycline. Of the tetracyclines, doxycycline has been found to have inferior activity to rifampin and erythromycin within monocytes in 1 study, and less activity than perfloxacin and erythromycin in another guinea pig model study [9, 10]. Intracellular concentrations of tigecycline are significantly greater than doxycycline and, when studied in guinea pig models, have been shown to be active against *L. pneumophila* when actively growing [6]. In human monocyte-derived macrophages, tigecycline has poor activity against *L. pneumophila* in extracellular time-kill studies compared with levofloxacin and erythromycin, but in intracellular time-kill experiments, it has strong activity superior to levofloxacin and erythromycin. This is attributed to the rapid concentration of tigecycline in human cells and extracellular inactivation of tigecycline in the medium in which *L. pneumophila* is grown [7].

Tigecycline's use in human subjects for treatment of Legionnaire's is limited to 2 case reports [9, 11]. In the first, a liver transplant patient on immunosuppressants and steroids developed disseminated Legionnaires' with isolation of the organism from a chronic leg ulcer and from bronchoalveolar lavage with corresponding lung infiltrates. The patient was initially treated with moxifloxacin, but had worsening of clinical status until tigecycline was added, 3 weeks following moxifloxacin monotherapy [9]. In the second, a neutropenic patient presented with severe Legionnaires' requiring mechanical ventilation with additional isolation of *Acinetobacter baumanii*, refractory to 2 weeks of levofloxacin monotherapy. The patient fully recovered with the addition of tigecycline to his regimen [11].

Our study has several limitations, including its retrospective design, with a lack of blinding of investigators, small sample size, and lack of standardized protocol. A major limitation is that 7 of 8 patients studied were treated with combination therapy, and only 1 was treated with tigecycline alone. It is therefore difficult to know whether improvement was due to the addition of tigecycline or a delayed response to the original regimen. Adding the results of our small case series, we believe that tigecycline can be considered as a second-line treatment or added as combination therapy in cases of refractory disease. Further investigation in prospective studies is warranted to confirm these findings.

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Potential conflicts of interest. All authors: No reported Conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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