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MINOCYCLINE IV IS EFFECTIVE AND WELL-TOLERATED IN THE TREATMENT OF PNEUMONIA AND BACTEREMIA DUE TO *STENOTROPHOMONAS MALTOPHILIA*

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ABSTRACT

- **Background:** Infections caused by multi-drug resistant Gram-negative bacteria (MDR-GNB) are associated with significant morbidity and mortality. Selection of microbiologically active empiric therapy for MDR-GNB, such as *Stenotrophomonas maltophilia* (Sm), can be particularly challenging. Prevalence of Sm is increasing; it is the fifth most common GN pathogen (5.1%) responsible for bacterial pneumonia in hospitalized ICU patients in US Hospitals, 2015-2017 (SENTRY).
- **Methods:** A retrospective multi-center observational study in 71 adult patients who received minocycline IV (MINIV) ≥ 48 hrs at 6 hospitals for treatment of GNB infections was conducted. We sought to analyze the cohort of patients infected with Sm, the major pathogen recovered.
- **Results:** Thirty patients received MINIV for pneumonia (n=25) or BSI (n=5) due to Sm. Significant co-morbidities for infection were observed in 73% of patients, and included structural lung disease (30%), cancer (27%) and neutropenia (13%). Mechanical ventilation was common (63%; median, 28d, range, 4-86d). Twelve (40%) patients had been hospitalized within the prior 6 months. All isolates were susceptible to minocycline at baseline: MIC_{50}, MIC_{90} and MIC range were 0.5 mg/L, 1.0 mg/L and 0.25-2.0 mg/L, respectively (FDA, CLSI susceptible MIC ≤ 4.0 mg/L). Mean time between hospital admission and first dose of MINIV was 17.8d; patients received MINIV primarily in an ICU setting (73%). All patients received 100 mg BID except one (200 mg BID); mean and median duration of MINIV was 8.0d and 6.5d, respectively. Patients with pneumonia (n=25) or bacteremia (n=5) due to Sm exhibited favorable clinical and microbiologic responses of 79% and 72%, respectively. Four patients were switched to other antibiotics due to clinical failure of MINIV. There were 9 (30%) deaths in the cohort. No serious treatment-emergent adverse events were reported. Serum magnesium levels during MINIV were within normal limits including patients with severe renal impairment or receiving IHD/CRRT.
- **Conclusions:** MINIV demonstrated high in vitro susceptibility against *S. maltophilia* and good clinical and microbiologic outcomes in an immunocompromised and seriously ill patient population. MINIV merits consideration as a treatment option for infections due to susceptible strains of Sm particularly as resistance to TMP/SMX increases. MINIV is currently approved in the US for use in *Acinetobacter* spp infections.

INTRODUCTION

- **Burden of disease.** Infection caused by multi-drug resistant Gram-negative bacilli (MDR-GNB) is associated with significant morbidity and mortality among immunocompromised patients, such as those with cancer, advanced age, structural lung disease, and immunosuppressive drug therapy.[1-3]
- **Early active therapy.** Selection of microbiologically active empiric therapy for highly drug resistant pathogens, such as *Stenotrophomonas maltophilia,* which not only expresses acquired resistance phenotypes but a range of intrinsic drug resistance, can be particularly challenging.[4,5] One key predictor of clinical outcome from serious infections due to MDR-GNB is time to microbiologically active antimicrobial therapy.[1-3]
- **Antibiograms.** Reliance on cumulative institution-level antibiogram data provides a resource for designing rational antibiotic therapies based on local resistance patterns. These reports may not include less common (i.e., < 30 isolates) bacterial species, such as *S. maltophilia,* even when associated with high mortality or morbidity.[6]

INTRODUCTION (CONT'D)

- **Minocycline.** Minocin® (minocycline for injection) is an intravenous (IV) formulation of minocycline that has been approved in the United States since 1972 for the treatment of infections due to susceptible strains of several important Gram-positive and Gram-negative pathogens, including *Acinetobacter* species and methicillin-resistant *Staphylococcus aureus* (MRSA). Minocycline was reformulated with a lower volume of infusion and was approved in the US on 17 April 2015.[7]
- **Existing studies.** No randomized controlled studies of minocycline IV in patients with Gram-negative infection exist; however, clinical efficacy data are available from published non-comparative case series that indicated successful treatment of infections caused by *S. maltophilia*.[8,9]

METHODS

- This was a retrospective chart review of 71 consecutive patients who received minocycline IV between May 1, 2015 and February 6, 2018 at 6 hospitals in the US. Patients who received at least 48 hours of minocycline intravenous (Minocin® [minocycline for injection]), regardless of transition to oral minocycline, and for treatment of presumed or culture-confirmed gram-negative infection, were eligible for inclusion. Each site identified at least 10 consecutive patients. Results from a cohort of patients (n=30) with serious infections due to *S. maltophilia*, specifically pneumonia and bacteremia, are presented.
- Additional criteria for inclusion included the following: age ≥ 18 years; first course of minocycline IV administered during admission; at least 60 days since the last dose of minocycline IV; and, not pregnant or nursing at the time of inclusion.
- Infection was defined according to specific standard definitions. Patients with a positive culture without active inflammation or systemic signs and symptoms at the culture site were determined to be colonization and were not included.
- The current formulation contains magnesium; accumulation of this element was deemed important to measure. Magnesium accumulation was defined as a shift from concentrations below lower limits of normal (< LLN) or within normal limits (WNL) at baseline to concentrations at end-of-therapy exceeding upper limits of normal (> ULN).
- The protocol provided a 30-day window to capture clinical and microbiologic outcomes following the last dose of minocycline IV. Given the complicated courses endured by many of these patients, it was not possible to assign in-hospital death as infection-related. Therefore, death was not used as criteria for clinical failure; however, causes of death were collected from Investigators.
- Safety definitions were established by the sponsor's Global Pharmacovigilance Committee according to standard Regulatory practice. Safety data were collected up to 30 days following the last dose of minocycline IV. All SAEs, adverse events of special interest (AESIs), and pregnancies were reported by the investigator to the Sponsor within 24 hours of the identification during chart review.

RESULTS

TABLE 1. Baseline Characteristics of Patients with Pneumonia or Bacteremia Due to *S. maltophilia* (n=30)

Parameter	Value
Age (yr)	
Mean (SD)	58.2 (13.9)
Range	27-77
≥ 65 yr (%)	40.0
Male (%)	63
BMI (kg/m^2)	
Mean (SD)	29.3 (7.9)
Median	27.5
Range	18-51
Hospital LOS (d)	
Mean (SD)	38.1 (27.3)
Median	37
ICU LOS (d) (73.3%)	
Mean (SD)	28.8 (18.3)
Median	24

Characteristic	Value
Major co-morbidities (%)	73.3
Diabetes	33.3
Structural lung disease	30.0
Active cancer	26.8
Immunosuppresion	20.0
CRI or ESRD/HD	20.0
Neutropenia	13.3
Transplantation	10.0
Risk for HAI (%)	
Recent hospitalization	40.0
Infection-related hospitalization	20.0
Mechanical ventilation (d) (63.3%)	
Mean (SD)	34.5 (24.0)
Median	28

Structural lung disease includes emphysema, COPD, and other pulmonary function modifying conditions. Transplantation is HSCT or SOT. Risk for HAI includes history within 6 months prior to inclusion in study. Active cancer defined as < 6 months from last dose of chemotherapy. Immunosuppression includes: chemotherapy within the past 6 months, biological immune modulators, anti-rejection drugs, and chronic doses of prednisone or equivalent > 20 mg/day. Neutropenia is defined as absolute neutrophil count (ANC) < 1000 neutrophils/cu mm at any time during hospitalization.

- **TABLE 1** demonstrates a patient population that was generally seriously ill and at high risk of hospital-associated infections, primarily via the respiratory tract.

TABLE 2. Antimicrobial Susceptibility of Baseline and Post-Therapy Isolates to Minocycline

Baseline Isolates	
Number of isolates tested	20 (67%)
AST device	
Disk diffusion	1
MIC gradient strip (manual) or Phoenix (automated)	19
Susceptible at baseline (%)	100%
Baseline MIC results (mg/L) (n=19)	
MIC_{50}	0.5
MIC_{90}	1.0
MIC range	0.25 – 2.0
Post-therapy MIC results (mg/L)	
Isolates with increased MIC	3 (16%)
Post-therapy susceptible MICs	2
Isolates with > 2-dilution increase*	1

CLSI and FDA breakpoints for minocycline against *S. maltophilia*: S ≤ 4, I = 8, R ≥ 16 mg/L.
*One patient experienced an isolate of *S. maltophilia* with a baseline MIC of 0.75 mg/L. The patient was treated for 12 days with minocycline IV 100 mg twice daily as monotherapy. End-of-therapy MIC was 8.0 mg/L (intermediate). The patient was a clinical failure with microbiological persistence.

- **TABLE 2** shows 100% susceptibility against minocycline for 20 isolates of *S. maltophilia*. This is consistent with data from other sources.[4] A single patient showed emergence of resistance during therapy, and different infecting strains of *S. maltophilia* could not be ruled out.

RESULTS (CONT'D)

TABLE 3. Minocycline Treatment Characteristics in 30 Patients With Pneumonia or Bacteremia Due to *S. maltophilia*

Minocycline IV Therapy	Value
Mean time (d) between hospital admission and first dose of minocycline IV	17.8
Patient receiving minocycline IV in an ICU setting	73%
Minocycline IV dosing (load and maintenance)	
200 mg BID	1
200 mg x 1, then 100 mg BID	9
100 mg BID (no loading dose)	20
Duration of therapy (d)	
Mean	8.0
Median	6.5
Range	2 – 21

- Twenty-one (70%) patients received non-minocycline agents concomitant with minocycline IV. Most of these agents were used to treat other infections, such as MRSA and *P. aeruginosa*. Ten (33%) patients received the other agent for presumed synergy.
- Fourteen patients received no additional antibiotics following the course of minocycline IV; 2 patients were de-escalated to oral minocycline.

TABLE 4. Clinical and Microbiologic Outcomes in the Evaluable Population (n=29)

Outcome of Therapy	% (n/N)
Clinical success	79.3 (23/29)
BSI	100 (5/5)
Pneumonia	75 (18/24)
Microbiologic response	72.4 (21/29)
Clinical failures switched to alternative agents	4 of 6
In-hospital mortality	30.0 (9/30)

One patient with pneumonia was not clinically or microbiologically evaluable.
Clinical response includes cure or improvement. Microbiologic response includes documented eradication at end-of-therapy or presumed eradication based on clinical outcome without post-therapy cultures.

- **Safety.** The evaluable safety cohort consisted of 71 patients who received at least 48 hours of minocycline IV. There were no serious adverse reactions reported. Only one patient experienced a MINIV-related adverse event. The patient had elevated post-baseline LFT measurements (ALT or AST ≥ 3 x ULN and total bilirubin ≥ 2 x ULN) with normal values at baseline. The patient completed minocycline therapy, deemed a clinical cure, and had normalization of laboratory indices. The patient was not amongst those infected with *S. maltophilia*. There were no clinical symptoms of hypermagnesemia in any patient; magnesium concentrations showed relatively small increases from baseline in 4 patients (0.1 mEq/L to 0.4 mEq/L) and did not exceed 2.3 mEq/L.
- Readmission in the *Stenotrophomonas* infected cohort was observed in 4 (19%) patients alive at 30 d following last dose of minocycline IV, but no episode was associated with infection relapse.

CONCLUSION

- **Burden of disease.** Infections due to *S. maltophilia* is associated with high mortality[10] and have increased in prevalence in the last decade. Sader et al recently showed a frequency of 5.1% for *S. maltophilia* as a cause of gram-negative pneumonia in hospitalized ICU patients in the U.S.[11]
- **Susceptibility testing.** Flamm et al documented minocycline susceptibility of *S. maltophilia* (U.S., n=202) of 99.5% compared to trimethoprim-sulfamethoxazole (TMP/SMX) 92.4%.[4] Resistance to TMP/SMX has created challenges at some institutions. In this cohort of isolates, 100% of baseline isolates were susceptible to minocycline. However, only 67% of isolates were tested for susceptibility to minocycline despite availability in several AST platforms such as disk diffusion, gradient MIC strips, automated panels, and MIC plates. CLSI recommends routine testing for minocycline where in vitro resistance to TMP-SMX is suspected or documented.[5]
- **Challenges of treating *S. maltophilia* infections.** *S. maltophilia was* the most commonly treated pathogen in this study (25 pneumonias, 5 bacteremias). Minocycline therapy was associated with clinical and microbiologic response rates of 79% and 72%, respectively. The clinical outcome data are encouraging, particularly as the patients enrolled in this study were critically ill, with prolonged hospital and ICU stays, multiple comorbid conditions, and mechanical ventilation. Encouraging results of minocycline IV for *S. maltophilia* have been seen in other clinical studies.[8,9] Finally, there are limitations to use of TMP/SMX for addressing infections due to *S. maltophilia*, including significant adverse events such as worsening renal function, hyperkalemia, and myelosuppression.[12]
- **Dosing and tolerability of minocycline IV.** The dose administered in most patients in this study (200 mg QD) was half the maximum daily dose listed in the minocycline IV prescribing information.[7] It may be prudent to base dosing decisions on both symptom resolution and in vitro minocycline MIC measurement. Minocycline was well-tolerated in *S. maltophilia*-infected patients as no drug-related adverse events were reported in that cohort. Serum magnesium did not show evidence of clinically significant accumulation despite renal dysfunction.
- **Limitations.** This study had several limitations. These include the retrospective, noncomparative, unblinded, and nonrandomized nature of the data from a limited number of sites. Whether the results of this study can be generalized to other acute care settings will require a larger multi-center prospective study with a focus on *S. maltophilia.*

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