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BRIEF REPORT (FAST TRACK - FIDSA MEMBERS ONLY)

Clinical and Safety Evaluation of Continuously Infused Ceftolozane/Tazobactam in the Outpatient Setting

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Background. Ceftolozane/tazobactam (C/T) is a novel cephalosporin/β-lactamase inhibitor currently dosed by 8-hour intervals to treat complicated and multidrug-resistant *Pseudomonas aeruginosa* infections in inpatients. This dosing strategy limits the ability to transition patients to outpatient antimicrobial therapy. There are limited data in the literature to support continuous infusion (CI) dosing.

Methods. This study is a retrospective chart review of patients who received CI C/T at an infusion center part of a community health system. Patients were evaluated from August 2016 through January 2018. Patients were included in the study if they were ≥18 years old and received their entire course of C/T as a CI in the outpatient setting. Patients were excluded if they received any part of their therapy as an inpatient.

Results. The primary outcome evaluated was symptom resolution. Secondary outcomes evaluated were microbiologic resolution as well as patient satisfaction. Seven patients received either 4.5 or 9 grams of continuous infusion C/T every 24 hours in the outpatient setting over the study period. For the primary outcome, 6 of 7 patients had symptom resolution. For the secondary outcomes, 3 of 3 patients had microbiologic resolution, and patient satisfaction scores were overall positive among respondents.

Conclusions. Ceftolozane/tazobactam delivered as a continuous infusion may be a safe, effective, and convenient way to treat infections caused by *P aeruginosa*. This novel treatment regimen can be an option for patients to avoid hospital admission or discharge to complete therapy as an outpatient.

Keywords. ceftolozane/tazobactam; OPAT.

Ceftolozane/tazobactam (C/T), a combination cephalosporin/β-lactamase inhibitor, is indicated for complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI), and now hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP). Current labeled dosing recommendations are 1.5 grams intravenously (IV) every 24 hours for cUTI and cIAI, and 3 grams IV every 24 hours for HABP/VABP. The spectrum of activity extends to most Gram-negative bacteria, including multidrug-resistant (MDR) *Pseudomonas aeruginosa* (defined as resistance to 3 or more classes of antimicrobials tested) [1, 2]. Current dosing recommends 8-hour intervals to meet the appropriate time of free drug concentration above the minimum inhibitory concentration, making outpatient delivery logistically difficult [1]. Other β-lactam/β-lactamase inhibitors, most notably piperacillin/tazobactam (P/T), have proven to be safe and effective when they are administered as a continuous infusion (CI) [3]. Ceftolozane/tazobactam is stable for up to 24 hours at room temperature, allowing for potential administration as a CI [1]. There is limited experience and research data with the use of C/T as a CI. We now report a case series from a retrospective chart review of patients who received their entire course of CI C/T as an outpatient for various infections.

METHODS

We generated a computerized list of all patients who received CI C/T from the first patient receipt in August 2016 through January 2018. Patients were included in the study if they were ≥18 years old and received their entire course of C/T as a CI in the outpatient setting. Patients were excluded if they received any part of their C/T therapy as an inpatient. A retrospective chart review was performed on patients who met inclusion and exclusion criteria to evaluate the use of CI C/T.

All patients received C/T via a Continuous Ambulatory Delivery Device (CADD) pump, which was delivered as 4.5 or 9 grams (ceftolozane [1 gram]/tazobactam [0.5 grams] per each 1.5 grams) in 240 mL normal saline IV every 24 hours infused at a rate of 10 mL/hour. Patients presented to the institution's outpatient infusion center to have the medication cassette replaced each day, including weekends, for the entire treatment duration. Background demographics including height, weight, age, sex, race, allergies, creatinine clearance, temperature, infectious diagnosis, and white blood cell count were collected on each patient. Details concerning therapy (dose, duration, previous and concomitant antibiotics, adverse effects) and microbiology (culture and susceptibility reports) were also collected. The primary outcome was symptom resolution at the end of therapy, which was defined as documented subjective patient

Received 27 December 2019; editorial decision 4 January 2020; accepted 8 January 2020.

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DOI: 10.1093/ofid/ofaa014

report of no complaints, distress, or disease-specific signs and/or symptoms at follow-up outpatient physician clinic visits. Secondary outcomes evaluated were microbiologic resolution, defined as having a clinically evaluable repeat culture after completion of therapy showing no growth, and patient satisfaction of outpatient administration of CI C/T. To evaluate patient satisfaction, a questionnaire adapted from the Patient Satisfaction Questionnaire Short Form (PSQ-18) [4] was provided to the patients via telephone call. The investigator read each statement, and patients responded with strongly disagree, disagree, neutral, agree, or strongly agree. Responses were assigned a numerical value of 1–5 with 1 indicating strongly disagree and 5 indicating strongly agree. All patients had completed their course of therapy when they received the follow-up phone call.

RESULTS

Baseline Demographics

Seven patients received CI C/T therapy as outpatients and were included in the study. Median age was 71 years (range, 59–86 years), median creatinine clearance was 55 mL/minute (range, 41–130 mL/minute), and 5 of the 7 patients were female. All patients were afebrile at baseline and had baseline white blood cell counts within normal range, with the exception of 1 value of 14.43 k/mm^3.

Primary and Secondary Outcomes

Table 1 summarizes the patients' infectious diagnosis, antibiotic allergies, C/T therapy, susceptibility, and average satisfaction survey score, if applicable. All patients received C/T therapy as an outpatient, but 3 patients received different antimicrobial treatment as inpatients before being transitioned to C/T as outpatients. Patient 3 received 8 days of cefepime and tobramycin before completing therapy as an outpatient with 6 days of CI C/T. Patient 6 received 5 days of cefepime as an inpatient before transitioning to outpatient CI C/T to complete 14 days. Patient 5 received 3 days of tobramycin before receiving 7 days of CI C/T for her cUTI. The labeled dosing of 1.5 grams every 8 hours was converted to a 24-hour dose of 4.5 grams/day for all but 1 patient. Patient 3, who received a total of 9 grams/day, was dosed based on pharmacokinetic modeling data needed for target attainment in pneumonia available at the time (3 grams every 8 hours) [5]. For the primary outcome, 6 of 7 patients (85.7%) had symptom resolution at the end of therapy. One patient (patient 4) reported unresolved back pain at the completion of a 6-week treatment course for discitis. For the secondary outcome of microbiologic resolution, 3 patients (patients 1, 5, and 6) had a clinically evaluable repeat culture demonstrating microbiologic resolution. Three patients completed the patient satisfaction survey, and 4 did not respond (2 were deceased, 2 did not return investigator calls). Patients who completed the survey responded with either agree (4 points) or strongly agree (5 points) to all statements. Their average survey score is reflected in the table. Of note, 4 patients were not tested for susceptibility. Two of the 4 had pan-susceptible isolates, and 1 had been previously tested and shown to be susceptible to C/T. No adverse effects were reported from patients receiving CI. It is important to note that 3 patients had a listed penicillin allergy. Two patients had previously tolerated cephalosporins, with listed allergies of itching and swelling, respectively. The third patient had a listed allergy of rash and had never previously been documented as having tolerated cephalosporins. None of the 3 patients had a documented reaction to C/T. From the patient satisfaction questionnaire, it was noted that 2 patients are now deceased. From review of chart, both patients completed therapy and were in the clinical cure group, but they later succumbed to comorbid conditions.

DISCUSSION

There are limited data published on the use of CI C/T. Nateson et al [6] have previously reported Monte Carlo simulations demonstrating possible use of C/T as a 24-hour infusion. We have previously detailed the first successful use of CI C/T in the outpatient treatment of a UTI caused by MDR *P aeruginosa* using 4.5 grams of C/T infused over 24 hours daily in a patient

Table 1. Patients Receiving CI C/T Outpatient Therapy

Patient	Infectious Diagnosis	Pathogen	Susceptible to C/T?	Antibiotic Allergies	Dose/Day (Grams)	Duration (Days)	Satisfaction Score (avg)
1[a,b]	cUTI	MDR *Pseudomonas aeruginosa*	Susceptible (25-mm zone diameter)	PCN	4.5	14	N/A
2[a]	Pneumonia	*P aeruginosa*	Not tested	None	4.5	17	N/A
3[a]	Pneumonia	*P aeruginosa*	Not tested	None	9	6	N/A
4	Discitis	*P aeruginosa*	Not tested	PCN	4.5	42	N/A
5[a,b]	cUTI	MDR *P aeruginosa*	Intermediate (Etest MIC = 8/4 mcg/mL)	Erythromycin	4.5	7	4
6[a,b]	Bacteremia	*P aeruginosa* *Escherichia coli*	Not tested	PCN, Sulfa	4.5	10	4.2
7[a]	Pneumonia	MDR *P aeruginosa*	Susceptible (Etest MIC 2/4 mcg/mL)	Doxycycline	4.5	14	5

Abbreviations: avg, average; CI, continuous infusion; C/T, ceftolozane/tazobactam; cUTI, complicated urinary tract infection; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; N/A, not applicable; PCN, penicillin.

[a]Clinical cure (6 of 7 patients).

[b]Microbiological cure (3 of 3 patients).

with documented intolerance of CI P/T. The patient experienced microbiologic resolution without side effects [7]. Two other cases have been reported: one detailed the treatment of a lung abscess caused by a carbapenem-resistant *P aeruginosa* treated for 42 days as an outpatient in an immunocompromised patient with renal insufficiency, and the detailed other a pulmonary exacerbation in a cystic fibrosis patient with augmented renal clearance that received 6 grams of C/T CI daily for 10 days [8, 9].

In this case series from a retrospective chart review, CI C/T was shown to be efficacious and safe in a limited patient population with various infectious diagnoses. Treatment was focused against *P aeruginosa* and varied in length for each diagnosis, with some patients receiving treatment with other antimicrobials as inpatients before transitioning to C/T for outpatient parenteral antimicrobial therapy. Although safety was not formally evaluated, no patients reported any adverse events during therapy, and all patients completed their prescribed course.

Patient satisfaction was evaluated due to the lack of oral treatment options in many of these infections (primarily *P aeruginosa*, including several MDR strains) and the ability to receive treatment as an outpatient for an antimicrobial that is normally given 3 times per day. Even though delivery of the medication required placement of a central line and daily visits to the infusion center, patients included from the survey agreed or strongly agreed that this was a better alternative to hospitalization to treat the infection. Increased importance has been given to patient satisfaction recently from the Hospital Consumer Assessment of Healthcare Providers and Systems program. Hospitals must now report these data on patient experiences for value-based incentive payments [10].

CONCLUSIONS

There is currently a need for safe and effective treatments that can be given to outpatients for difficult-to-treat infections or convenience. Overall, the use of CI C/T was a safe, well tolerated, and convenient way to treat infections caused by *P aeruginosa*. Although CI from a pharmacokinetic/pharmacodynamic standpoint is unnecessary in isolates reported susceptible to C/T, logistically it may be a feasible option for convenience in the outpatient setting to avoid admission or decrease length of stay. Patients that have a MDR *P aeruginosa* infection with limited treatment options may specifically benefit having transitions of care to outpatient infusion. More data are needed to demonstrate safety and efficacy of CI and specific use in the outpatient setting.

Acknowledgments

Financial support. This work was funded by the Merck Investigator Studies Program (MISP) (Grant Number 57720).

Potential conflicts of interest. B. M. J. and C. M. B. have both received grant funding through Merck. C. M. B. has served on the speaker's bureau for Merck. 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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