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Case Series

Ceftaroline for the Treatment of Osteomyelitis: A Case Series

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Abstract

There is limited evidence supporting the use of ceftaroline to treat osteomyelitis. We report a series of 5 patients who received ≥ 7 days of ceftaroline therapy for documented cases of osteomyelitis. One of 5 patients did not require additional antibiotics or surgical intervention 6 months after completion of therapy.

INTRODUCTION

Ceftaroline, a cephalosporin antibiotic with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and some enteric gram-negative bacilli, was approved by the FDA in 2010 for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community acquired bacterial pneumonia (CABP), making it the first beta-lactam antibiotic with activity against MRSA approved in the US [1]. Being well-tolerated in phase III clinical trials, along with the lack of need for therapeutic drug monitoring and its unique spectrum of activity, make ceftaroline an attractive option for the treatment of infections that require long courses of intravenous (IV) antibiotics, such as osteomyelitis (OM) [2-5].

In this case series we report 5 patients from October 2010 through March of 2015 who received at least one dose of ceftaroline for the treatment of documented OM at a VA Health Care System. For purposes of this case series, we considered courses "clinically successful" if patients did not require additional antibiotics or any unplanned surgical intervention for OM in the 6 months after ceftaroline therapy was discontinued (Table 1).

PATIENT CASES

Course 1

A 66 year old Caucasian with a history of diabetes presented to an outside hospital with right great toe osteomyelitis. An ulcer on the toe was treated with a short course of oral ciprofloxacin and clindamycin and wound care, but then recurred approximately one year later. The patient received multiple courses of oral antibiotics and continued wound care without resolution of the ulcer. A bone scan performed at and the outside hospital demonstrated OM of right great toe and the patient was admitted there for a planned 6-8 week course of antibiotics. Outside cultures reportedly grew MRSA and *Citrobacterfruendi,* only resistant to cefazolin, and *Klebsiellaoxytoca*, only resistant to

ampicillin. The patient was placed on ceftazidime and tigecycline at the outside hospital but, due to formulary preference, was changed to ceftazidime and vancomycin when they were transferred to our institution for surgical evaluation. On day 4 at our facility the patient was evaluated by the infectious diseases consult service and, in order to simplify his antibiotic regimen while still providing broad coverage, his antibiotics were changed to ceftaroline 600mg every 8 hours plus metronidazole 500mg by mouth every 8 hours. The surgery team determined no intervention was necessary and the patient was transitioned to a long-term care facility where he completed a 42 day course of ceftaroline and metronidazole. One week after therapy was completed purulent material began draining from the right great toe ulcer; the patient was admitted to an outside hospital and underwent an unplanned right great toe amputation.

Course 2

A 62 year-old Caucasian male initially presented to an outside hospital with complaints of hip and back pain. An MRI at the outside hospital revealed a psoas muscle abscess and an epidural (L5-S1) abscess; blood and abscess cultures obtained were positive for MRSA. The patient developed blurred vision after surgical drainage leading to concern for septic emboli to the eye. Additionally, drains placed in the area of the epidural abscess continued to drain for 10 days after the procedure despite vancomycin (unknown dose) therapy. After 12 days at the outside hospital the patient was transferred to a larger facility, where his antibiotic therapy was switched to ceftaroline 600mg IV every 8 hours for presumed "vancomycin failure." Subsequent blood cultures were negative, but a repeat MRI spine was concerning for vertebral OM and revealed another spinal abscess. Additional surgery was not recommended at this time and the patient was to remain on ceftaroline therapy for 8 weeks (Table 1). At our long-term care facility he completed 32 days of ceftaroline, but was transitioned to daptomycin 570 mg IV daily after he developed a fine, non-raised rash on his abdomen and chest. No additional surgical interventions or antibiotics were

Table 1: Ceftaroline Therapy.

Course	Organism(s) Cultured	Previous IV Antibiotics for OM? (Y or N)	Ceftaroline Dose	Total Days of Ceftaroline	Concomitant Antibiotic Therapy (Y or N)	Treatment Failure (Y or N)
1	MRSA *Citrobacterfreundii* *Klebsiellaoxytoca*	N	600mg q8h	42	Y	Y
2	MRSA	N	600mg q8h	32	N	N
3	NA	N	600mg q12h	21	Y	Y
4	MRSA, CNS, Group B *Streptococcus, Proteus* spss., *Alcaligenesfaecalis*	Y	400mg q12	24	Y	Y
5	MRSA	Y	600mg q8h	40	Y	Y

required within 6 months after therapy discontinuation; no additional imaging studies were available.

Courses 3 and 4

A 58 year-old Caucasian male was admitted for swelling and pain from ulcers on his right 2nd and 3rd toes. The patient was started on ertapenem 1 gram IV daily and vancomycin 1 gram IV every 12 hours. Plain film x-rays were obtained, and demonstrated soft-tissue swelling but no definitive evidence of OM. However, due to patient's elevated erythrocyte sedimentation rate (110 mm/hr) underlying OM was suspected by the ID consult service. Vancomycin and ertapenem were continued until 20 days into treatment patient presented with acute on chronic renal failure (serum creatinine increased from 2.86 mg/dL to 4.77 mg/dL) thought to be due to vancomycin. At this time the patient was transitioned to ceftaroline 600mg IV every 8 hours and metronidazole and completed 21 days of therapy without further incident. Within 6 months, however, the patient re-presented with a blister on the plantar surface of the right foot, which had opened and was draining purulent material. Inflammatory markers were elevated (erythrocyte sedimentation rate 70 mm/hr, C - reactive protein 13.78) and the patient was clinically diagnosed with a recurrence of OM. He received another course of ceftaroline (renally adjusted to 400mg IV every 12 hours) and incision and drainage, ultimately leading to a right transmetatarsal amputation. Because of this additional infection within 6 months of completion of the first course the patient was conservatively managed with 24 days of ceftaroline and metronidazole before a wound swab grew *Proteus* that was resistant to ceftaroline; at that time the patient was switched to cefepime and daptomycin. After completion of the second antibiotic course the patient had another recurrence within 6 months, which required antibiotic therapy and a right below the knee amputation.

Course 5

A 62 year-old Caucasian male with a history of OM and diabetes presented to the Emergency Department with right second toe swelling; plain film x-rays revealed acute OM of the distal phalanx of the right 2nd and 3rd toes. The patient was initiated on vancomycin, cefepime, and metronidazole and

underwent amputation of the right 2nd toe. Foot swabs obtained grew only MRSA, and the patient's antibiotic regimen was changed on discharge to ceftaroline 600mg IV every 8 hours and metronidazole for ease of administration at home. The patient completed 40 days of therapy with ceftaroline and metronidazole, but did require another course of antibiotic therapy for OM within 6 months.

DISCUSSION

In this small case series we report 5 patients treated with ceftaroline for OM. The median duration of therapy was 32 days and 80% (4/5) were on concomitant antibiotic therapy. High-dose ceftaroline therapy was used in all patients and clinical success was achieved in 20% (1/5) patients. Of note, no patient with a previous case of OM (2/5) had a successful outcome. It is also worth noting that the only patient reported here that did achieve a successful outcome received approximately 24 days of his planned course of therapy with daptomycin; it is difficult to say which agent contributed most significantly to his outcome.

Ceftaroline was first evaluated for OM in a rabbit model. The femurs of New Zealand white rabbits were inoculated with MRSA or Glycopeptide-intermediate *S. aureus* (GISA) and they received 4 days of therapy with either ceftaroline, vancomycin, or linezolid. In rabbits infected with MRSA, ceftaroline decreased organism counts in bone and bone marrow to a greater extent than vancomycin (2.95 $\log_{10}$cfu/g tissue and 2.83 $\log_{10}$cfu/g tissue decrease compared to 0.39 $\log_{10}$cfu/g tissue and 0.52 $\log_{10}$cfu/g tissue); there was no significant difference between the ceftaroline and linezolid groups [6].

While no prospective studies for ceftaroline in the treatment of OM have been completed, a few retrospective reports are available [7-9]. One of the earliest was a case report of a patient with a history of MRSA infections found to have endocarditis and OM after presenting to the ED with fevers. Initial blood cultures were positive for MRSA (vancomycin MIC_{90} =1, daptomycin MIC_{90} = 0.38) and patient was started on daptomycin 8mg/kg. Despite source control and daptomycin therapy, blood cultures drawn on day 22 grew MRSA with a daptomycin MIC_{90} = 3 mcg/mL. Ceftaroline was initiated on day 23 at a dose of 600mg every 12 hours, and blood cultures on day 29 and 32 were negative.

The patient successfully completed 44 days of ceftaroline with infection resolution [7].

Also reported in 2013 was a case series of 10 patients from a VA hospital with endocarditis or other deep seated MRSA infections; two of which had documented OM. Patient 1 had a residual MRSA infection in a metatarsal head adjacent to the site of a toe amputation. The patient received 6 weeks of therapy with daptomycin 6 mg/kg with no response, and was subsequently switched to ceftaroline 600mg every 8 hours. A second amputation was completed 6 days later and the patient finished 42 days of therapy with microbiologic and clinical cure. Patient 2 had Human Immunodeficiency Virus (HIV) infection and vertebral OM- the result of 2 previous psoas abscesses that extended into the vertebrae. The patient had failed at least one previous 4 week course of vancomycin and clindamycin, which was switched to 3 weeks of trimethoprim/sulfamethoxazole suppression. For the third recurrence of the infection the patient was treated with 6 weeks of ceftaroline 800mg every 12 hours and achieved microbiologic and clinical cure. No recurrence was noted on imaging studies at 7 and 10 months post therapy [8].

Finally, the most recent study provides the greatest number of patients with OM. This evaluation included retrospective data from 5 US institutions from January 2011 through June of 2013. A total of 81 patients were treated with ceftaroline for bone and joint infections (BJIs). Seventy-five patients with BJIs were clinically evaluable and 95% (71/75) achieved clinical cure [9]. It is unclear from the data provided how many patients in this group had joint infections and how many had OM.

It is also important to consider which dose of ceftaroline is optimal in treating OM. Because ceftaroline's half-life is approximately 2.6 hours in healthy subjects it has been postulated, and employed in some areas of clinical practice, that dosing the antibiotic every 8 hours instead of every 12 hours may be beneficial in deep seated infections [1,7-10]. In a hollow fiber model, two doses of ceftaroline (600mg every 12 hours and every 8 hours) were compared to vancomycin against six clinical MRSA isolates; two strains were heterogeneous vancomycin-intermediate *S. aureus* (hVISA). The percentage of free-drug time above the MIC ($\%fT > MIC$) was above 50% (the established goal for ceftaroline) for both frequencies against all isolates tested, with the exception of the Mu3 (hVISA) isolate ($\%fT>MIC$ was 69% vs. 46% for q8h and q12h dosing, respectively). However, there was no significant difference in bacterial densities observed at 24, 48, or72 hours between the q8h and q12h dosing regimens [10,11] While, based on the drugs half-life, it is reasonable to conclude increasing the frequency may beneficially increase antibiotic exposure, it is important to note that no prospective or retrospective clinical studies directly comparing this concept have been published.

In addition to spectrum of activity, ceftaroline's safety profile also makes it an attractive option for longer courses of therapy. Ceftaroline has been found to be a relatively safe cephalosporin antimicrobial, with no adverse reactions occurring in more than 5% of patients in phase III trials; diarrhea and nausea occurred in 5% and 4% of patients respectively [1-5]. In post marketing data neutropenia has become a potentially concerning adverse effect, with at least 6 individual cases being reported in the literature to date; these cases were generally associated with off-label dosing and/or longer durations of therapy [12-14]. Most recently, in a retrospective cohort of patients at a single center receiving >7 days of ceftaroline, 18% (7/39) of which developed clinically significant neutropenia. The median duration of therapy was 27 days and the median time to first neutropenic day was 17 days [15].

The results observed in this small case series did not appear consistent with previously published reports as only 20% of patients achieved a successful outcome. The response rate did not appear to be associated with dose, as all patients in this case series received high dose therapy. The patients represented here were complicated – all were switched to ceftaroline due to either inability to tolerate other agents, because it was a more convenient option, or because of complicated microbiology – but this is likely a true reflection of how ceftaroline is being used in clinical practice to manage OM. Additionally, these patients had many co morbidities and all required some type of surgical intervention to manage their infections. Only one patient, patient 2, had an OM that was associated with a site other than a foot. The site of infection could certainly contribute to the outcome, as OM of the spine is generally associated with a lower recurrence rate, but patient 2 did complete almost half his course of therapy with daptomycin. This case series is likely highly subject to selection bias, as the patients reported here represent some of the most complex and difficult to treat patients we would see. One patient did have therapy discontinued because of a rash, but ceftaroline was otherwise well-tolerated. Despite the low response rate observed here, it is important to consider that response rates to therapy in OM have traditionally been low; vancomycin has been associated with recurrence rates of 30-50% after 6 months of therapy [16]. Given the tolerability of ceftaroline and the lack of need for therapeutic drug monitoring, it remains an attractive option for the management of OM. Additionally, there appears to be no proven clinical benefit, in most cases, for using off-label dosing. Ceftaroline will likely continue to be used for the management of OM, but this small series highlights the need for more studies to best define how to use this antibiotic to treat these complicated infections.

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