A 74-year-old man with long-standing diabetes presented with advanced infection of the right forefoot associated with septic arthritis and osteomyelitis involving the second and third metatarsophalangeal joints. Polymicrobial infection, which included methicillin-resistant Staphylococcus aureus, was documented. First-line antibiotic therapy, which included vancomycin, was not tolerated. A durable cure was obtained following a six-week course of intravenous ceftobiprole medocaril combined with local surgery. The present report is the first to administer intravenous ceftobiprole medocaril to a patient with methicillin-resistant S aureus-associated septic arthritis and osteomyelitis.

CASE PRESENTATION

A 74-year-old man with long-standing diabetes mellitus complicated by hypertension, chronic renal insufficiency, peripheral neuropathy and a left below-knee amputation for gangrene that was performed in 2000. The patient was admitted on October 30, 2008, with a plantar ulcer over his right forefoot that had been present for approximately three to four weeks. On examination, there was exposure of the flexor tendon to the third metatarsal. A deep swab obtained at presentation grew methicillin-resistant Staphylococcus aureus (MRSA) and Enterobacter cloacae. The MRSA isolate was clindamycin and quinolone resistant, and the minimum inhibitory concentration of vancomycin was less than 2 µg/mL. The patient was initiated on therapy with 160 mg/800 mg of co-trimoxazole (one tablet) taken orally twice a day combing placement of a peripherally inserted central catheter. His baseline creatinine level was 128 µmol/L, with an estimated glomerular filtration rate of 48 mL/min/1.73 m². Vancomycin and piperacillin/tazobactam were replaced by 500 mg of intravenous ceftobiprole medocaril given every 12 h for renal insufficiency. The switch to monotherapy was made due to the difficulty of administering two parenteral agents during home intravenous therapy and the significant potential for further vancomycin-associated complications.

The patient was referred to the orthopedic surgery department and, under local anesthetic, underwent excision of the second and third metatarsal heads followed by loose surgical closure on January 25, 2009. The patient was subsequently discharged to continue home intravenous antibiotic therapy with ceftobiprole for a total duration of 42 days. The patient's complete blood count normalized and renal function remained stable during the treatment course. At the end of therapy, the wound was fully healed and the patient gradually resumed ambulation.

At one-year follow-up, the foot remains fully healed with no evidence of relapsed osteomyelitis.

DISCUSSION

Ceftobiprole medocaril is a novel cephalosporin with a high affinity for the penicillin-binding protein PBP2a, eliciting bactericidal activity of the mid-forefoot. Sterile exploration of the wound and preliminary debridement revealed septic arthritis and bony destruction involving both the second and third metatarsophalangeal joints.

The patient was initiated on intravenous antibiotic therapy with vancomycin and piperacillin/tazobactam. He developed vancomycin-induced superficial thrombophlebitis while awaiting placement of a peripherally inserted central catheter. His baseline creatinine level was 128 µmol/L, with an estimated glomerular filtration rate of 48 mL/min/1.73 m². Vancomycin and piperacillin/tazobactam were replaced by 500 mg of intravenous ceftobiprole medocaril given every 12 h for renal insufficiency. The switch to monotherapy was made due to the difficulty of administering two parenteral agents during home intravenous therapy and the significant potential for further vancomycin-associated complications.

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activity against MRSA (1). It has broad-spectrum microbiological activity, which includes most aerobic cocci, Enterobacteriaceae (except Proteus vulgaris), Pseudomonas species and Gram-positive anaerobes. This spectrum of activity has positioned ceftobiprole for the treatment of diabetic foot and other complicated skin and skin structure infections. Results of two randomized, double-blind trials (2,3) on skin and skin structure infections showed similar efficacy between ceftobiprole and comparator treatment arms. A treatment duration of seven to 14 days was stipulated in these trials; patients with joint or bone infections were excluded. The present study is the first to report on the use of ceftobiprole in a patient with chronic osteomyelitis and septic arthritis.

Although aerobic Gram-positive cocci are the predominant pathogens in early diabetic foot infection, chronic ulcers with advanced infection and deep structure involvement usually include Gram-negative rods and anaerobic flora, as demonstrated in the present patient (4). Therapy for diabetic foot infection has been further complicated by the increasing influence of antibiotic-resistant organisms, particularly MRSA, which in recent international studies (3,5), accounts for at least 30% of S. aureus isolates from diabetic foot infection. MRSA infection in the diabetic foot has been associated with a worse outcome than other pathogens (6). The presence of MRSA osteomyelitis in the context of diabetic foot infection generally requires at least two antimicrobial agents to provide appropriate coverage because of their polymicrobial nature (7). The broad-spectrum activity of ceftobiprole makes it an ideal agent for monotherapy in this setting.

The diagnosis and treatment of diabetic foot osteomyelitis remains highly controversial and this is further complicated by the presence of MRSA. Surgical resection is generally believed to play a crucial role in therapy, because it appears to be associated with a higher rate of cure, enables a shorter duration of antimicrobial therapy and has the potential to correct underlying structural abnormalities (7). Several reports (7-9) on nonsurgical treatment have shown that high cure rates require treatment durations of at least three months, with 50% of this duration being required if surgical resection can be performed.

Our patient was a good candidate for combined surgical and medical therapy because he had good arterial perfusion; had a localized, easily identifiable osteomyelitis focus; and had structural deformity with prominent metatarsal heads. One study (10) documented that patients with MRSA diabetic foot osteomyelitis undergo a greater number of surgical procedures before achieving a cure compared with patients with osteomyelitis caused by methicillin-sensitive S. aureus (10).

There is no consensus as to the drug of choice for MRSA-induced osteomyelitis. While vancomycin is generally considered to be the first-line therapy, it is only slowly cidal and the concentrations achievable in bone may be inadequate (11). This is further supported by the high vancomycin failure rate observed in the treatment of osteomyelitis, pneumonia and endocarditis in patients with methicillin-sensitive S. aureus compared with beta-lactam antibiotics (12-14). Linezolid is bacteriostatic for MRSA, and prolonged therapy can be complicated by bone marrow suppression and peripheral neuropathy. The limited clinical data available for linezolid in MRSA osteomyelitis demonstrated a clinical cure rate of 81.8% in one study (15).

There are no human studies on the use of tigecycline in MRSA osteomyelitis. This broad-spectrum, bacteriostatic agent demonstrated a 90% MRSA clearance rate compared with 82% for vancomycin in a rabbit model after a four-week treatment course (16).

Daptomycin has been shown to be comparable with vancomycin in animal models of MRSA-induced osteomyelitis (17). Clinical success with this agent in osteoarticular MRSA infection has been reported (18).

Rouse et al (19) demonstrated that ceftobiprole had in vitro bactericidal activity against 100% of MRSA isolates recovered from bone and joint infections. Ceftobiprole was found to be more active than vancomycin and linezolid in a rabbit model of tibial MRSA osteomyelitis (20). In this model, MRSA was below the limit of detection, after a four-week treatment course, in 100% of infected tibias treated with ceftobiprole compared with 73% of those treated with linezolid or vancomycin. Ceftobiprole plasma and infected tibiae concentrations exceeded the minimum inhibitory concentration for MRSA for greater than 40% of the dosing interval (20).

Until long-term comparative trials of antibiotic therapy for MRSA osteoarticular infection become available, vancomycin will continue to be the first-line agent in the treatment of these infections. Newer agents will tend to be used in the setting of vancomycin failure, vancomycin-associated adverse events, or situations in which treatment simplification to a single antimicrobial agent is desirable. Currently, ceftobiprole or tigecycline are the only available agents that can be used as monotherapy in the setting of a mixed polymicrobial osteoarticular infection containing MRSA.

Ceftobiprole has been well tolerated in all of the studies conducted thus far (2,3). The most common adverse drug reactions observed in clinical trials have been nausea (9.1%) and vomiting (4.8%), which are significantly reduced if the infusion time is extended to 2 h. Ceftobiprole undergoes minimal hepatic metabolism, and dose adjustment is unnecessary in patients with hepatic impairment. Because it is eliminated predominately by the kidney, dosage adjustment is necessary in patients with a creatinine clearance of less than 50 ml/min. Although significant laboratory abnormalities have not been observed with short-course therapy with ceftobiprole, it would be prudent to monitor patients with regular hematological, electrolyte, renal and liver enzyme testing if undergoing longer course therapy.

The present preliminary report indicates that ceftobiprole is safe and well tolerated during a six-week period of infusion for MRSA osteomyelitis complicating diabetic foot infection, with durable cure at one-year follow-up. Ceftobiprole may be an important new agent for the treatment of MRSA osteomyelitis; further research is required to investigate its role for this indication.

CONFLICT OF INTEREST: Dr Dow has previously participated on a ceftobiprole advisory board, and has received honoraria from Janssen-Ortho Inc. The authors have no other conflicts of interest to declare.

REFERENCES


