Ceftolozane/tazobactam in the treatment of SSTI and osteomyelitis due to extensively drug-resistant Pseudomonas aeruginosa (XDR-P): clinical and microbiological outcomes

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Background: Ceftolozane/tazobactam (CT) is a novel cephalosporin/beta-lactamase inhibitor approved for the treatment of complicated intra-abdominal and complicated urinary tract infections. Data on its off-label use is minimal. Our aim is to report the efficacy and safety of CT in the treatment of skin and soft tissue infections (SSTI) and osteomyelitis due to extensively drug-resistant Pseudomonas aeruginosa (XDR-P).

Material/methods: Design: Observational retrospective study. Setting: Acute care hospital (384 beds). Period: April-October 2016. Study Subjects: All patients with SSTI or osteomyelitis due to XDR-P susceptible to ceftolozane/tazobactam and treated with CT. Study Variables: demographics, comorbidities (Charlson score), source of infection, diagnostic methods, management, dose, duration and adverse effects of antibiotic treatment. Clinical and microbiological cure, reinfections and superinfections were also recorded.
**Results:** Seven patients received ceftolozane/tazobactam for treatment of SSTI (n=3; 43%) and osteomyelitis (n=4; 57%). Median age was 82.3 years (IQR= 11.2); 71% were men. Median Charlson score was 6.50 (IQR= 2.7). Glomerular filtration rate (GFR) <60 mL/min/1.72m² was present in 43%. Diagnosis was established based on wound biopsy (n=3; 43%), bone biopsy, synovial fluid, percutaneous aspiration and superficial swab (1 each, 14.3%). Two patients (29%) needed surgical debridement and 3 (43%) minor amputations. Standard doses (GFR>60: 1/0.5 g/8h; GFR 30-50: 500/250 mg/8h) and a close monitoring of GFR was applied. In two patients (29%) CT was used as rescue therapy after developing toxicity to standard treatment; in 5 (71%) it was used as initial directed therapy in the setting of elderly people and/or renal injury. Mean ceftolozane/tazobactam MICs for *P. aeruginosa* in the first isolate (n=7) were 1 μg/mL (range; 0.75-1.5) and in subsequent isolates (n=5) was 1 μg/mL (range; 0.75-2). Median duration of therapy was 27 days (IQR= 31). Length of stay was of 48 days (IQR= 53). Clinical cure and documented microbiologic eradication were achieved in 100% and in 80% patients, respectively. One patient (17%) presented a reinfection due to *S.aureus* 12 weeks after the first episode. Superinfection was diagnosed in 2 patients (29%) due to *Enterococcus faecium* and *Candida spp.* No adverse effects were identified. All patients survived.

**Conclusions:** Our preliminary experience indicates that ceftolozane/tazobactam achieved good clinical and microbiological outcomes when used as directed monotherapy against XDR-P infections in SSTI and osteomyelitis. Ceftolozane-tazobactam may be a suitable alternative in a scenario of increasing rates of XDR-P infections in an aging population at higher risk of toxicity.