Successful treatment of post-surgical osteomyelitis caused by XDR Pseudomonas aeruginosa with ceftolozane/tazobactam monotherapy

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Sir,

Pseudomonas aeruginosa is a Gram-negative bacterium that causes relevant healthcare-associated infections.\(^1\) The best treatment of P. aeruginosa infection is still debated.\(^2\) Even more challenging is the treatment of MDR or XDR isolates.\(^3\) A novel promising option against difficult-to-treat P. aeruginosa is ceftolozane/tazobactam, a combination of a new-generation cephalosporin with a \(\beta\)-lactamase inhibitor.\(^4\) This compound is approved for complicated infections of the urinary tract and abdomen; information regarding other clinical contexts stems from case reports or case series.\(^4\)

Here we describe the case of a man in his mid-fifties affected by XDR P. aeruginosa osteomyelitis successfully treated with ceftolozane/tazobactam. The patient came to our observation because of recurrence of a bone (left femur) infection. The first osteomyelitis episode occurred after a traumatic fracture and was successfully treated with a 12 week course of trimethoprim/sulfamethoxazole and minocycline. Three months later, the infection recurred. Culture of a deep bone fragment and microbiological examination showed P. aeruginosa susceptible only to colistin with an MIC of 1 mg/L and high MICs of meropenem (64 mg/L) and fosfomycin (32 mg/L). Therefore, the patient was admitted and started therapy with colistin at standard dosage (9 million units as leading dose and 4.5 million units q12h as maintenance dosage) plus rifampicin (300 mg q12h).

Upon admission, serum C-reactive protein (CRP) was 2.49 mg/dL. After 18 days of therapy, the measured glomerular filtration rate (mGFR) showed a decreasing trend and a urine test revealed tubulopathy. Thus, the dose of colistin was progressively reduced and was withdrawn (together with rifampicin) after 26 days when mGFR decreased to 33.1 mL/min; at this time CRP was 0.55 mg/dL.

On day 27, authorized off-label therapy with ceftolozane/tazobactam (not included in the antimicrobial susceptibility testing) was started at 500 mg/250 mg q8h (the dose was halved because of the reduced mGFR) and, after 14 days, when mGFR exceeded 50 mL/min, it was administered at standard dosage. CRP was <0.33 mg/dL 5 days after this new treatment. We continued ceftolozane/tazobactam to complete an 8 week course. At the end of therapy, CRP was negative and we referred the patient to the orthopaedic centre for the planned surgical revision. At the last follow-up visit (3 months after surgery) the patient was infection-free.

To our knowledge, this is the first report of the clinical success of ceftolozane/tazobactam used as monotherapy against an XDR P. aeruginosa strain as the causative agent of a monomicrobial osteomyelitis. Notably, ceftolozane/tazobactam plus vancomycin was very recently reported to be effective against MDR P. aeruginosa and diphtheroids in polymicrobial osteomyelitis.\(^5\)

There are no data about bone penetration of ceftolozane/tazobactam; however, like other \(\beta\)-lactams, parenteral administration of the drug should guarantee levels exceeding the MIC for...
aetiological bacteria in infected bones. Furthermore, ceftolozane/tazobactam, like β-lactams, has a good safety profile and low risk of drug–drug interaction, thereby enabling prolonged therapy. Given its stability against the most common resistance mechanisms in P. aeruginosa, ceftolozane/tazobactam exerts optimal in vitro activity even against strains not susceptible to carbapenems. This finding guided our therapeutic choice in the absence of information about the MIC of the drug.

In conclusion, ceftolozane/tazobactam may be a valuable option, even in monotherapy, against XDR P. aeruginosa in the case of bone infections.

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Transparency declarations
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References

Sir,
Successful ART has substantially increased the life expectancy of HIV patients; however, ART-related long-term toxicities have led to the emergence of novel treatment strategies, such as NRTI-free dual therapy. The combination of the integrase inhibitor dolutegravir and the ritonavir-boosted PI darunavir may play a key role in this setting. Therefore, the potent integrase strand transfer inhibitor dolutegravir, in combination with the boosted PI with the highest known resistance barrier, darunavir, might offer a potentially tolerable, safe and effective ART strategy. No data for once-daily 50mg dolutegravir in combination with 800/100mg darunavir/ritonavir are available to date. The aim of the present study was thus to investigate the efficacy and pharmacokinetics, as well as to determine the drug combination effect profile, after a switch to this dual regimen in virologically controlled, pretreated patients.