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CASE REPORT

Ceftolozane/tazobactam for the treatment of MDR *Pseudomonas aeruginosa* left ventricular assist device infection as a bridge to heart transplant

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Abstract
Background Ceftolozane/tazobactam (C/T) is a novel antibiotic with enhanced microbiological activity against multidrug-resistant (MDR) gram-negative bacteria, including MDR *Pseudomonas aeruginosa*.
Case report Five months after left ventricular assist device (LVAD) implantation, a 49-year old man developed fever and blood culture was positive for MDR *P. aeruginosa*, susceptible only to aminoglycosides, ciprofloxacin and colistin. A diagnosis of LVAD-related infection was made based on persistent bacteremia associated with moderate 18 F-fluorodeoxyglucose positron emission tomography/CT uptake in the left ventricular apex. Disk diffusion testing for C/T was performed (MIC 2 µg/mL) and intravenous antibiotic therapy with C/T and amikacin was started, with clinical and microbiological response. Initial conservative management with 6 weeks of systemic antibiotic therapy was attempted, but the patient relapsed one month after antibiotic discontinuation. Priority for transplantation was given and after 4 weeks of antibiotic therapy (C/T + amikacin), LVAD removal and heart transplant were performed, with no infection relapse.
Conclusions We reported the first off-label use of C/T in the management of MDR *P. aeruginosa* LVAD infection as a bridge to heart transplant. C/T has shown potent anti-pseudomonal activity and good safety profile making this drug as a good candidate for suppressive strategy in intravascular device-associated bloodstream infections caused by MDR *P. aeruginosa*.

Keywords Ceftolozane/tazobactam · MDR *Pseudomonas aeruginosa* · Left ventricular assist device infection · Heart transplant · Device infections · MDR gram negative bacteria

Introduction

Ceftolozane/tazobactam (C/T) is a new β-lactam/β-lactamase inhibitor combination approved for complicated abdominal and urinary tract infections with very high in vitro activity against multidrug-resistant (MDR) Gram-negative bacteria [1]. Anecdotal reports have been recently published describing the off-label usage of C/T for MDR *Pseudomonas aeruginosa* bacteremia [2] and few retrospective studies support the use of C/T to treat carbapenem-resistant (CR) *P. aeruginosa* [3].

Case report

A 49-year-old men developed a congestive heart failure after an acute *Haemophilus influenzae* myocarditis in March 2016 and was referred to our hospital. The patient was supported

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with inotropic therapy, intra-aortic balloon pump (IABP) and peripheral awake veno-arterial extracorporeal membrane oxygenation (awake VA-ECMO). Myocardial recovery did not occur and 3 weeks later an axial continuous flow long-term left ventricular assist device (LVAD) Jarvik 2000 was successfully implanted with abdominal driveline exit site, as a bridge to recovery or transplantation therapy. The patient was successfully discharged with periodic follow-up.

Five months after discharge, he was admitted to our hospital with a history of 3-day fever (T_{max} 102.2 °F) without associated symptoms. The patient was hemodynamically stable at presentation. The sternotomy wound and LVAD abdominal driveline exit site appeared normally healed without evidence of soft tissue infection. Laboratory tests showed elevated white blood cell count (WBC) of 19.650 / µL (normal range 3.500–10.500 µL), serum C-reactive protein (CRP) of 195 mg/L (normal value < 5.0) with platelet count, and creatinine and liver function tests within normal range. Urine and chest-X-ray were unremarkable.

Three sets of blood cultures drawn at different times over a 24 h period were all positive for MDR *P. aeruginosa*, resistant to meropenem (MIC 16 µg/mL) and susceptible only to amikacin (MIC ≤ 4 µg/mL), gentamicin (MIC 2 µg/mL), ciprofloxacin (MIC 0.5 µg/mL) and colistin (MIC 1 µg/mL). Disk diffusion testing demonstrated susceptibility to C/T (MIC 2 µg/mL).

To identify the infection origin, a transesophageal echocardiogram (TEE), a total body computed tomography (CT) scan and a 18 F-fluorodeoxyglucose positron emission tomography/CT (18 F-FDG PET/CT) were performed. TEE and CT scan were negative, while 18 F-FDG PET/TC showed moderate FDG (uptake in the left ventricular apex around the LVAD (SUV 4).

Intravenous antibiotic therapy with C/T (1.5 g in continuous infusion every 8 h) and amikacin (7.5 mg/Kg/day) was started. Clinical and microbiological response (with negative blood cultures) was achieved 48 h after the antibiotic was started. The case was discussed with a multidisciplinary team and a conservative management with 6 weeks of systemic antibiotic therapy was attempted.

One month after antibiotic discontinuation, the patient developed fever (102.4 °F) and positive blood cultures (3 out of 3 sets) for MDR *P. aeruginosa* with an identical susceptibility pattern. Disk diffusion testing confirmed susceptibility to C/T (MIC 2 µg/mL). He was hospitalized and a new course of antimicrobial treatment with C/T and amikacin was administered. After 48 h of adequate antibiotic therapy, blood cultures showed no growth. A diagnosis of LVAD-related infection was made based on persistent bacteremia associated with moderate 18 F-FDG PET/CT uptake in the left ventricular apex without an identifiable extra-device source. Priority for heart transplantation was given. After 4 weeks of systemic antibiotic therapy, orthotropic heart transplantation with bicaval technique and LVAD removal were performed. During the surgical procedure, a pouch with serohematic material was found in the apical pericardium and around the LVAD tube. Intraoperative samples were negative, with no *P. aeruginosa* growth, and C/T antibiotic therapy was discontinued 72 h after transplant. The patient had a brilliant recovery and at the last follow-up visit (6 months after surgery), the patient was infection free.

Discussion

Ceftolozane/tazobactam (C/T) is a new β-lactam/β-lactamase inhibitor combination approved for complicated abdominal and urinary tract infections with very high in vitro activity against multidrug-resistant (MDR) Gram-negative bacteria [1, 4]. Anecdotal reports have been recently published describing the off-label usage of C/T for MDR *P. aeruginosa* bacteremia [2] and few retrospective studies support the use of C/T to treat carbapenem-resistant (CR) *P. aeruginosa* [3].

To the best of our knowledge, there are no data about C/T use in intravascular device-associated bloodstream infections caused by MDR *P. aeruginosa.* Our experience could offer some interesting clues. C/T overcomes the most prevalent resistance mechanisms of *P. aeruginosa* (chromosomal AmpC, loss of outer membrane porin, upregulation of efflux pumps) and demonstrates activity against CR strains not producing a carbapenemase [5, 6]. In line with recent in vivo published data, our experience suggests that C/T may be a useful option for severe infections caused by CR *P. aeruginosa* that are confirmed to be in vitro susceptible [5]. The addition of amikacin to C/T provided a further strategy to obtain a high antimicrobial activity against highly resistant strains [7].

Bloodstream infection during LVAD support poses a unique clinical problem with no clear guidelines for diagnosis or management [8]. 18 F-FDG PET/CT is a promising imaging modality and in our case provided accurate information on the localization of LVAD related infection [9]. The LVAD driveline and pump pocket are ideal surfaces for the formation of biofilms with high rates of antibiotic resistance. C/T has shown a low propensity for the selection of resistance against *P. aeruginosa*, requiring multiple mutations and arising more slowly than mutants resistant to other antibiotics [4]. Although C/T apparently does not show high activity against biofilms formed by *P. aeruginosa* [10], our experience revealed that chronic suppression therapy with C/T could be an efficient strategy as a bridge to device removal.

C/T has been licensed for intravenous administration every 8 h in 1-h infusion. However, on the basis of previous in vitro simulations of alternative C/T dosing schemes and

C/T biochemical structure (molecule stable up to 24 h at room temperature), we opted for a CI every 8 h to maximize the time above the MIC [11]. In addition, in our experience C/T showed a good safety profile with excellent tolerability, enabling prolonged therapy [12].

In conclusion, C/T potent anti-pseudomonal activity and good safety profile make this drug a good candidate for suppressive strategy in intravascular device-associated bloodstream infections caused by MDR *P. aeruginosa.*

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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