Case Report

Successful ceftolozane/tazobactam treatment of chronic pulmonary infection with pan-resistant *Pseudomonas aeruginosa*

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Introduction: The treatment of chronic *Pseudomonas aeruginosa* infections is challenging, with resistance and antibiogram diversity accumulating during successive therapies. Some isolates are resistant to all licensed agents, creating treatment problems and an urgent need for new therapies. Among antibiotics in advanced development, ceftolozane/tazobactam has potent *in vitro* antpseudomonal activity, with low MICs even for strains with AmpC β-lactamase-, impermeability- and efflux-mediated resistance to other β-lactams.

Case presentation: A bronchiectasis exacerbation in a 59-year-old man involved pan-resistant *P. aeruginosa*. Meropenem/colistin therapy failed. Named-patient ceftolozane/tazobactam 2+1 g every 8 h for 14 days restored baseline respiratory and inflammatory marker status, and the patient was discharged; the ceftolozane/tazobactam MIC was 8 μg ml^{-1}, with most growth inhibited at 2 μg ml^{-1}.

Conclusion: A positive outcome in this difficult infection due to an otherwise pan-resistant *P. aeruginosa* is notable, especially as the patient had failed prior therapy with other agents. We urge formal evaluation of ceftolozane/tazobactam in chronic pseudomonal lung infections.

Keywords: bronchiectasis; ceftolozane-tazobactam; pan-resistance; *Pseudomonas aeruginosa*.

Introduction

We present the case report of a 59-year-old man with chronic bronchiectasis whose pulmonary flora included *Pseudomonas aeruginosa* variants that were pan-resistant to licensed agents, and who failed to improve during therapy with high-dose meropenem combined with intravenous (i.v.) and nebulized colistin. Symptoms resolved during named-patient therapy with ceftolozane/tazobactam, a novel cephalosporin β-lactamase inhibitor combination, which was then under regulatory review and has subsequently been licensed by the US Food and Drug Administration for two non-pulmonary indications (Anonymous, 2014). Ceftolozane/tazobactam is notable for *in vitro* activity against *P. aeruginosa*

(Livermore *et al.*, 2009; Shlaes, 2013) and is expected to count towards the Infectious Disease Society of America's $10 \times '20$ Antimicrobial Initiative (Boucher *et al.*, 2013).

Case report

The patient had a long history of respiratory illness. He was a heavy smoker (30 day^{-1}) for almost 30 years but stopped in 1998. Since 1995, he had been admitted to hospital over 55 times, always for chest infections. He was diagnosed with bronchiectasis in 1997 and with chronic obstructive pulmonary disease (COPD) in 2004. Repeated exacerbations of COPD were treated with numerous courses of i.v. and *per os* (p.o.) antibiotics as well as steroids. Throughout 2007, he was treated with antibiotics every 5–6 weeks; later he was prescribed prophylactic doxycycline (100 mg every 24 h) for 1 week every month, aiming to reduce the need for rescue treatment. From 2009, his chest was colonized with *P. aeruginosa* and meticillin-resistant *Staphylococcus*

aureus (MRSA) and he was administered long-term nebulized colistin twice daily thereafter; he also received long-term oxygen therapy at home. By 2014, his self-reported exercise tolerance was 100 yards walking when well. He had received meropenem for 3 weeks around a month before the episode described here, and multiple courses of piperacillin/tazobactam (4.5 g every 8 h) around 4 months previously.

In April 2014 (day 0), the patient was admitted as an emergency case with an exacerbation of bronchiectasis. Symptoms included increased shortness of breath, increased oxygen requirement and increasing green sputum production. Sputum culture on day 1 grew MRSA and *P. aeruginosa* that was pan-resistant to licensed antibiotics, as confirmed by reference laboratory testing (Table 1). He was given linezolid 600 mg every 12 h p.o. and continued on nebulized colistin 10^6 U every 12 h. From day 2, the inhaled anti-pseudomonal therapy was supplemented with meropenem 2 g every 8 h i.v. and colistin 2×10^6 U every 8 h i.v., despite *in vitro* resistance to both agents. Meropenem infusion times were not extended. During this treatment, the patient deteriorated clinically, with white cell counts of 21.6×10^9–26.2×10^9 l^{-1} and C-reactive protein (CRP) of 200–326 µg ml^{-1}. His oxygen requirement rose to 70 % and he produced copious purulent green sputum. Linezolid was stopped on day 14, but the meropenem and i.v. colistin were continued until day 27 when, as there was little else to offer, a palliative care referral was made. The patient was discharged home, continuing on the long-term nebulized colistin and oxygen therapies (4 l min^{-1}). He was also given a further course of linezolid 600 mg every 12 h p.o., although there was no recent MRSA isolate. His condition continued to deteriorate and he was re-admitted on day 30 with shortness of breath at rest.

Further reference laboratory testing of the day 0 *P. aeruginosa* isolate with unconventional and developmental agents revealed a ceftolozane/tazobactam MIC of 8+4 µg ml^{-1} (see below), and the combination was sourced from Cubist Pharmaceuticals for 'named-patient' administration. Other antibiotics (linezolid, meropenem and colistin) were stopped and, on day 35, the patient began i.v. treatment with ceftolozane/tazobactam, 2+1 g every 8 h, administered as 1 h infusions. At this stage, his white cell count was 22.6×10^9 l^{-1} and has CRP was 152 µg ml^{-1}.

Progressive improvement was achieved during the ceftolozane/tazobactam therapy and, by the end of a 14-day course (day 49), the patient had ceased to produce sputum, no longer required supplemental oxygen and was breathing normally on air. His white cell count and CRP returned to baseline values of 14.7×10^9 l^{-1} and 21 µg ml, respectively. On day 58, he was discharged on linezolid 600 mg twice a day for 2 weeks (although, again, there was no recent MRSA isolate) and continued on long-term nebulized colistin. He was re-admitted on day 100 and remained in hospital until day 118 with a further infective exacerbation of bronchiectasis, for which he was administered meropenem 1 g every 8 h and gentamicin 5 mg kg^{-1} every

24 h, and also linezolid following re-isolation of MRSA on day 105. He was discharged on day 118, again on the nebulized colistin and with the infection controlled. He died on day 153.

Microbiological investigations

Susceptibility testing at the local laboratory was by British Society for Antimicrobial Chemotherapy (BSAC) disc diffusion (British Society for Antimicrobial Chemotherapy, 2012), whilst *P. aeruginosa* isolates sent to Public Health England's Antimicrobial Resistance and Healthcare Associated Infections Reference Unit were tested by BSAC agar dilution (Andrews, 2001) with BSAC/EUCAST breakpoints (European Committee on Antimicrobial Susceptibility Testing, 2014). Ceftolozane and piperacillin were tested with a fixed 4 µg tazobactam ml^{-1}. Referred isolates were fingerprinted by variable number tandem repeat (VNTR) typing (Turton *et al.*, 2010).

Local susceptibility results, which spanned exacerbations in late 2013 as well as the proximate episode, varied over time, with a trend to increasing resistance and with no agent retaining consistent activity (Table 1). The day 1 isolate received by the reference laboratory was resistant to all licensed anti-pseudomonal agents, including meropenem and colistin, which the patient was then receiving. This prompted testing of ceftolozane/tazobactam, where the MIC was recorded as 8+4 µg ml^{-1}, although with the majority population inhibited at 2+4 µg ml^{-1} with only isolated colonies growing on the 2 and 4 µg ml^{-1} plates. Typing revealed that the fully susceptible day −181 isolate and the highly resistant day 1 isolates shared the same VNTR profile (8, 3, 4, 5, 2, 3, 5, 2, 11), implying that a single infective strain was present, with fluctuating populations of variably resistant and susceptible variants.

Discussion

This patient, with a long history of pulmonary disease and treatment, had a complex pulmonary *P. aeruginosa* flora. As in cystic fibrosis (Ashish *et al.*, 2013), it is likely that this variation reflected repeated antibiotic use selecting for multiple subpopulations of the infective strain in the lung, varying in resistance but retaining a consistent VNTR type. The patient's exacerbation around day 0–1 involved a variant resistant to all licensed antibiotics and, in keeping with these *in vitro* results, he responded poorly to a meropenem/colistin regimen. Given this therapeutic failure, we afford little significance to isolating variants on days 11 and 22 (i.e. during the meropenem/colistin therapy) that were susceptible to one or both of these agents. This led to compassionate 'named-patient' therapy with ceftolozane/tazobactam, leading to a considerable clinical improvement.

There were no breakpoints available at the time when this patient was treated, but the combination has good penetration to the lung (Chandorkar *et al.*, 2012) and the MIC

Table 1. Susceptibility testing results

Antibiotic	Prior admissions*					Admission described here and subsequently				
	Day −181 Ref lab MIC (μg ml^{-1})	Day −146 Local	Day −33 Local	Day −29 Local	Day −6 Local	Day 1 Ref lab MIC (μg ml^{-1})	Day 11 Local	Day 22 Local	Day 52 Local	Day 56 Local
Amikacin	4 (S)	–	–	–	–	64 (R)	–	–	–	–
Gentamicin	2 (S)	S	S	S	S	32 (R)	S	S	S	R
Tobramycin	0.5 (S)	–	–	–	–	32 (R)	–	–	–	R
Ciprofloxacin	0.25 (S)	R	R	R	S	>8 (R)	R	R	R	R
Colistin	2 (S)	–	S	S	S	>32 (R)	S	S	R	S
Aztreonam	–	–	–	–	–	>64 (R)	–	–	–	–
Ceftazidime	2 (S)	–	R	R	R	32 (R)	R	R	R	S
Imipenem	0.25 (S)	–	–	–	–	64 (R)	–	–	–	–
Meropenem	2 (S)	–	S	S	R	32 (R)	R	S	R	R
Doripenem	–	–	–	–	–	8 (R)	–	–	–	–
Carbenicillin	64 (S)	–	–	–	–	512 (R)	–	–	–	–
Piperacillin	4 (S)	–	–	–	–	>64 (R)	–	–	–	–
Piperacillin/tazobactam	4 (S)	S	R	R	R	>64 (R)	R	R	S	S
Ceftolozane/tazobactam	–	–	–	–	–	2–8†	–	–	–	–

R, resistant; S, susceptible.

*Counted from the admission day that led to administration of ceftolozane/tazobactam.

†Most growth inhibited at 2 μg ml^{-1}; a few isolated colonies only inhibited at 8 μg ml^{-1}.

Bold font is used for reference laboratory MIC data and interpretation.

found (8 µg ml^{-1}, Table 1) was inferred to predict susceptibility based on: (i) analogy to ceftazidime, which has the same maximum dosage and a shorter half-life, with BSAC/EUCAST breakpoints of: sensitive, ≤8; resistant, >8 µg ml^{-1} (European Committee on Antimicrobial Susceptibility Testing, 2014) and (ii) pharmacodynamic modelling, indicating 1 log killing up to an MIC of 16 µg ml^{-1} (Lepak et al., 2014; VanScoy et al., 2014). As the MIC nevertheless was high compared with typical ceftolozane values of 0.25–0.5 µg ml^{-1} for P. aeruginosa (Livermore et al., 2009), a 2+1 g every 8 h regimen was employed, as presently in phase III trials for ventilator pneumonia, rather than the 1+0.5 g every 8 h regimen used in phase III urinary and intra-abdominal trials. The recent US Food and Drug Authority license for the latter two indications indicates P. aeruginosa breakpoints of sensitive, ≤4 µg ml^{-1}; intermediate, 8 µg ml^{-1}; resistant, ≥16 µg ml^{-1}, predicated on a 1+0.5 g every 8 h regimen (Anonymous, 2104), and the decision to use the higher-dose regimen is further justified with reference to these criteria.

In vitro studies show that the MICs of ceftolozane for P. aeruginosa typically are approximately four- to eightfold lower than for ceftazidime, which previously was the most active licensed cephalosporin against this species. MICs of ceftolozane for P. aeruginosa strains with upregulated efflux or derepressed AmpC β-lactamase rarely exceed 2–4 µg ml^{-1}, whereas ceftazidime MICs for isolates with these mechanisms range from 16 to 128 µg ml^{-1} (Livermore et al., 2009; Juan et al., 2010); High-level ceftolozane resistance in P. aeruginosa appears confined to strains with metallo-carbapenemases, PER and VEB extended-spectrum β-lactamases and some cystic fibrosis isolates with complex mixtures of mechanisms (Livermore et al., 2009; Juan et al., 2010). Tazobactam protects ceftolozane against the extended-spectrum β-lactamases of Enterobacteriaceae but has limited relevance to anti-pseudomonal activity (Shlaes, 2013). Given these data, and assuming regulatory approval, it seems likely that ceftolozane/tazobactam will often be the most active agent in vitro against difficult P. aeruginosa strains from chronic pulmonary infections, including cystic fibrosis and COPD. We urge that trials should be done in these settings to validate its therapeutic potential and to test whether the success described here is representative.

Acknowledgements

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