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Letter to the Editor

Salvage therapy for complex bone and joint infections with ceftaroline: a multicentre, observational study

Sir,

Bone and joint infections (BJIs) require complex treatment strategies, including surgical procedures and prolonged antimicrobial therapy, and are associated with significant morbidity and mortality. Multidrug-resistant micro-organisms, particularly staphylococci, represent a therapeutic challenge, with high rates of treatment failure [1].

Ceftaroline fosamil is a broad-spectrum cephalosporin antibiotic with activity against Enterobacteriaceae and Gram-positive organisms, including methicillin-resistant staphylococci [2]. Based on its in vitro activity, ceftaroline could be a potential therapeutic option for the treatment of prosthetic joint infection (PJI), either polymicrobial or caused by methicillin-susceptible or methicillin-resistant (MR) *Staphylococcus aureus* and *Staphylococcus epidermidis*. The activity of ceftaroline has been established in experimental MR *S. aureus* acute osteomyelitis and PJI [3,4]. However, there are only a few clinical data assessing the role of ceftaroline in the management of BJI as well as regarding optimal dosing and the safety of prolonged exposure.

Therefore, a retrospective study was performed to evaluate the efficacy and safety of ceftaroline for the treatment of BJI in three regional reference centres in France. All patients presenting between January 2013 and January 2015 with a microbiologically documented BJI and treated with ceftaroline for ≥48 h were selected. BJI was defined as the presence of local signs of infection with or without symptoms of general sepsis. Microbiological documentation required at least one positive culture from surgical specimens in the case of a typical micro-organism, such as *S. aureus* or Enterobacteriaceae, and at least two identical samples yielding the same pathogen in the case of a skin bacterium, such as coagulase-negative staphylococci (CoNS), *Propionibacterium* spp., *Corynebacterium* or *Lactobacillus*. Clinical outcome was assessed by the treating physician using standard criteria. Microbiological failure associated with clinical failure was defined as either a superinfection when a new pathogen was identified or as a recurrence when the initial micro-organism persisted.

Baseline clinical and microbiological characteristics as well as treatment duration and outcome for the 19 patients included in the study are shown in Table 1. Most infections (16/19) involved orthopaedic devices (11 prosthesis and 5 osteosynthesis). Patients had experienced a mean of 3 surgical procedures [interquartile range (IQR) 5], most of them for BJI (11/15). *Staphylococcus epidermidis* was considered the causative agent of infection in 15 of 19 cases, with 11 (73.3%) of the 15 isolates being MR. The infection was polymicrobial in 16 cases (84.2%). Ceftaroline was administered for a median duration of 6 weeks (IQR 5.5 weeks) at a dose of 600 mg twice daily (b.i.d.) ($n = 11$) or 600 mg three times daily (t.i.d.) ($n = 8$). Ceftaroline was given in combination with at least one other antibiotic in 17 cases (89.5%), mostly rifampicin ($n = 7$), trimethoprim/sulfamethoxazole (SXT) ($n = 3$), fosfomycin ($n = 2$), linezolid ($n = 2$), vancomycin ($n = 1$), daptomycin ($n = 1$) or metronidazole ($n = 2$). Two cases of neutropenia were reported during treatment with ceftaroline, one in a 16-year-old male after 2 weeks of treatment at a dose of 600 mg t.i.d. and one in an 86-year-old woman after 8 weeks at a dose of 600 mg b.i.d. In both cases, ceftaroline was discontinued with rapid recovery of neutropenia. Two rashes were deemed related to ceftaroline and led to treatment interruption. The final outcome was cure in seven cases with a median follow-up of 6 months after the end of treatment, and failure in seven cases (six superinfections and one recurrence).

To the best of our knowledge, this is the largest report on the clinical use of ceftaroline for the treatment of BJI. Owing to the retrospective design of the study and the complexity of management of many cases, it is difficult to draw definitive conclusions on the efficacy of this broad-spectrum cephalosporin and its specific role in this clinical situation. Nevertheless, it is noteworthy that only one recurrence was encountered, the other failures being superinfections due to other bacteria. CoNS, and among them *S. epidermidis*, cause an increasing number of BJIs, especially PJIs. These commensal skin bacteria behave like opportunistic pathogens and frequently carry genes leading to multidrug resistance, with up to 80% of strains being MR. Of note, in this series, susceptibility to levofloxacin and fusidic acid was observed in only 35% of cases. Hence, there is a need to evaluate the clinical efficacy and safety of antimicrobials with in vitro activity against isolates associated with BJI, and particularly resistant micro-organisms found in BJI. Haematological tolerance to ceftaroline is an issue that has been recently raised. In one study, the incidence of neutropenia was 14% and 21% in patients exposed for >2 weeks and >3 weeks, respectively [5]. Such an adverse event is well known with other β-lactams and, although there are no comparative figures, its incidence seems higher with ceftaroline. The exact mechanism of ceftaroline-induced myelosuppression is still unknown. In the current series, neutropenia occurred in a patient receiving a high dose of 600 mg t.i.d., but also in one patient with the standard 600 mg b.i.d. We cannot exclude that co-administration of SXT might have played a part in the first case. From a practical point of view, except duration of exposure, it seems impossible to identify other risk factors for myelotoxicity at the present stage of our knowledge, and it is probably wise to monitor complete blood counts weekly for the full course of treatment.

In conclusion, ceftaroline is a treatment option for the management of BJI, either polymicrobial or due to multidrug-resistant CoNS, but close monitoring of haematological parameters is warranted in patients receiving >2 weeks of treatment.

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Table 1
Clinical and microbiological characteristics of 19 patients treated with ceftaroline (CPT) for bone and joint infection.

Patient	1	2	3	4	5	6	7	8	9	10
Patient characteristics										
Age (years)	70	16	61	23	83	38	88	84	44	86
Sex	F	M	M	M	F	F	F	M	F	F
BMI (kg/m^2)	21	23.7	28.7	15.8	25	19.9	37.1	19.5	20.3	22.7
CL_{Cr} (mL/min)	50.6	137	132	143	73.8	107.9	60	28.7	140.7	86.2
Orthopaedic device	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
No. of previous surgical procedures	3	7	2	3	5	0	0	0	3	9
Microbiological data										
Polymicrobial infection	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bacteria 1	MRSE	MRSE	MRSE	MRSE	MRSE	*Pseudomonas aeruginosa*	MRSE	MSSE	MRSE	MSSE
Bacteria 2	*Proteus mirabilis*	MRSE	*Enterococcus faecalis*	*Staphylococcus capitis*	*Peptostreptococcus asaccharolyticus*	*Streptococcus mitis*		*Enterococcus faecium*	*Corynebacterium aurimucosum*	MRSE
Bacteria 3		MRSE	*Enterobacter cloacae*	*Escherichia coli*		*Streptococcus parasanguinis*			*S. mitis*	
Bacteria 4				*P. mirabilis*		MSSE				
Bacteria 5				*Propionibacterium avidum*		*Candida albicans*				
Bacteria 6				*Bacteroides fragilis*						
Antibiotic treatment										
Reason of CPT choice	Multiresistant staphylococci	Multiresistant staphylococci	Multiresistant staphylococci	Polymicrobial infection	Multiresistant staphylococci	Polymicrobial infection	Renal failure	Renal failure	Multiresistant staphylococci	Multiresistant staphylococci
CPT daily dose	600 mg × 3	600 mg × 3	600 mg × 3	600 mg × 3	600 mg × 3	600 mg × 2	600 mg × 2	600 mg × 2	600 mg × 2	600 mg × 2
Associated antibiotics	Rifampicin	SXT	Rifampicin, levofloxacin	Fosfomycin, SXT, metronidazole, fluconazole	Rifampicin, clindamycin	Colistin, metronidazole, fluconazole	Rifampicin	Linezolid	Rifampicin	Daptomycin
CPT duration (weeks)	12	4	12	2	6	17	6	5	4	27
Reason for CPT discontinuation	EOT	Neutropenia	EOT	Simplification	EOT	EOT	Suppressive treatment	Suppressive treatment	Simplification	Neutropenia
Outcome										
EOT	Clinical cure	Clinical cure	Clinical cure	Clinical cure	Failure	Clinical cure	Failure	Failure	Clinical cure	Failure
6 months	NR	Clinical cure	Failure	Clinical cure	Failure	Clinical cure	Failure	Failure	Clinical cure	Failure
1 year	NR	Failure	Failure	Clinical cure	Failure	Failure	Failure	Failure	NR	Failure

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