Ceftaroline-Fosamil Efficacy against Methicillin-Resistant *Staphylococcus aureus* in a Rabbit Prosthetic Joint Infection Model

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Ceftaroline (CPT), the active metabolite of the prodrug ceftaroline-fosamil (CPT-F), demonstrates *in vitro* bactericidal activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and is effective in rabbit models of difficult-to-treat MRSA endocarditis and acute osteomyelitis. However, its *in vivo* efficacy in a prosthetic joint infection (PJI) model is unknown. Using a MRSA-infected knee PJI model in rabbits, the efficacies of CPT-F or vancomycin (VAN) alone and combined with rifampin (RIF) were compared. After each partial knee replacement with a silicone implant that fit into the tibial intramedullary canal was performed, 5×10^7 MRSA CFU (MICs of 0.38, 0.006, and 1 mg/liter for CPT, RIF, and VAN, respectively) was injected into the knee. Infected animals were randomly assigned to receive no treatment (controls) or CPT-F (60 mg/kg of body weight intramuscularly [i.m.]), VAN (60 mg/kg i.m.), CPT-F plus RIF (10 mg/kg i.m.), or VAN plus RIF starting 7 days postinoculation and lasting for 7 days. Surviving bacteria in crushed tibias were counted 3 days after ending treatment. Although the *in vivo* mean $\log_{10}$ CFU/g of CPT-treated (3.0 ± 0.9 , $n = 12$) and VAN-treated (3.5 ± 1.1 , $n = 12$) crushed bones was significantly lower than those of controls (5.6 ± 1.1 , $n = 14$) ($P < 0.001$), neither treatment fully sterilized the bones (3/12 were sterile with each treatment). The mean $\log_{10}$ CFU/g values for the antibiotics in combination with RIF were 1.9 ± 0.5 (12/14 were sterile) for CPT-F and 1.9 ± 0.5 (12/14 were sterile) for VAN. In this MRSA PJI model, the efficacies of CPT-F and VAN did not differ; thus, CPT appears to be a promising antimicrobial agent for the treatment of MRSA PJIs.

Orthopedic joint replacement is an increasingly common surgical procedure worldwide, reflecting the aging of the population (1). While prosthetic joint infection (PJI) is uncommon, it can be a serious complication which entails major morbidity and high costs (1). Perioperative contamination is responsible for most PJIs, which are mainly caused by *Staphylococcus aureus* or *Staphylococcus epidermidis* (2). These microorganisms are often resistant to many commonly used antibiotics. At present, vancomycin (VAN) or daptomycin (DAP) combined with rifampin (RIF) is recommended as the first-line therapy of device-related osteoarticular infections due to methicillin-resistant *S. aureus* (MRSA) (3). However, the efficacy of VAN might not be optimal when the MIC of the responsible strain is $>1 \mu\text{g/ml}$ (3, 4). Strains with reduced susceptibilities to DAP were described in experimental PJI models and in patients without treatment and in those after VAN or DAP administration (4, 5). Thus, alternative therapies are still needed.

Ceftaroline (CPT) is a broad-spectrum cephalosporin with a high *in vitro* affinity for penicillin-binding protein 2a and bactericidal activity against MRSA. CPT is the active metabolite of the prodrug ceftaroline-fosamil (CPT-F). This compound was recently approved in the United States for the treatment of complicated skin and skin structure infections caused by Gram-positive bacteria. It was effective against rabbit models of difficult-to-treat MRSA endocarditis and acute osteomyelitis (6, 7), but the *in vivo* efficacy of CPT against a MRSA PJI model (4, 8, 9) has not been tested. This study was undertaken to compare the efficacies of CPT-F or VAN alone or combined with RIF against MRSA in a knee PJI model in rabbits that closely simulates human infection. The *in vivo* emergence of strains with reduced susceptibilities to VAN, DAP, RIF, or CPT in untreated and treated rabbits was also investigated.

(This work was presented in part at the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Denver, CO, 9 to 13 September 2013 [10]).

MATERIALS AND METHODS

Test strain. This study used MRSA strain ST20121238, which had been isolated from a patient with an infected knee prosthesis. Its virulence was maintained by intraperitoneal injection into mice.

***In vitro* antibiotic susceptibility testing.** CPT, VAN, and RIF MICs were determined with the Etest method (bioMérieux, La Balme-les-Grottes, France), as recommended by the manufacturer. A single inoculum, which was adjusted to a McFarland standard of 0.5 in distilled water, was used. Mueller-Hinton agar plates (Bio-Rad, Marnes-la-Coquette, France) were inoculated with swabs that were saturated with a suspension of the test organism and incubated for 18 h at 37°C. The MIC was defined as the value at which the inhibition zone intersected the scale of the Etest strip.

Time-kill curve studies. The bactericidal activities of CPT or VAN alone or combined with RIF were determined. Overnight cultures were diluted in 10 ml of fresh Mueller-Hinton broth to yield an inoculum of 10^6 CFU/ml. The antibiotic concentrations used were equivalent to $4 \times \text{MIC}$ for CPT, VAN, or RIF. After 0, 3, 6, and 24 h of incubation in a shaking water bath at 37°C, serial dilutions of 0.1-ml samples were subcultured on Mueller-Hinton agar plates (Bio-Rad) and incubated at 37°C for 24 h.

Received 11 June 2014 Returned for modification 7 July 2014

Accepted 10 August 2014

Published ahead of print 18 August 2014

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doi:10.1128/AAC.03600-14

before the numbers of CFU were counted. A bactericidal effect was defined as a ≥ 3 -log₁₀ decrease of the initial inoculum. Synergy was defined as a decrease of ≥ 2 log₁₀ CFU/ml for the combination versus its most active constituent after 24 h of incubation.

Experimental PJI. New Zealand White rabbits, each weighing 2.5 to 3 kg, were used. They were housed in individual cages with natural light-dark cycles. The experimental protocol was in keeping with French legislation on animal experimentation and was approved by the Animal Use Committee of Maisons Alfort Veterinary School.

This model was previously described in detail (11). Briefly, each rabbit underwent partial right knee replacement with a tibial component by an orthopedic surgeon. The surgery was carried out under general anesthesia induced by intramuscular (i.m.) injection of ketamine (Ketamine 1000; Virbac, Carros, France) (25 mg/kg of body weight) and 25 mg/kg of 2% xylazine (Rompun; Bayer Santé, Division Santé Animal, Puteaux, France) and then by continuous inhalation of 1% isoflurane (Vetflurane; Virbac). The skin overlying the right leg was shaved before the operation and cleaned with an iodine solution prior to surgery. A longitudinal skin incision was made, and the knee joint was exposed. After dislocation of the tibia, the epiphyseal plates were removed. The metaphysis was exposed, and the cancellous bone of the medullary cavity of the proximal metaphysis was reamed. A silicone elastomer implant, commonly used in arthroplasty of the first metatarsophalangeal joint (Silastic, great toe implant HP; Swanson Design, Dow-Corning [provided by Wright Medical France, Créteil, France]), was implanted as a tibial prosthetic component. The stem of the nail-shaped silicone implant (14 mm long) was inserted into the intramedullary canal of the tibia; the implant head (15 mm in diameter and 5 mm high) replaced the tibia plateau. Then, the deep fascia and the skin were closed. Immediately after surgery, the animals were inoculated with 5×10^7 MRSA CFU in a final volume of 0.5 ml in phosphate-buffered saline by injection into the knee close to the prosthesis. Each rabbit was given patch analgesia (Durogesic; Janssen-Cilag SA, Issy-les-Moulineaux, France) for 7 days following surgery. At least 12 rabbits were randomly assigned to each untreated or treated group, with five groups in total.

Plasma CPT levels. Plasma CPT levels in the uninfected rabbits were determined. Initial doses were selected based on previous experimental studies in rabbits (6, 7), and we verified that they achieved pharmacokinetic (PK) and pharmacodynamic (PD) parameters equivalent to those obtained in humans who had received 600 mg of CPT intravenously (i.v.) twice daily (b.i.d.) (i.e., similar areas under the concentration-time curve from 0 to 24 h [AUC₀₋₂₄]) and the plasma CPT concentration in this study was at least the MRSA strain ST20121238 MIC for 50% of the 12-h between-dose periods (12). To achieve equivalence, five rabbits received three i.m. injections of CPT-F. To determine the CPT concentrations, blood was drawn after the injections at 15 min and at 1, 2, 4, 6, 8, and 12 h and frozen until assayed. Samples were analyzed by liquid chromatography-mass spectrometry with an API4000 triple-quadrupole mass spectrometer equipped with a Leap auto sampler and Shimadzu high-performance liquid chromatograph. Samples were processed on ice to minimize ceftaroline hydrolysis. Basic PK parameters were calculated by Phoenix WinNonlin V6.2 using noncompartmental analysis. The lower limit of quantitation was 0.001 mg/liter.

Treatment and evaluation. At 7 days postinfection, rabbits began treatment with CPT-F (60 mg/kg of body weight i.m. b.i.d.) or VAN (60 mg/kg i.m. b.i.d.) alone or combined with RIF (10 mg/kg i.m. b.i.d.). VAN and RIF doses were selected based on previous experiments (13) that showed that they obtained concentrations close to those recommended for humans (i.e., trough VAN concentrations of 15 to 20 mg/liter and RIF doses equivalent to a 900-mg daily dose) (3). The CPT-F dose was selected based on the PK study described above. Each regimen was administered for 7 days. Controls were untreated.

Each animal was killed by i.v. injection of pentobarbital 3 days after the end of therapy (i.e., on day 17) to allow for bacterial regrowth after stopping treatment while avoiding the persistence of residual antibiotic in the

bone. Untreated control rabbits were also killed on day 17. Each right hind leg was dissected, and the tibia and femur were separated from the surrounding soft tissues. A smear of the prosthesis was performed on a blood agar plate. For quantitative bacterial counts, the upper third of the tibia (3 cm long), including compact bone and marrow, was isolated, split with a bone crusher, weighed, cut into small pieces, and crushed in an autopulverizer (MM 200; Retsch GmbH, Haan, Germany). The pulverized bone was suspended in 20 ml of sterile water; serial dilutions were made (by adding 9 ml of sterile water to 1 ml of the first suspension and repeating this operation 5 times to obtain a 1/100,000 dilution) and plated (100 μ l of diluted suspensions) on Columbia agar with 5% sheep blood agar (bioMérieux, Marcy l'Etoile, France). After 24 h of incubation at 37°C, the number of viable microorganisms was determined. Results are expressed as means $\pm$ standard deviations (SD) of the log₁₀ CFU/g of bone and as the number of animals with sterile bone. Bone was considered sterile when the culture showed no growth after incubation for 48 h at 37°C and the number of CFU recorded was the lowest detectable bacterial count (1.64 to 1.84 log₁₀ CFU/g of bone, depending on sample weight).

In vivo selection of mutants. Mutated MRSA resistant to CPT, VAN, or RIF was sought in all control and treated rabbits with positive bone cultures at the end of the treatment period. DAP-resistant strains were also sought in the control and treated rabbits, because previous findings (4) showed that they were found in untreated and VAN-treated rabbits. Each undiluted bone homogenate (50 μ l) was plated onto Mueller-Hinton II agar and onto Mueller-Hinton II agar supplemented with VAN (0.25, 0.5, 1, or 2 mg/liter), CPT (0.125, 0.25, or 0.5 mg/liter), or DAP (0.5, 1, or 2 mg/liter) plus calcium chloride (50 mg of Ca²⁺/liter) to detect potentially emerging resistant mutants after 72 h of incubation at 37°C. When bacterial growth was observed, the colonies were counted, and *S. aureus* identification was confirmed using matrix-assisted laser-desorption ionization-time of flight mass spectrometry (Vitek MS; bioMérieux). An inoculum at a 0.5 McFarland standard was used to determine the DAP, VAN, RIF, CPT, and oxacillin MICs with Etests (bioMérieux). The Etest was read after 20 h of incubation at 37°C. The results are expressed quantitatively as the number of bacteria grown on antibiotic-containing medium and are reported as the number of mutants/g of bone. Mutants were defined as having a 3-fold-greater MIC than that of the initial strain.

Statistical analyses. The results are expressed as means $\pm$ SD. Bacterial densities in bone were compared among the experimental groups by analysis of variance, followed by Scheffé's test for multiple comparisons. *P* values of <0.05 defined significance.

RESULTS

In vitro studies. The CPT, VAN, RIF, and DAP MICs were 0.38, 1, 0.006, and 0.064 mg/liter, respectively.

In vitro killing. Curves obtained at 4 $\times$ MIC (Fig. 1) showed CPT bactericidal activity with or without RIF. RIF enhanced the VAN and CPT killing rates by approximately 2 log₁₀ CFU and 1 log₁₀ CFU, respectively, at 24 h.

CPT levels in rabbits. After three CPT-F injections (60 mg/kg i.m. b.i.d.), the mean peak plasma concentration (15 min after injection) in five uninfected animals was 37.9 mg/liter at a maximum time of 1 h postinjection. The mean AUC₀₋₂₄ was 76.2 mg $\cdot$ h/liter. With this dose, the plasma concentrations exceeded that of the test-strain MIC >50% of the time between two injections.

Therapeutic studies. All control animals infected with MRSA strain ST20121238 had positive prosthesis smear cultures, and the mean $\pm$ SD bacterial count in these animals was 5.66 ± 1.15 log₁₀ CFU/g of bone (Table 1). Only three of the 12 CPT-treated animals and three of the 12 VAN-treated animals had sterile bones, even though their mean bone bacterial densities were significantly lower than that of the control animals (*P* < 0.01). The mean bacterial counts of CPT- and VAN-treated animals were comparable. Adjunctive RIF with CPT or VAN was significantly more effective

FIG 1 *In vitro* time-kill curves for methicillin-resistant *Staphylococcus aureus* strain ST20121238, using different antibiotics and combinations thereof at concentrations equivalent to 4× MIC. CPT, ceftaroline; VAN, vancomycin; RIF, rifampin.

than monotherapy. VAN-RIF and CPT-RIF achieved sterile bone in 12 of 14 rabbits in each group. The mean bacterial counts of the two groups were significantly lower than those of the untreated controls and of the groups treated with either agent alone (Fig. 2).

Subpopulation analysis of untreated and treated rabbits. No CPT-, VAN-, or RIF-resistant mutant strains were detected in the treated or untreated animals. Conversely, DAP-resistant mutant strains (i.e., MICs of 0.75 mg/liter [$n = 2$] or 1 mg/liter [$n = 1$]) emerged in 3/11 untreated rabbits, with >100 mutant CFU/g of bone in each of the three animals. In 3/9 VAN-treated animals, DAP-resistant mutant strains emerged and had MICs of 0.5 mg/liter ($n = 1$) and 1.5 mg/liter ($n = 2$), and the strain with a 1.5-mg/liter MIC reached the DAP breakpoint of 1 mg/liter. Mutant density ranged from 3 to >100 CFU/g (Tables 2 and 3). DAP-resistant mutant strains did not emerge with CPT alone, CPT-RIF, or VAN-RIF.

All six postinfection DAP-resistant mutant strains had reduced oxacillin MICs (i.e., a seesaw effect). In contrast, the CPT and VAN MICs remained stable in those mutant strains (Table 3).

DISCUSSION

The results of this study show that VAN or CPT-F had comparable efficacies alone or combined with RIF in a rabbit model of MRSA PJI when a CPT dose equivalent to a human dose of 600 mg i.v. b.i.d. was administered (12). Indeed, the mean CPT AUC_{0–24} in the rabbits was 76.2 mg · h/liter versus 65 mg · h/liter in healthy

FIG 2 Antibiotic effect against a rabbit methicillin-resistant *Staphylococcus aureus* strain ST20121238 prosthetic knee infection model. Rabbits were injected for 14 days with ceftaroline (CPT) (60 mg/kg i.m. b.i.d.) or vancomycin (VAN) (60 mg/kg i.m. b.i.d.) alone or combined with rifampin (RIF) (10 mg/kg i.m. b.i.d.). Bone was considered sterile when the culture showed no growth after incubation for 48 h at 37°C and the number of recorded CFU was the lowest detectable bacterial count (1.64 to 1.84 CFU/g of bone, depending on the weight of the sample).

adults (12), and the mean peak plasma concentrations in the rabbits and in healthy adults were 38 mg/liter and 31 mg/liter, respectively. With this equivalent dose the plasma CPT concentration in this study exceeded the test strain MIC for >50% of the 12-h between-dose periods; this concentration provided a suitable PD parameter to obtain a bactericidal effect *in vitro* and *in vivo* (14).

Unlike linezolid, CPT was bactericidal *in vivo* against a rabbit model of MRSA endocarditis (6). In that model, the efficacy of linezolid did not differ from that of VAN. In an acute MRSA-infected osteomyelitis rabbit model (7), CPT significantly decreased the bacterial densities in joint fluid, bone marrow, and bone, while VAN was poorly active and caused no significant reduction of the bacterial densities after 4 days of treatment. A combination with RIF was not tested.

In our PJI model, the VAN and CPT-F monotherapies were

TABLE 1 Antibiotic efficacy against experimental methicillin-resistant *Staphylococcus aureus* prosthetic knee infection model in rabbits

Treatment ^a	No. of rabbits with sterile bone/total no. of rabbits	log ₁₀ CFU/g of bone (mean ± SD)
None	0/14	5.66 ± 1.15
CPT-F	3/12	2.96 ± 0.92 ^b
VAN	3/12	3.51 ± 1.10 ^b
CPT-F plus RIF	12/14	1.87 ± 0.46 ^c
VAN plus RIF	12/14	1.91 ± 0.46 ^c

^a For 7 days, rabbits were injected with CPT-F (60 mg/kg i.m. b.i.d.) or VAN (60 mg/kg i.m. b.i.d.) alone or combined with RIF (10 mg/kg i.m. b.i.d.).

^b Significantly different versus untreated controls ($P < 0.01$).

^c Significantly different versus monotherapy ($P < 0.01$).

TABLE 2 Emergence of DAP-resistant mutants^a in rabbits with methicillin-resistant *Staphylococcus aureus* prosthetic knee infection

Treatment group	DAP-resistant mutant emergence by antibiotic (MIC [mg/liter] of the initial strain) ^b		
	VAN (1)	DAP (0.064)	CPT (0.38)
Control	0/11	3/11	0/11
VAN	0/9	3/9	0/9
CPT-F	0/9	0/9	0/9

^a A mutant strain was defined as having a 3-fold-greater MIC than that of the initial strain.

^b Numbers of rabbits with DAP-resistant mutants appearing/total no. of rabbits in group.

TABLE 3 Antibiotic MICs of the DAP-resistant mutant strains that showed a seesaw effect in six rabbits

Treatment group and rabbit no.	MIC (mg/liter) (initial MIC, mg/l) for:			
	DAP (0.064)	VAN (1)	Oxacillin (1)	CPT (0.38)
Control				
1	0.75	2	0.19	0.5
2	0.75	2	0.25	0.5
4	1	2	0.38	1
VAN				
21	0.5	2	0.38	0.5
30	1.5	2	0.38	0.5
38	1.5	2	0.38	0.5

effective. The combination with RIF significantly increased their efficacies and sterilized bone in most of the animals. This remarkable efficacy achieved with additional RIF is not surprising. It was previously described in the same model (4) and in other experimental bone and joint models with other companion drugs long ago (9). It is thought to be due to the bactericidal activity of RIF against slow-growing enclosed bacteria (15). However, our results confirm its efficacy in combination with CPT-F, with no emergence of RIF-resistant strains in this model of difficult-to-treat infection, and its ability to allow retention of the infected prosthesis.

We previously showed that less susceptible DAP-resistant mutant strains were selected in untreated animals with PJI (4). The natural emergence of DAP-resistant mutant strains could reflect the organism's exposure to endogenous host defense cationic peptides, because those strains exhibited cross-resistance to those peptides (5). Similar mutant emergence was observed herein, which thereby confirms the reproducibility of this phenomenon. VAN did not prevent the emergence of DAP-resistant mutant strains, as in our previous study (4), despite the unchanged VAN MICs of those DAP-resistant mutant strains. In contrast, no DAP-resistant mutant strain could be detected in the CPT-treated rabbits. This absence may be explained by the bactericidal effect of CPT on the DAP-resistant strains (i.e., no cross-resistance). Indeed, DAP-resistant strains were susceptible to CPT; the MICs were unchanged compared to those of the initial strain. Interestingly, the oxacillin MICs of all of those mutant strains were diminished 2-fold, which suggests a so-called oxacillin-DAP seesaw effect (5). CPT-F might be a therapeutic option for treatment failures due to the emergence of DAP-resistant strains as either an alternative therapy or combined with DAP. Indeed, clinical observations (16) and *in vitro* data (17) suggest that adding CPT to DAP could restore DAP susceptibility to DAP-resistant strains (16).

Our study has several limitations. The main one is that, like most experimental studies, we used a single MRSA strain. The CPT MIC of this strain was less than the MIC₉₀ of MRSA (18), and a higher CPT-F dose might be necessary for strains that have higher MICs. Also, we used a silicone elastomer implant, and microbiological findings may be modified by the use of other compounds (e.g., metallic implants, such as titanium or stainless steel), which are often used in orthopedic surgery. Moreover, treatment was started 7 days postinoculation to simulate an acute postoperative infection, and antibiotics might be less effective against a more chronic infection. Advantages of the rabbit model used in this study include its similarity with human acute early postoperative PJI and its reproducibility.

In conclusion, in this experimental rabbit model of MRSA PJI, CPT-F was as effective as VAN. CPT-F appears to be a promising antimicrobial agent for the treatment of MRSA PJIs.

ACKNOWLEDGMENTS

This work was supported in part by a research grant from AstraZeneca, France.

We thank Omar Aimé and Thomas Lilin's team for their help during the experimental process.

A.-C.C. has received grants from Janssen-Cilag, Novartis, AstraZeneca, Aventis, and Heraeus for consultancies, workshops, and travel to meetings and accommodations. The other authors report no conflicts of interest regarding this study.

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