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## Evaluation of the *in vivo* efficacy of intramuscularly administered ceftaroline fosamil, a novel cephalosporin, against a methicillin-resistant *Staphylococcus aureus* strain in a rabbit endocarditis model

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Sir,

Ceftaroline fosamil is the prodrug form of a novel, parenteral, broad-spectrum cephalosporin, ceftaroline, exhibiting bactericidal activity against Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), as well as

common Gram-negative pathogens.<sup>1</sup> To date, Phase III trials using intravenous (iv) administration of ceftaroline fosamil (herein after referred to as ceftaroline) have been completed for complicated skin and skin structure infections and for community-associated pneumonia.

Pathogens such as MRSA are becoming more virulent and are no longer confined to acute-care settings.<sup>2</sup> Ceftaroline may be administered by both iv and intramuscular (im) routes, facilitating outpatient antibiotic therapy for MRSA. Recently, Ge *et al.*<sup>3</sup> assessed the pharmacokinetic profile for iv and im ceftaroline treatment in different animal species, and demonstrated favourable pharmacokinetic profiles following im administration. Teicoplanin, a glycopeptide antibiotic, may be administered either intravenously or intramuscularly and was used as a positive control.

The aim of the present study was to assess the *in vivo* activity of three different doses of ceftaroline against MRSA compared with teicoplanin after im administration in a rabbit model of endocarditis.

In the present study, we used an MRSA strain (P9) isolated from blood cultures exhibiting heterogeneous high-level methicillin resistance (methicillin MIC = 128 mg/L).<sup>4</sup> MICs of ceftaroline, teicoplanin and vancomycin were 1, 0.5 and 1 mg/L, respectively.

*In vivo* studies were performed with New Zealand white female rabbits weighing 2.5–3.0 kg. Animals were treated in accordance with institutional policies and the guidelines stipulated by the animal welfare committee. The Committee of Animal Ethics of the University of Nantes approved all animal experimentation in this study. Using a well-established rabbit endocarditis model,<sup>5</sup> experimental endocarditis was induced with an inoculum of 10<sup>8</sup> cfu of the MRSA isolate. Treatment was started 24 h after inoculation and antibiotics (ceftaroline and teicoplanin) were administered twice daily using the im route for 4 days. Animals (10 per group) were randomly assigned to no treatment (controls), 40 mg/kg ceftaroline im twice daily, 20 mg/kg ceftaroline im twice daily, 5 mg/kg ceftaroline im twice daily or 20 mg/kg teicoplanin im twice daily.

Animals were euthanized at the beginning of the treatment period (controls) or at the end of the im treatment (12 h after the last injection). Aortic valve vegetations were excised, weighed and homogenized in 0.5 mL of saline buffer and used for quantitative cultures on agar. Bacterial counts were determined after 24 h of incubation at 37°C. The lower detection limit was 1 cfu per 50 µL of undiluted vegetation homogenate.

Statistical analyses were performed with GraphPad Prism software (version 4.0; GraphPad Software, San Diego, CA, USA). Analysis of variance was used to compare the antibacterial effects (bacterial counts) between the different groups, followed by a Bonferroni's test to compare groups two by two. A *P* value of ≤0.05 was considered significant.

After im administration of 5, 20 and 40 mg/kg doses of ceftaroline, the *C*<sub>max</sub> increased approximately in proportion to the dose (5.18, 15.75 and 37.85 mg/L, respectively) and the plasma half-life increased from 0.74 to 1.14 h.

The *in vivo* outcome after a 4 day treatment regimen and the rate of sterilization of the vegetations produced by the MRSA strain are shown in Table 1. A dose-dependent response was

**Table 1.** Bacterial titres in vegetations after 4 days of treatment

Regimen	Mean $\pm$ SD log <sub>10</sub> cfu/g of vegetation (no. of sterile vegetations/total no. of vegetations) (%)
Controls	8.99 $\pm$ 0.47 (0/10) (0)
Ceftaroline 40 mg/kg im	2.45 $\pm$ 0.14 (10/10) (100) <sup>a,b,c</sup>
Ceftaroline 20 mg/kg im	3.14 $\pm$ 1.38 (8/10) (80) <sup>a,d</sup>
Ceftaroline 5 mg/kg im	5.26 $\pm$ 2.73 (3/9) (33) <sup>a</sup>
Teicoplanin 20 mg/kg im	3.07 $\pm$ 0.66 (6/10) (60) <sup>a,d</sup>

<sup>a</sup> $P < 0.001$  versus controls.

<sup>b</sup> $P < 0.001$  versus 5 mg/kg ceftaroline im regimen; Bonferroni's test after analysis of variance.

<sup>c</sup> The titres for vegetations from all animals in the group were below the limit of detection.

<sup>d</sup> $P < 0.05$  versus 5 mg/kg ceftaroline im regimen.

observed with sterilization rates for ceftaroline of 100%, 80% and 33% for the 40, 20 and 5 mg/kg ceftaroline doses, respectively. The difference between the 20 and 40 mg/kg doses was not statistically significant ( $P > 0.05$ ). *In vivo* bactericidal activity was consistent across all animals tested at the 40 mg/kg dose and for most animals (8/10) at the 20 mg/kg dose of ceftaroline. As a positive control, 20 mg/kg teicoplanin im demonstrated bactericidal activity, with a sterilization rate of 60%.

Using murine thigh and lung infection models, Andes and Craig<sup>6</sup> determined that the  $T_{>MIC}$  was the pharmacokinetic-pharmacodynamic parameter that best correlated with efficacy of ceftaroline. In our study, the mean % $T_{>MICs}$  for a 1 mg/L target with 20 mg/kg ceftaroline given by im injection were 46% and 31% over 8 and 12 h, respectively.

Using an infective endocarditis rabbit model, the % $T_{>MICs}$  attained with im administration were associated with bactericidal activity against MRSA after a 4 day treatment. The efficacy of im ceftaroline in the present study was similar to that achieved previously with iv ceftaroline administered in a regimen simulating the human dose (i.e. 600 mg twice daily).<sup>6</sup> As expected, 20 mg/kg teicoplanin im displayed activity against the MRSA strain, with a sterilization rate of 60%, and bacterial titres appeared to be similar to those observed with vancomycin against the same MRSA strain.<sup>7</sup> Currently, teicoplanin is the only anti-MRSA drug approved as an im injection; however, it is not available in the USA. However, reduced susceptibilities of MRSA strains to glycopeptides, and isolation of both daptomycin-non-susceptible *S. aureus* and linezolid-resistant *S. aureus* strongly emphasize the need for new therapeutic options unsusceptible to these resistance mechanisms. Ceftaroline may provide a valuable option for the im treatment of MRSA infections. An example of the type of infection that might be appropriate for im treatment would be complicated skin infections in nursing home patients for whom iv administration is not readily available.

After a 4 day treatment regimen, im ceftaroline demonstrated bactericidal activity against the MRSA strain at 20 and 40 mg/kg twice-daily doses in a rabbit endocarditis experimental

model. These findings are consistent with a favourable im pharmacokinetic profile and strongly support the development of im ceftaroline as an effective therapeutic option for the treatment of severe MRSA infections.

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## Transparency declarations

D. B. is an employee of Cerexa, Inc., a subsidiary of Forest Laboratories, Inc. (New York, NY, USA), which is developing ceftaroline. D. B. holds stock and options in Forest Laboratories, Inc. Y. G. was an employee of Cerexa at the time these studies were carried out. All other authors: none to declare.

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