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Ceftobiprole Is Superior to Vancomycin, Daptomycin, and Linezolid for Treatment of Experimental Endocarditis in Rabbits Caused by Methicillin-Resistant *Staphylococcus aureus*[▽]

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Beta lactam agents are the most active drugs for the treatment of streptococci and methicillin-susceptible *Staphylococcus aureus* endocarditis. However, methicillin-resistant *S. aureus* (MRSA) is resistant to all beta lactam agents licensed to date, and alternative treatments are limited. Ceftobiprole is a novel broad-spectrum cephalosporin that binds with high affinity to PBP 2a, the penicillin binding protein that mediates the methicillin resistance of staphylococci and is active against MRSA. Ceftobiprole was compared to vancomycin, daptomycin, and linezolid in a rabbit model of MRSA aortic valve endocarditis caused by the homogeneously methicillin-resistant laboratory strain COL. Residual organisms in vegetations were significantly fewer in ceftobiprole-treated rabbits than in any other treatment group ($P < 0.05$ for each comparison). In addition, the numbers of organisms in spleens and in kidneys were significantly lower in ceftobiprole-treated rabbits than in linezolid- and vancomycin-treated animals ($P < 0.05$ for each comparison). Anti-MRSA beta lactam agents such as ceftobiprole may represent a significant therapeutic advance over currently available agents for the treatment of MRSA endocarditis.

Endocarditis is one of the most difficult infections to treat in humans, with an in-hospital mortality rate of ~20% even in most recent series, despite significant advances in surgical treatment over the last decades (2, 17). In addition, *Staphylococcus aureus*, which has emerged as the most common cause of endocarditis worldwide (16), is associated with a high rate of severe complications, such as heart failure and central nervous system emboli. Guidelines for the treatment of streptococci and methicillin-susceptible *S. aureus* (MSSA) endocarditis include a beta-lactam agent whenever possible (2) because of the bactericidal effect of these drugs and the possibility to use high doses with most agents. However, none of the currently licensed beta-lactam agents are clinically active against methicillin-resistant *S. aureus* (MRSA), and the alternative agents available for the treatment of MRSA endocarditis are limited. Vancomycin, which remains the first choice in recent guidelines, has a narrow therapeutic index, while recent reports have documented a gradual increase in MICs for MRSA over time (10, 33, 34). Moreover, *in vitro* studies and clinical data suggest that vancomycin is less active than beta-lactams in the treatment of MSSA bacteremia (35). Daptomycin is an alternative, given its rapid bactericidal activity, but clinical data are limited in left-sided endocarditis (15), and the ideal dose has still to be determined, leaving clinicians "guessing" doses, frequently at even numbers of mg per kg of body weight per day. The emergence of resistance during daptomycin therapy and reports of cross-resistance in non-vancomycin-susceptible *S. aureus* are also of concern (4, 31, 32). Lastly, linezolid, which has proved its value in the treatment of pneumonia and complicated skin and skin structure infections due to multidrug-resistant Gram-positive organisms (25), has been disappointing for the treatment of bloodstream infections (12) and is considered only with reluctance for the treatment of endocarditis given its lack of bactericidal effect. With the worldwide emergence of community-associated MRSA (3, 8), the limits of our therapeutic armamentarium against MRSA endocarditis are a growing concern.

Ceftobiprole (BPR) (formerly BAL9141), is a novel, broad-spectrum, bactericidal cephalosporin with MICs of ≤4 μg/ml for clinical isolates of *S. aureus*, including MRSA (5, 27). The anti-MRSA activity of ceftobiprole stems from its high affinity for PBP 2a, the penicillin binding protein chiefly responsible for the methicillin-resistant phenotype of staphylococci (1). In addition, ceftobiprole is stable to class A penicillinases produced by *S. aureus*. To improve solubility, ceftobiprole is administered as its dioxolenylmethyl carbamate prodrug, ceftobiprole medocaril (formerly BAL5788) (1). The purpose of the present study was to test the hypothesis that ceftobiprole would be superior to vancomycin, daptomycin, and linezolid for the treatment of MRSA in the rabbit model of aortic valve endocarditis.

MATERIALS AND METHODS

Bacterial strain. *S. aureus* strain COL is a homogeneous, β-lactamase-producing, highly methicillin-resistant clinical isolate (nafcillin MIC = 256 μg/ml) (36). The MICs of vancomycin, daptomycin, linezolid, and ceftobiprole are, respectively, 1, 1, 2, and 4 μg/ml.

Rabbit endocarditis model. To establish endocarditis, anesthesia was induced with a buprenorphine-ketamine-xylazine combination and maintained with isoflurane. A cut-down over the right carotid artery was performed, and a polyethylene catheter was positioned across the aortic valve of a 2.4- to 2.6-kg New Zealand White rabbit. The catheter was secured in place for the duration of the experiment. Postoperative pain was managed with buprenorphine. Forty-eight

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TABLE 1. Organism titers in vegetations, spleens, and kidneys of untreated and antibiotic-treated rabbits infected with MRSA COL strain

Treatment (no. of rabbits)	Mean organism titer ($\log_{10}$ CFU/g ± SD) (no. sterile)			Comparison between ceftobiprole and other groups (*P*)			Comparison between control and other groups (*P*)		
	Vegetation	Spleen	Kidneys	Vegetation	Spleen	Kidneys	Vegetation	Spleen	Kidneys
Ceftobiprole (7)	2.1 ± 1.0 (6)	1.8 ± 0.2 (5)	1.7 ± 0 (7)				<0.001	<0.001	<0.001
Control (6)	8.4 ± 0.7 (0)	5.1 ± 0.9 (0)	4.4 ± 1.0 (0)	<0.001	<0.001	<0.001			
Daptomycin (7)	3.6 ± 1.4 (1)	2.3 ± 0.7 (2)	2.6 ± 1.1 (3)	0.030	0.080	0.055	<0.001	<0.001	0.011
Vancomycin (6)	5.9 ± 2.8 (1)	3.3 ± 1.6 (2)	3.1 ± 1.5 (3)	0.006	0.025	0.036	0.050	0.035	0.102
Linezolid (5)	5.9 ± 1.2 (0)	2.9 ± 0.4 (0)	2.5 ± 0.6 (1)	<0.001	0.001	0.005	0.001	<0.001	0.007

hours after the positioning of the catheter, 1 ml of 0.9% saline containing approximately 1.5×10^7 CFU of COL was injected intravenously into each rabbit. Antibiotic treatment was commenced 16 to 18 h after infection. The rabbits were randomized to one of five groups: (i) an untreated control group, which was euthanized at the initiation of therapy to determine baseline bacterial burdens in aortic valve vegetations, spleens, and kidneys; (ii) a group treated with vancomycin at a dose of 30 mg/kg of body weight intravenously every 12 h for 4 days (9); (iii) a group treated with daptomycin at a dose of 18 mg/kg of body weight intravenously every 24 h for 4 days; (iv) a group treated with linezolid at a dose of 75 mg/kg of body weight subcutaneously every 8 h for 4 days; and (v) a group treated with ceftobiprole medocaril at a dose of 25 mg/kg (equivalent to 19 mg of active drug [ceftobiprole] per kg) intramuscularly every 8 h for 4 days. The concentrations of antibacterial agents in plasma were determined for at least three rabbits in each group from blood samples obtained 1 h after dosing. Assays were performed by high-performance liquid chromatography (HPLC). Ceftobiprole was monitored at 320 nM, daptomycin and vancomycin at 240 nM, and linezolid at 270 nM. Values were averaged from two separate HPLC determinations. Concentrations were calculated from regression lines based on standard curves in plasma. The limit of detection for the compounds was ≤0.5 μg/ml. Rabbits that died any time after initiation of therapy were scored for mortality, but only those surviving beyond the first 48 h of treatment were included in the analysis of tissue bacterial titers. Surviving rabbits were euthanized 12 h after the last dose of drug for vancomycin, linezolid, or ceftobiprole and 24 h after the last dose of drug for daptomycin. Aortic valve vegetations, spleens, and kidneys were removed. Tissues were homogenized in 0.5 ml of 0.9% saline, and 100-μl volumes were quantitatively cultured on blood agar to determine the number of bacteria present. The limit of detection of this method is 5 CFU per vegetation, or approximately 1.7 $\log_{10}$ CFU/g.

Data analysis. The bacterial titers in the aortic valve vegetation, kidneys, and spleen of each rabbit were expressed as $\log_{10}$ numbers of CFU per gram of tissue. Cultures yielding no growth were scored as sterile and assigned a value of 1.7. Differences between mean titers of the treatment groups were tested for statistical significance (defined as a P value of < 0.05) by Student's t test. Significant differences in rates of mortality were determined by Fisher's exact test. As part of the study design, an interim analysis was planned after at least 5 rabbits had been included in each group, and the study was to be discontinued if one treatment group was superior to every other group regarding the primary outcome, bacterial titers in vegetations.

RESULTS

Thirty-three rabbits were included in this study. One rabbit randomized to the ceftobiprole group and one rabbit randomized to the linezolid group died before having received 48 h of treatment and were thus both excluded from data analysis. Three additional deaths occurred during treatment, one at day 3 in the vancomycin group and two at day 4 in the ceftobiprole group; there were no deaths in the daptomycin group. Mortality rates were not significantly different among treatment groups. Mean plasma concentrations (± standard deviations) achieved 1 h after dosing were 34 ± 9.6 μg/ml for vancomycin (3 rabbits), 28.2 ± 6.1 μg/ml for linezolid (5 rabbits), 14.4 ± 7.7 μg/ml for ceftobiprole (6 rabbits), and 93.3 ± 13.3 μg/ml for daptomycin (3 rabbits), similar to those observed in humans. No vancomycin trough concentrations were measured in this study, but in prior studies, troughs ranged between 0 and 5 μg/ml and were, on average, less than 2 μg/ml (26). Taking into account the mean plasma concentrations achieved 1 h after dosing in this study (34 μg/ml) and the vancomycin half-life in this model (80 min), the vancomycin serum concentration would be below 1 μg/ml after 8 h.

The burdens of organisms in vegetations were significantly lower in ceftobiprole-treated rabbits than in rabbits treated with vancomycin, linezolid, or daptomycin (Table 1). Likewise, the burdens of organisms in spleens and in kidneys were significantly lower in ceftobiprole-treated rabbits than in linezolid- or vancomycin-treated animals ($P < 0.05$ for each comparison).

DISCUSSION

The activity of ceftobiprole was superior to those of vancomycin, daptomycin, and linezolid for the treatment of aortic valve endocarditis in rabbits infected with the COL MRSA strain. These results are concordant with those obtained for a rat model of MRSA aortic valve endocarditis, in which ceftobiprole proved to be superior to vancomycin following 3 days of treatment for the two MRSA strains surveyed (7, 14). We previously compared ceftobiprole to vancomycin at the same dosages and in the same model of rabbit endocarditis, but with two different strains: ceftobiprole was superior to vancomycin for the treatment of endocarditis due to the vancomycin-intermediate *S. aureus* (VISA) strain HIP5836, but there were no differences between ceftobiprole and vancomycin for the treatment of endocarditis caused by a highly virulent vancomycin-susceptible MRSA strain, 76. However, it should be stressed that mortality was very high in both arms with strain 76, as 10 of 21 ceftobiprole-treated rabbits (48%) and 9 of 19 vancomycin-treated rabbits (47%) died, with most deaths occurring during the first 2 days of treatment (9). These high rates of early deaths may have precluded the observation of any significant difference in treatment effect. Daptomycin and linezolid have both demonstrated significant activity for the treatment of MRSA endocarditis in the rabbit model of aortic valve endocarditis (11, 13, 19, 23, 24, 30), although discordant results have been observed with the latter (11, 19). For both drugs, a dose-dependent efficacy was reported (6, 13, 30). Taking these data into account, in this study we used the highest doses previously reported in this model (i.e., 18 mg/kg/day for daptomycin, which approximates the 10 mg/kg/day in humans, and 225 mg/kg/day for linezolid), and we documented the fact that high plasma concentrations were obtained, probably close to the tolerance threshold in humans. Thus, it is unlikely that further

increasing the doses would be an option for these drugs. For linezolid, improved efficacy in this model has been reported with continuous infusion (19) or by combining the drug with gentamicin (18), imipenem (22), or ertapenem (20). Of note, ceftaroline, another broad-spectrum cephalosporin active against MRSA that is currently under development, has recently also been found to be superior to vancomycin and linezolid in the rabbit model of aortic valve endocarditis (21).

Ceftobiprole appears to have sufficient activity to be efficacious for human infections caused by MRSA (37), and the present *in vivo* data confirm this. Ceftobiprole has been safe and well tolerated in the two phase 3 clinical trials that have been published to date (27–29). The activity of ceftobiprole is not expected to be affected by reduced susceptibility to vancomycin based on the known mechanisms of action of these compounds, *in vitro* data, and the results of endocarditis models of MRSA and VISA infection (7). Beta lactam agents have long been the first choice for the medical treatment of endocarditis due to streptococci, MSSA, enterococci, *Enterobacteriacae*, and HACEK organisms (2). The findings in this study suggest that beta lactam agents active against MRSA, such as ceftobiprole, may also be of interest for the treatment of MRSA endocarditis.

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