Journal of Global Antimicrobial Resistance 22 (2020) 147–151

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

Ceftaroline versus vancomycin in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) in an experimental MRSA meningitis model☆

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ARTICLE INFO

Article history:
Received 28 July 2019
Received in revised form 2 January 2020
Accepted 2 February 2020
Available online 14 February 2020

Keywords:
Nosocomial meningitis
Methicillin-resistant staphylococci
Central nervous system infection
Glycopeptides
Animal model
Pharmacokinetics

ABSTRACT

Objectives: The aim of this study was to compare the antibacterial activity of ceftaroline versus vancomycin in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) meningitis in an experimental rabbit meningitis model.
Methods: The antibacterial activity of ceftaroline was compared with vancomycin in the treatment of meningitis induced by MRSA strain ATCC 43300 in an experimental rabbit meningitis model. Quantitative cerebrospinal fluid (CSF) cultures were performed at the beginning of antibiotic treatment and 24 h and 73 h after the first antibiotic dose. Furthermore, in vitro time–kill data were investigated at 0, 2, 4, 6, 8, 12 and 24 h in sterile human serum.
Results: The difference between the control group versus both treatment groups was significant when comparing the decrease in colony counts in CSF both at 24 h and 73 h after the first antibiotic dose ($P < 0.05$). At the end of the experiment, there was a significant difference in survival between both the ceftaroline-treated group and the vancomycin-treated group versus the control group, but not between the two treatment groups.
Conclusion: These results suggest that the antibacterial activity of both ceftaroline and vancomycin are similar in the treatment of MRSA meningitis in an experimental rabbit meningitis model.

1. Introduction

Hospital-acquired meningitis remains an important cause of mortality and morbidity. One of the most important causative agents of hospital-acquired meningitis is methicillin-resistant *Staphylococcus aureus* (MRSA), for which there are limited treatment options [1–12]. Vancomycin is the mainstay of treatment for MRSA meningitis but failures are not rare, especially in cases with a vancomycin minimum inhibitory concentration (MIC) of >2 mg/L [1]. Ceftaroline is a fifth-generation cephalosporin with activity against MRSA [1,13–20]. In contrast to bloodstream infections [12,13], data on the current use of ceftaroline for meningitis and central nervous system (CNS) infections caused by MRSA are limited [14–20]. Therefore, the current study was conducted in an in vivo experimental animal model to investigate the activity of ceftaroline in cerebrospinal fluid (CSF) compared with the standard-of-care treatment.

2. Materials and methods

An in vivo experimental study was conducted using an animal model of bacterial meningitis described previously [1,3–5]. The aim of this study was to investigate the efficacy of ceftaroline compared with vancomycin in eradicating *S. aureus* from the CSF of rabbits with experimental meningitis. For this purpose, intravenous administration of ceftaroline and vancomycin as well

☆ Part of this study was presented as a poster presentation at the 27th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), 22–25 April 2017, Vienna, Austria, and as an oral presentation at the Turkiye-Ekmud National Annual Congress, 5–8 April 2017, Antalya, Turkey.

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http://dx.doi.org/10.1016/j.jgar.2020.02.001

as a control group without any treatment was evaluated by measuring drug levels and bacterial eradication rates in CSF of study animals.

2.1. Test strain

MRSA strain ATCC 43300 was used as the causative agent of meningitis. Vancomycin and ceftaroline MICs were determined to be 1 mg/L by the Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution method [2]. A bacterial suspension was prepared from MRSA ATCC 43300 at a density of 2×10^7 CFU/mL to inoculate each rabbit [3]. The number of rabbits that met the criteria for meningitis in the ceftaroline, vancomycin and control groups was 12, 11 and 7, respectively.

2.2. In vivo studies

New Zealand rabbits weighing 2.5–3.0 kg were anaesthetised with ketamine (35 mg/kg) and xylazine (5 mg/kg) approximately 10–15 min before each intracisternal injection of MRSA [4]. Each rabbit was inoculated intracisternally with a suspension containing MRSA ATCC 43300 at a density of $\sim 2 \times 10^7$ CFU/mL (0.3 mL) using a 22 G syringe (Hayat Ticaret, Istanbul, Turkey). Then, 28 h following the induction of infection, meningitis criteria were determined. A white blood cell count in the CSF of >1000 mm^{-3} and a bacterial count of $\geq 10^3$ CFU/mL were accepted as indicators of meningitis [5]. Animals were then separated into three groups. The two treatment groups comprised the ceftaroline group, which received 10 mg/kg ceftaroline (Pfizer, New York, NY, USA) every 12 h (q12 h), and the vancomycin group, which received 20 mg/kg vancomycin (Kocak Farma, Istanbul, Turkey) q12 h via a peripheral ear vein [3,4,19]. The control group did not receive any drug or placebo treatment. CSF and blood samples were collected at the beginning (28 h after infection induction) and after 24 h (trough drug level; C_{min}) and 73 h of antibiotic treatment (drug level 1 h after the last antibiotic dose; C_{max}) and were stored at −80 °C prior to examination. CSF and serum drug levels were measured by a bioassay technique in samples obtained at 24 h and 73 h after the drug treatment. At the end of the 73 h (1 h after the last dose of antibiotics), animals were sacrificed by intravenous infusion of a high dose of anaesthetic [5].

2.3. Measurement of bacterial concentrations

Bacterial concentrations in the CSF were measured at the beginning (28 h after infection induction) and 24 h and 73 h after initiation of drug treatment by plating undiluted and serial 10-fold and 100-fold dilutions of CSF on 5% sheep blood agar followed by incubation at 37 °C for 48 h. The response was evaluated for three endpoints: full response (sterilisation of CSF); partial response (any decrease in bacterial count); and bacteriological failure (unchanged or increased bacterial count) [3,4].

2.4. Antibiotic assay

Drug levels in rabbit serum and CSF were measured twice using a bioassay technique. *Kocuria rhizophila* ATCC 9341 and *Bacillus subtilis* ATCC 6633 were used for levels of ceftaroline and vancomycin, respectively. Drug standards were prepared fresh on the day of use in pooled rabbit serum for determination of serum drug levels and in 5% rabbit serum for determination of CSF drug levels. Assay curves were produced using standard dilutions including 0.5, 1, 2, 4, 8, 16, 32 and 64 mg/L ceftaroline and vancomycin [3,5,21,22]. For each test, including control rabbit serum samples, a concentration of 20 mg/L ceftaroline or vancomycin was used [3,5,21,22]. Following incubation of plaques at 35 °C for 18 h, the diameters of the zones of growth inhibition were measured and plotted (on the abscissa) versus the logarithm of the vancomycin concentration (on the ordinate). The sensitivity of the bioassay was 0.12 mg/L for ceftaroline and 0.5 mg/L for vancomycin.

2.5. In vitro time–kill assays

The study strain MRSA ATCC 43300 was grown in sterile human serum (H4522; Sigma-Aldrich, St Louis, MO, USA) and was then diluted 4000-fold to 10^4 CFU, corresponding approximately to bacterial concentrations in the CSF of rabbits before initiation of therapy [6]. Ceftaroline and vancomycin were added at concentrations corresponding to 1×, 5× and 10× MIC (1, 5 and 10 mg/L). Bacterial titres were determined at 0, 2, 4, 6, 8, 12 and 24 h by serial dilution of samples plated on agar plates containing 5% sheep blood and incubated at 37 °C for 24 h. Experiments were performed in twice and, at the end of the incubation period, the arithmetic mean of bacterial colony counts detected in the two samples was converted to the mean ± standard deviation (S.D.) $\log_{10}$ CFU/mL and the killing curve against time was obtained.

2.6. Ethical approval

The study was performed according to the National Institutes of Health '*Guide for the care and use of laboratory animals*' (revised 1978) with the approval of the Institutional Review Board of Ege University (Izmir, Turkey).

2.7. Statistical analysis

Data were evaluated using SPSS Statistics v.13.0 (SPSS Inc., Chicago, IL, USA). The Mann–Whitney *U*-test and Kruskal–Wallis test were used for comparison of continuous variables (CSF bacterial colony counts and decrease in CSF bacterial colony counts), and Fisher's χ^2 test was used for comparison of categorical variables (mortality). A *P*-value of <0.05 was considered statistically significant.

3. Results

At 28 h after the induction of infection, 30 of 47 rabbits (ceftaroline group, 12/18; vancomycin group, 11/17; and control group, 7/12) met the criteria for meningitis. In addition to the abovementioned criteria, all included rabbits had fever and appeared ill.

3.1. Bacterial growth in cerebrospinal fluid

There was no difference in colony counts (calculated as mean ± S.D. $\log_{10}$ CFU/mL) between the three groups at the beginning of treatment (control group, 3.968 ± 0.521 $\log_{10}$ CFU/mL; ceftaroline group, 3.974 ± 0.603 $\log_{10}$ CFU/mL; vancomycin group, 3.967 ± 0.527 $\log_{10}$ CFU/mL; $P > 0.05$) (Table 1). There was no statistically significant difference between the groups in terms of surviving rabbits at 24 h of antibiotic treatment ($P > 0.05$). At the end of the experiment (73 h after the first antibiotic dose), there was a significant difference in survival between both the ceftaroline group and the vancomycin group versus the control group, but not between the two treatment groups (Table 1). When the reductions in CSF colony counts at 24 h and 73 h of treatment were compared, the difference between the control group and the two treatment groups was significant [at 24 h control group, $+3.682 \pm 3.543$ $\log_{10}$ CFU/mL, ceftaroline group, -2.608 ± 3.279 $\log_{10}$ CFU/mL, and vancomycin group, -2.167 ± 3.612 $\log_{10}$ CFU/mL ($P < 0.05$); and at 73 h, ceftaroline group, $-3.804 \pm$

Table 1
Number of surviving rabbits at 0, 24 and 73 h and bacterial culture results in cerebrospinal fluid.

Treatment	Colony count (mean ± S.D. $\log_{10}$ CFU/mL)			
	0 h	24 h	73 h	Difference (73 h – 0 h)
Control**	3.968 ± 0.521 (n = 7)	4.81 ± 0.95 (n = 7)	–(n = 0) [a]	– [a]
Ceftaroline**,***	3.974 ± 0.603 (n = 12)	1.94 ± 1.90 (n = 11)	0.95 ± 1.5 (n = 6)	−3.804 ± 0.649
Vancomycin**,***	3.967 ± 0.527 (n = 11)	3.24 ± 1.52 (n = 10)	1 ± 1.15 (n = 4)	−3.887 ± 0.678

S.D., standard deviation.
[a] There were no surviving rabbits in the control group at 73 h.
** Difference between the control group and the two treatment groups was significant both at 24 h and 73 h.
*** No statistically significant difference between the ceftaroline and vancomycin groups at either 24 h or 73 h.

0.649 $\log_{10}$ CFU/mL, and vancomycin group, −3.887 ± 0.678 $\log_{10}$ CFU/mL ($P > 0.05$)] but there was no statistically significant difference between the ceftaroline and vancomycin groups.

3.2. In vitro time–kill assays

In vitro time–kill data were investigated at 0, 2, 4, 6, 8, 12, and 24 h in sterile human serum at 1×, 5× and 10× MIC of the antibiotics. Ceftaroline performed better at all time points and achieved bacterial sterility at 8 h. Vancomycin time–kill analyses resulted in bacterial sterility only at 10 mg/L (10× MIC) at 24 h. Although ceftaroline exhibited stronger bactericidal activity than vancomycin by in vitro time–kill data, at the end of the 24-h period the difference remained relatively unchanged and vancomycin was able to sterilise human serum at a level of 10× MIC (Fig. 1).

3.3. Drug levels in cerebrospinal fluid and blood

The C_{min} of ceftaroline in CSF was below the lower limit of detection (LLOD) (0.12 mg/L) in all rabbits (n = 12). Ceftaroline C_{max} data in CSF were available in all six surviving rabbits and was a mean of 1.50 ± 1.09 mg/L in five rabbits with drug levels above the LLOD. The C_{min} of ceftaroline in serum could be measured in only five rabbits for technical reasons, while only one rabbit had a drug level (1 mg/L) above the LLOD. Ceftaroline serum C_{max} data were available for five of six surviving rabbits. The mean C_{max} in serum was 3.2 ± 3.3 mg/L. The CSF penetration ratio of ceftaroline was 38.3%, 39.6%, 55.5% and 70% (mean 51 ± 15%) in four rabbits with paired (data for both CSF and serum drug level available in the same rabbit) detectable drug serum and CSF drug levels.

Vancomycin C_{min} data in CSF were available in 9 of 10 surviving rabbits and the C_{min} was above the LLOD (≥0.5 mg/L) in two rabbits (0.5 mg/L and 2 mg/L). Mean vancomycin C_{min} data in serum were available in 7 of 10 surviving rabbits and was a mean of 6.1 ± 5.9 mg/L (range 1.6–18.7 mg/L). Data for vancomycin C_{max} in serum were available in three of four surviving rabbits (with levels of 4.2, 8.2 and 11.5 mg/L). Data for vancomycin C_{max} in CSF were available in three of four surviving rabbits and the value was above the LLOD (≥0.5 mg/L) in two rabbits (1.3 mg/L and 1.7 mg/L). The CSF penetration ratio of vancomycin was 14.7% and 35.5%, respectively, in the two rabbits that had paired drug levels above the LLOD of the bioassay (≥0.5 mg/L). Drug levels in CSF and serum and data related to CSF penetration of ceftaroline and vancomycin are summarised in Table 2.

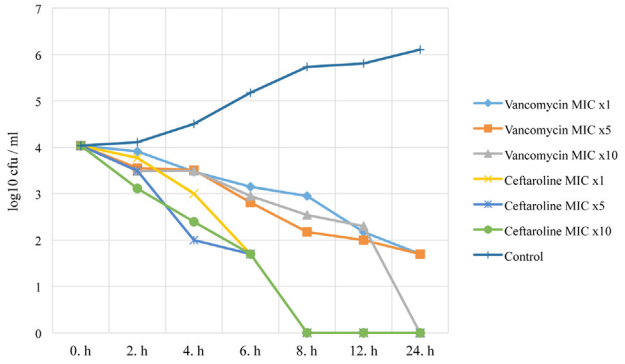

Fig. 1. Time–kill results for ceftaroline and vancomycin against methicillin-resistant *Staphylococcus aureus* (MRSA) strain ATCC 43300 at 1×, 5× and 10× MIC (1, 5 and 10 mg/L). MIC, minimum inhibitory concentration.

4. Discussion

MRSA meningitis usually develops following CNS procedures and the first treatment option is considered to be vancomycin [8,9]. Other options may be linezolid, daptomycin, teicoplanin, trimethoprim/sulfamethoxazole or rifampicin in combination with vancomycin and intrathecal vancomycin [1,3,8,9]. Failures with vancomycin and other alternatives in MRSA meningitis are not rare, especially in strains with higher MICs [1,8,10,11]. Hence, new and more effective treatments are required.

Ceftaroline is a fifth-generation cephalosporin approved for community-acquired pneumonia and complicated skin and soft-tissue infections. It is a novel alternative in the treatment of infections by multidrug-resistant Gram-positive bacteria [12]. Ceftaroline is reported to result in rapid clearance of MRSA bacteraemia and endocarditis [13]. Despite some successful case reports, detailed data are limited regarding the use of ceftaroline in CNS infections [14,15]. Recently, Britt et al. reported 18 cases treated with ceftaroline-including regimens and reported mortality in one case (6%) and a 44% re-admission rate at 1 month [16]. However, there are no details about additional treatments, aetiology and other clinical data related to meningitis.

In the literature, there are a few studies comparing ceftaroline in experimental meningitis models with different antimicrobial agents [17–19]. A study by Stucki et al. compared the efficacy of ceftaroline with cefepime in an experimental rabbit meningitis model caused by *Klebsiella pneumoniae* (ceftaroline MIC = 1 mg/L; cefepime MIC = 0.25 mg/L) [17]. Ceftaroline (40 mg/kg) and cefepime (100 mg/kg) were administered at 0 h and 4 h. Following 8 h of ceftaroline treatment, the bacterial count decreased by 5.61 $\log_{10}$ CFU/mL while cefepime led to a decline of 3.54 $\log_{10}$ CFU/mL (P = 0.0007).

In another study by Bardak-Ozcem et al., daptomycin and vancomycin were compared in an experimental MRSA meningitis model [5]. The study used the same study strain as the current study and the time–kill assay was continued for 8 h. Both daptomycin and vancomycin were found to be similar at the end of 8 h when in vitro time–kill data were evaluated [5]. When the vancomycin data from the present study are compared with the time–kill results at 8 h from Bardak-Ozcem et al. [5], as expected the results were similar in both studies, with a decrease in the CSF bacterial load of ~1 $\log_{10}$ CFU/mL.

Table 2
Drug levels in cerebrospinal fluid (CSF) and serum, and CSF penetration ratio of ceftaroline and vancomycin.

	Ceftaroline (LLOD > 0.12 mg/L)				Vancomycin (LLOD > 0.5 mg/L)			
	CSF		Serum		CSF		Serum	
	C_{min}	C_{max}	C_{min}	C_{max}	C_{min}	C_{max}	C_{min}	C_{max}
Mean (mg/L)	ND	1.50 ± 1.09	1	3.2 ± 3.3	1.30 ± 1.13	1.05 ± 0.28	6.1 ± 5.9	8 ± 3.7
S/M/D [a]	11/11/0	6/6/5	11/5/1	6/5/5	10/9/2	4/3/2	10/7/7	4/3/3
Penetration ratio into CSF	38.3%, 39.6%, 55.5% and 70% respectively (four rabbits) (mean ± S.D. 51 ± 15%)				14.7% and 35%, respectively (two rabbits)			

LLOD, lower limit of detection; C_{min}, trough drug level (after 24 h of antibiotic treatment); C_{max}, peak drug level (after 73 h of antibiotic treatment, i.e. 1 h after the last antibiotic dose); ND, no data; S.D., standard deviation.
[a] S = number of surviving rabbits; M = number of rabbits with measurable C_{min} or C_{max} drug level; D = number of rabbits with drug levels above the LLOD.

In the current experimental study, vancomycin and ceftaroline dosages were adopted from previously published animal studies that used the routine human clinical dosage of 20 mg/kg vancomycin q12 h (corresponding to ~1 g q12 h) and 10 mg/kg ceftaroline q12 h (corresponding to ~600 mg q12 h) [3,4,18]. A bioassay method was used instead of high-performance liquid chromatography (HPLC) owing to limited research funding. The LLOD was 0.12 mg/L for ceftaroline and 0.5 mg/L for vancomycin. The study by Stucki et al. reported a mean penetration of ceftaroline into the CSF of 15% in an experimental rabbit meningitis model [17], whilst in another study conducted by Cottagnoud et al. penetration of ceftaroline into the CSF was reported to be 14 ± 5% [18]. In the current study, CSF penetration ratios of ceftaroline were 38.3%, 39.6%, 55.5% and 70% (mean 51 ± 15%) in four rabbits with paired detectable serum and CSF drug levels (≥0.12 mg/L). A recent study by Chauzy et al. reported ceftaroline CSF pharmacokinetics of one dose of ceftaroline in nine neurosurgical patients with an external ventricular drain but without meningitis [20]. The C_{max} was 18.29 ± 3.33 mg/L in plasma (total concentration) and 0.22 ± 0.17 mg/L in CSF (unbound concentration). The model-estimated CSF input/CSF output clearance ratio was 9.4%, attesting to extensive efflux at the blood–CSF barrier. Although it is not easy to comment on relatively higher CSF penetration in the current study compared with other animal studies, we may speculate that this might have been affected by the longer duration of treatment (73 h vs. 8 h). Compared with the only human study, the presence of meningitis (the only human data are from uninfected cases) as well as different bacterial counts and/or varying meningeal inflammation might have increased the CSF transmission rate of ceftaroline in the present study.

Bardak reported a penetration rate of vancomycin of 7.1–44.4% using the same method as in the current study to measure vancomycin level (Selin Bardak and Oguz Resat Sipahi, personnel communication). Similarly, the CSF penetration ratio of vancomycin was 14.7% and 35.5% in the two rabbits that had paired drug levels above than LLOD of the bioassay (≥0.5 mg/L) in the present study.

In the current experimental study, a bioassay method was used instead of HPLC owing to cost issues. This method was insufficient to detect especially C_{min} drug levels both in CSF and blood.

Use of a bioassay to detect drug levels, the relatively limited number of animals, lack of drug level measurement in blood or CSF samples of some study rabbits for technical reasons, and the inability to measure the inflammatory response such as cytokine or apoptosis in the brain parenchyma owing to funding issues are the main limitations of the present study. Furthermore, we do not know the exact time point at which the animals died since we did not continuously monitor the animals throughout the study period. We could not determine the efficacy of the ceftaroline–vancomycin combination to see their possible additive effect owing to a limited study budget. Nevertheless, we are planning a new study on this issue. Despite these disadvantages, the duration of treatment in the present study is longer compared with other rabbit meningitis model studies using ceftaroline or vancomycin. This has led to the evaluation and comparison of the efficacy of the treatment in a way more suited to clinical practice.

Although vancomycin is suggested as the first-line treatment option for MRSA meningitis, problems in treatment still exist in cases with MIC >1 mg/L [17]. To our knowledge, there is no human or animal study comparing ceftaroline with vancomycin for MRSA meningitis, and this is the first study to compare the antibacterial efficacy of ceftaroline and vancomycin. The current results suggest that the antibacterial activity of both ceftaroline and vancomycin are similar in the treatment of MRSA meningitis in an experimental rabbit model. Additional randomised clinical data are necessary to confirm these results in humans.

5. Conclusions

These results suggest that the antibacterial activity of ceftaroline and vancomycin are similar in the treatment of MRSA meningitis in an experimental rabbit model.

Funding

This study was funded by Ege University (Izmir, Turkey).

Competing interests

None declared.

Ethical approval

This study was performed according to the National Institutes of Health '*Guide for the care and use of laboratory animals*' (revised 1978) with the approval of the Institutional Review Board of Ege University [approval no. 2015-050].

Acknowledgments

The authors would like to thank the European Study Group for Infections of the Brain (ESGIB) for their collaboration in analysis and interpretation of the data. The authors also thank Ismail Zonguldak and Ercument Karasulu for help during the performance of the study. Ceftaroline was kindly supplied by Astra Zeneca/Pfizer.

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