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Samia Arshad
Henry Ford Health, sarshad1@hfhs.org

Vanthida Huang

Pamela Hartman
Henry Ford Health

Mary Perri
Henry Ford Health, MPERRI1@hfhs.org

Daniela Moreno
Henry Ford Health

See next page for additional authors

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Authors
Samia Arshad, Vanthida Huang, Pamela Hartman, Mary Perri, Daniela Moreno, and Marcus J. Zervos

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Ceftaroline fosamil monotherapy for methicillin-resistant *Staphylococcus aureus* bacteremia: a comparative clinical outcomes study

Samia Arshad[a,*], Vanthida Huang[b], Pamela Hartman[a], Mary B. Perri[a], Daniela Moreno[a], Marcus J. Zervos[a,c]

[a] *Division of Infectious Diseases, Henry Ford Hospital, 2799 West Grand Blvd, CFP 314, Detroit, MI 48202, USA*
[b] *Midwestern University College of Pharmacy–Glendale, Glendale, Arizona, USA*
[c] *Wayne State University, School of Medicine, Detroit, Michigan, USA*

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SUMMARY

Objectives: Vancomycin is the treatment of choice for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia; however, its use has been subject to scrutiny due to failure in severe infections. Ceftaroline fosamil (CPT-F) is approved for MRSA acute bacterial skin and skin structure infections, but not for bloodstream infections. The clinical outcomes of treatment with CPT-F in patients with MRSA bacteremia were evaluated.

Methods: Patients diagnosed with MRSA bacteremia at Henry Ford Hospital in Detroit, Michigan, USA, involving isolates with a vancomycin minimum inhibitory concentration ≥1.0 mg/l and susceptible in vitro to CPT-F, were systematically reviewed retrospectively. Ceftaroline fosamil-treated patients were matched with at least two vancomycin- and/or one daptomycin-treated control patient based on age-patients age 65 years or greater or less than 65 years of age. Outcomes evaluated included the duration of hospitalization, duration of therapy, adverse events, relapse, hospital readmission, and death.

Results: Thirty consecutive cases of MRSA bacteremia treated with CPT-F during the period May 2011 to June 2013 were identified; these patients were matched to 56 MRSA bacteremia patients treated with vancomycin and 46 MRSA bacteremia patients treated with daptomycin. The primary source of MRSA bacteremia in the cohort treated with CPT-F was endocarditis ($n = 7$, 23%), skin/wound ($n = 9$, 30%), and bone/joint ($n = 8$, 27%). The MRSA bacteremia in those treated with CPT-F was community-acquired in 43% of cases, healthcare-associated in 43%, and hospital-acquired in 13%. The mean length of hospital stay for these patients was 22 days. The overall 30-day mortality rate was 13% ($n = 4$) in CPT-F patients versus 24% ($n = 11$) in daptomycin patients and 11% ($n = 6$) in vancomycin patients ($p = 0.188$).

Conclusions: CPT-F demonstrated comparable clinical outcomes in MRSA bacteremia patients compared with the other agents, especially as salvage therapy.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections (BSI) continue to have high mortality, with rates of 20–30% reported in recent studies.[1] According to the US Centers for Disease Control and Prevention (CDC), an attributable 94 360 invasive infections and 18 650 deaths occur annually in the USA.[2] Due to the high rates of mortality, an improvement in the outcomes through better safety and efficacy of treatment, a reduction in infection rates, and better prevention measures to decrease readmission rates and hospitalization costs is required.

The initial treatment of choice for serious MRSA infections is vancomycin.[3,4] However, there have been increasing reports of vancomycin failures and failures attributed to elevated vancomycin minimum inhibitory concentrations (MICs).[5] Consensus guidelines recommend the consideration of alternative agents in this setting[3,6]; thus, optimal therapeutic options for serious MRSA infections remain to be determined.[3]

Ceftaroline fosamil (CPT-F) is a novel cephalosporin approved by the US Food and Drug Administration (FDA) for the treatment of

* Corresponding author. Tel.: +1 917 449 3734; fax: +1 313 916 2993.
E-mail address: sarshad1@hfhs.org (S. Arshad).

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acute bacterial skin and skin structure infections caused by MRSA and for community-acquired bacterial pneumonia.[7] Ceftaroline – the active metabolite of the prodrug CPT-F – has been used for the treatment of serious infections, and case observations have been reported.[8–11] However, there are no data from studies that have evaluated comparative outcomes with this approach, and there is minimal evidence for the use of ceftaroline therapy for strains with vancomycin heteroresistance, reduced in vitro susceptibility within the susceptible range, or in patients who have failed treatment with or are intolerant to vancomycin. To date, the role of ceftaroline in the treatment of severe MRSA infections has not been evaluated. Therefore, this study was performed to evaluate CPT-F as monotherapy versus daptomycin and vancomycin in the treatment of MRSA bacteremia caused by strains with vancomycin MICs of ≥1.0 mg/l.

Methods

This was a retrospective matched cohort study conducted at Henry Ford Hospital in Detroit, Michigan, USA, which was approved by the hospital institutional review board. Patients aged ≥18 years who had been diagnosed with MRSA bacteremia, with a vancomycin MIC ≥1.0 mg/l and susceptible to CPT-F, between November 2009 and December 2013, were identified. The selection of antibiotics was made at the discretion of the infectious disease (ID) physicians caring for the patient.

Patients treated with CPT-F were matched with two control patients treated with vancomycin and two control patients treated with daptomycin based on age (≥65 years), intensive care unit (ICU) status during MRSA bacteremia-related admission, and severity of illness. Severity was defined by the source of the BSI, which was classified into one of three categories: low-risk sources (related mortality rate <10%), which included intravenous catheter, urinary tract, ear–nose–larynx, gynecological sources, and several manipulation-related sources; intermediate-risk sources (associated mortality rate 10–20%), which included osteoarticular, soft tissue, and unknown sources; and high-risk sources (mortality rate >20%), which included endovascular, lower respiratory tract, abdominal, and central nervous system foci, as described previously.[12,13]

Demographic information and outcome measures collected included the duration of hospitalization and therapy, adverse events, 42-day relapse, 30-day hospital readmission, and 30-day mortality from onset of infection.

The initial identification of isolates and susceptibility testing (Vitek 2; bioMérieux, Inc., Durham, NC, USA) was performed by the clinical microbiology laboratory. The MICs for CPT-F, daptomycin, and vancomycin were determined for all isolates utilizing epsilometer tests (Etest; bioMérieux, Durham, NC, USA), which were performed in accordance with the manufacturer's instructions. The MICs for vancomycin were also determined for all isolates by broth microdilution, according to Clinical and Laboratory Standards Institute (CLSI) guidelines.[14] Isolates were screened for heteroresistance to vancomycin using the macrodilution method Etest (AB Biodisk, Solna, Sweden).[15]

A sample size collection of charts was estimated from a total of 150 patients who were hospitalized with MRSA bacteremia during the study period, with approximately 30 patients (20%) treated with ceftaroline and 120 patients (80%) treated with other therapeutic agents. Patients treated with ceftaroline versus vancomycin or daptomycin were matched 1:4 to yield a sufficient sample size for comparative analysis, using a two-sided significance level for α of 0.05 and 80% power.

Patient demographics were evaluated using descriptive statistics. Categorical variables were compared using the Chi-square test or Fisher's exact test when the sample size was small. Continuous variables were compared using the two-sample *t*-test. Conditional logistic regression modeling was used throughout to account for the case–control matching. A *p*-value of <0.05 was considered statistically significant. All data were analyzed using both IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA) and SAS software version 9.2 (SAS Institute Inc, Cary, NC, USA). The primary outcome was composite failure defined as the presence of any of the three main efficacy endpoints: mortality within 30 days from onset of infection, infection relapse within 42 days, or readmission within 30 days after the end of treatment.

Results

From a total 132 patients, 30 consecutive cases of MRSA bacteremia treated with CPT-F were identified during the period May 2011 to December 2013. The matched control group consisted of 102 MRSA bacteremia patients: 46 treated with daptomycin and 56 treated with vancomycin during the period November 2009 to May 2013. Baseline demographic information for all three treatment groups is shown in Table 1.

The baseline demographic characteristics were similar in the three treatment groups. However, patients treated with CPT-F had a longer duration of bacteremia ($p = 0.075$) than the other two cohorts; this may be attributable to more than half of the ceftaroline patients ($n = 17$, 57%) initially failing standard treatment and consequently being switched to CPT-F due to a documented poor clinical response, per the consulting ID physician. The origin of the MRSA bacteremia for patients treated with CPT-F versus those treated with the standard of care was 43% vs. 61% community-acquired, 43% vs. 34% healthcare-associated, and 13% vs. 6% hospital-acquired, respectively. Overall, mortality within 30 days from onset of infection was observed in 13.3% of patients treated with CPT-F, 24% of those treated with daptomycin, and 11% of those treated with vancomycin ($p = 0.188$). In the group treated with CPT-F, three of four patients who died were endocarditis bacteremia patients and two had left-sided endocarditis with an APACHE II score of 15–20 points.

Tables 2 and 3 show the univariable and multivariable logistic regression results for the composite failure outcome. The results indicate that treatment with CPT-F was not significantly associated (either univariably or multivariably) with composite failure (mortality/relapse/readmission). The composite failure outcome was seen in seven of 30 CPT-F patients (23.3%) and 22 of 102 non-CPT-F patients (21.6%); this difference was not statistically significant ($p = 0.837$).

Patient-related factors associated with composite failure were African American race ($p = 0.026$, odds ratio (OR) 7.1) and chronic obstructive pulmonary disease (COPD) ($p = 0.038$, OR 6.4) (Table 3).

The duration of intravenous therapy for all patients was 4–8 weeks. All but one of the patients treated with CPT-F had microbiological cure at the end of treatment (97%). Susceptibility testing results for the CPT-F group were as follows: the vancomycin MIC_{90} was 1.7 mg/l by Etest; the mean vancomycin MIC was 1.13 mg/l by automated test (Vitek 2; bioMérieux, Inc., Durham, NC, USA); the mean daptomycin MIC was 0.52 mg/l and CPT-F MIC was 0.65 mg/l by Etest. For the control group, the vancomycin MIC_{90} was 1.6 mg/l by Etest and 1.06 mg/l by Vitek. The mean MICs for CPT-F and daptomycin were 0.62 mg/l and 0.52 mg/l, respectively, with one isolate that was intermediate-susceptible to CPT-F with a MIC of 1.5 mg/l. None of the isolates in either treatment group demonstrated heteroresistance to vancomycin. All susceptibilities were performed on all isolates with vancomycin utilizing the Etest, Vitek 2, and manual broth microdilution methods, while CPT-F and daptomycin MICs were performed using only the Etest.

Table 1
Baseline demographic characteristics of patients with MRSA bacteremia stratified by treatment group.

Variable		Ceftaroline (n = 30)	Daptomycin (n = 46)	Vancomycin (n = 56)	Overall p-value
Age, years	Number	30	46	56	0.721
	Mean (SD)	55.9 (12.7)	53.5 (15.4)	54.9 (16.7)	
Sex, n (%)	Female	13 (43%)	23 (50%)	24 (43%)	0.745
	Male	17 (57%)	23 (50%)	32 (57%)	
Race, n (%)	African American	16 (57%)	30 (68%)	35 (69%)	0.439
	Caucasian	9 (32%)	13 (30%)	15 (29%)	
	Other	3 (11%)	1 (2%)	1 (2%)	
APACHE II score	Number	30	46	56	0.978
	Mean (SD)	11.8 (4.7)	12.2 (5.7)	11.8 (5.3)	
Previous hospitalization 90 days from onset of infection, n (%)		15 (50%)	28 (61%)	28 (50%)	0.491
Staphylococcus aureus infection 1 year prior to admission, n (%)		9 (30%)	10 (22%)	8 (14%)	0.219
Source of bacteremia, n (%)					
	Endocarditis	7 (23%)	19 (41%)	13 (23%)	0.096
	Bone/joint	8 (27%)	10 (22%)	9 (16%)	0.492
	Skin/wound	9 (30%)	10 (22%)	15 (27%)	0.704
ICU ever during admission, n (%)		12 (40%)	27 (59%)	20 (36%)	0.057
Cancer, n (%)		2 (7%)	5 (11%)	6 (11%)	0.867
HIV, n (%)		2 (7%)	2 (4%)	4 (7%)	0.810
Diabetes mellitus, n (%)		16 (53%)	16 (35%)	19 (34%)	0.170
Liver disease, n (%)		7 (23%)	12 (26%)	13 (23%)	0.937
IV drug user, n (%)		7 (23%)	16 (35%)	12 (21%)	0.285
Acute renal failure, n (%)		8 (27%)	11 (24%)	7 (13%)	0.195
Congestive heart failure, n (%)		5 (17%)	11 (24%)	6 (11%)	0.205
Vascular disease, n (%)		3 (10%)	4 (9%)	9 (16%)	0.483
COPD, n (%)		4 (13%)	5 (11%)	7 (13%)	0.943
Clinical outcomes, n (%)					
	30-day mortality	4 (14%)	11 (24%)	6 (11%)	0.188
	42-day relapse	2 (7%)	1 (2%)	1 (2%)	0.443
	30-day readmission	2 (7%)	3 (7%)	3 (5%)	1.000

MRSA, methicillin-resistant *Staphylococcus aureus*; SD, standard deviation; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; IV, intravenous; COPD, chronic obstructive pulmonary disease.

Discussion

The treatment of choice for MRSA bacteremia for over four decades, since its discovery, has been vancomycin. However, in recent decades there have been increasing reports of vancomycin failure in patients with serious MRSA infections, such as bacteremia and infective endocarditis.[12,13] Furthermore, the reporting of increasing vancomycin MICs poses a challenge for clinicians in maximizing the pharmacodynamic parameters of vancomycin to achieve the appropriate treatment dose for these infections.[3,4,12,13]

The optimal management of MRSA bacteremia is uncertain. The Infectious Diseases Society of America (IDSA) currently recommends trough serum levels of vancomycin of 15–20 mg/l for serious infections.[3] These trough serum levels, however, have not been shown to be safe, with an associated risk of nephrotoxicity reported in recent studies.[16,17] Nephrotoxicity, recurrence of infection, microbiological failure, and mortality must be considered in the selection and overall clinical success of therapy. Therefore, recommendations have been made for the consideration of alternative agents, although most of the alternative agents do not have FDA indications for use in these serious infections, which has proven a challenge for clinicians.

Table 2
Univariable logistic regression results for the composite failure outcome (30-day mortality/42-day relapse/30-day readmission).

Variable	p-Value	OR	95% CI
Ceftaroline treatment	0.623	1.295	0.463–3.621
Age	0.118	1.041	0.990–1.094
Male sex	0.615	0.772	0.282–2.116
African American race	0.156	2.485	0.707–8.738
APACHE II	0.919	0.995	0.903–1.097
Previous hospitalization 90 days from onset of infection	0.680	0.818	0.315–2.124
Staphylococcus aureus infection 1 year prior to admission	0.143	0.356	0.089–1.419
Source of bacteremia			
Endocarditis	0.580	0.584	0.087–3.914
Bone/joint	0.178	0.367	0.086–1.575
Skin/wound	0.201	2.519	0.611–10.376
Cancer	0.754	0.794	0.187–3.366
HIV	0.485	2.062	0.270–15.749
Diabetes	0.548	0.733	0.266–2.021
Liver disease	0.495	1.538	0.446–5.306
IV drug user	0.768	0.823	0.226–2.998
Acute renal failure	0.202	2.182	0.658–7.241
Congestive heart failure	0.729	1.218	0.398–3.726
Vascular disease	0.732	1.338	0.252–7.100
COPD	0.056	3.652	0.970–13.753

OR, odds ratio; CI, confidence interval; APACHE II, Acute Physiology and Chronic Health Evaluation II; IV, intravenous; COPD, chronic obstructive pulmonary disease.

Table 3
Multivariable logistic regression results for the composite failure outcome (30-day mortality/42-day relapse/30-day readmission)[a].

Variable	*p*-Value	OR	95% CI
Ceftaroline treatment	0.633	1.390	0.360–5.368
Age	0.124	1.062	0.984–1.146
African American race	0.026[b]	7.118	1.269–39.918
Staphylococcus aureus infection in previous year	0.071	0.170	0.025–1.160
Bone/joint infection source	0.206	0.265	0.034–2.077
COPD	0.038[b]	6.388	1.112–36.707

OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.
[a] Note: Variables with univariable *p*-values of <0.20 have been included, along with ceftaroline treatment.
[b] Statistically significant, $p < 0.05$.

Daptomycin is recommended as an alternative for the treatment of MRSA bacteremia in the IDSA guidelines. In 2012, Moore et al. demonstrated that daptomycin was associated with better outcomes than vancomycin in the treatment of MRSA bacteremia with higher vancomycin MICs (defined as a MIC >1 mg/l).[18] A year later, Murray et al. demonstrated that an early switch to daptomycin compared to vancomycin for the treatment of MRSA bacteremia with a vancomycin MIC >1 mg/l significantly improved outcomes.[19] In addition, they showed a decrease in 30-day mortality with daptomycin (20.0% vs. 48.2%; $p < 0.001$). However, in 2011, van Hal et al. reported daptomycin resistance in a daptomycin-naïve patient and the need for optimal management in such cases.[20] Investigators have shown the benefit of combination therapy with the addition of a β-lactam antibiotic such as CPT-F to daptomycin versus daptomycin monotherapy in preventing daptomycin resistance and sustaining killing in the treatment of MRSA bacteremia.[20–22] Cunha et al. also reported a case of daptomycin resistance in an acute bacterial endocarditis patient following a week of vancomycin therapy for MRSA bacteremia, who subsequently died.[23] A randomized controlled trial comparing daptomycin vs. vancomycin for the treatment of MRSA bacteremia with a high vancomycin MIC (defined as ≥1 mg/l) remains ongoing.[24] The experience of the present authors along with the data reported in previously published studies demonstrates inconsistent results for daptomycin therapy in MRSA bacteremia with an elevated vancomycin MIC.[4,25]

There is a paucity of data in the previous literature on the use of CPT-F in the treatment of MRSA bacteremia. A case series of 10 patients reported by Lin et al. found CPT-F to treat severe MRSA infections effectively, with a microbiological cure rate of 70%.[10] There are seven recent reports of studies that have investigated the utility of CPT-F in serious MRSA infections in patients who have not responded to standard therapy.[8–11,26] The largest study was a multicenter retrospective evaluation of the efficacy and safety of CPT-F in which Casapao et al. evaluated 527 patients who received CPT-F for at least 72 h.[26] Bacteremia was noted in 28% (148/527) of the patients and CPT-F was prescribed after approximately 6 days of vancomycin or daptomycin therapy. Ceftaroline was most often used in the treatment of *S. aureus* infections, especially BSI.

The present study demonstrated that CPT-F is not inferior to the standard treatment for patients with MRSA bacteremia. Approximately 90% of patients treated with CPT-F for MRSA bacteremia survived, despite the difficulties associated with treatment options for MRSA, an increasingly resistant pathogen. A high prevalence of left-sided infective endocarditis was found in the cohort treated with CPT-F (27%), which is an independent risk factor associated with mortality. The patients treated with CPT-F had a longer duration of bacteremia ($p = 0.0053$) than the control group patients, which is likely due to the use of ceftaroline for patients with refractory MRSA BSI and alteration from standard therapy to CPT-F; this is in agreement with the findings of Polenakovik and Pleiman[8] and Casapao et al.[26]

The limitations of this study include its retrospective design and single-center setting. The strengths include the consecutive patient and strain selection and the large sample size for off-label use, and the study is unique in providing strong, comparative matching criteria for each CPT-F-treated patient.

In conclusion, CPT-F was found to be efficacious in the treatment of serious infections due to MRSA, as well as *S. aureus* strains with reduced susceptibility to vancomycin and non-susceptibility to daptomycin. MRSA bacteremia infections are complex; this was highlighted by the group of patients who failed on standard therapy with vancomycin and daptomycin and subsequently responded to treatment with CPT-F. Ceftaroline is a safe antimicrobial. Nevertheless, clinicians should be cautious of hematological toxicity and the possibility of eosinophilic pneumonia when CPT-F is used in the long term (> 14 days).[27] The use of ceftaroline in the future for serious infections warrants its investigation as monotherapy versus combination therapy in a randomized trial to optimize its role as a therapeutic option.

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Conflict of interest

No conflict of interest to declare.

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