IN VITRO SUSCEPTIBILITY OF MRSA CLINICAL ISOLATES TO CEFTAROLINE

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ABSTRACT

Objective: To determine the in vitro susceptibility of MRSA clinical isolates to ceftaroline, using interpretation of zones of inhibition by disk diffusion method.

Study Design: Descriptive cross sectional.

Place and Duration of Study: The study was carried out at the Department of Microbiology, Combined Military Hospital Peshawar, from Jan to Dec 2014.

Material and Methods: To carry out this descriptive cross sectional study, clinical specimens were obtained from indoor and outdoor patients of Combined Military Hospital Peshawar. All the isolates of MRSA cultured with CLSI guidelines and identified with standard microbiological procedures, from clinical specimens of pus, body fluid, urine, tissue and blood were included in the study. The antimicrobial susceptibility pattern of ceftaroline was determined according to CLSI guidelines. The data was analyzed in SPSS (version 19) software.

Results: Out of a total 190 MRSA isolates, 183 (96.3%) were susceptible to ceftaroline in vitro, whereas 5 (2.6%) were resistant and 2 (1.1%) were intermediate in their response to ceftaroline.

Conclusion: Ceftaroline can be used effectively against infections caused by MRSA as it has shown very high in vitro activity against MRSA strains of clinical origin.

Keywords: Antimicrobial susceptibility, Ceftaroline, MRSA.

INTRODUCTION

Staphylococcus aureus is an opportunistic pathogen and one of the leading cause of community acquired and nosocomial infections. Methicillin-resistant Staphylococcus aureus (MRSA) was first reported in United Kingdom in 1961[1]. In 1981, first major epidemic was seen in United States among intravenous drug users. With the emergence of MRSA, the choices of antimicrobials to treat infections caused by such isolates have become limited[2]. MRSA associated infections range from soft tissue infections to more serious systemic infections such as necrotizing pneumonia, urinary tract infections, endocarditis, osteomyelitis and septicemia[3]. In hospitals, colonization among patients and health care providers are the chief sources of *S. aureus.* including MRSA colonizes different parts of healthy humans and patients such as the anterior nares, hair line, skin crease and vagina. The prevalence of MRSA carriage in one of carried out survey was reported 18.5%, 27.3% and 13.6% among physicians, nurses and sanitary workers, respectively[4]. In particular; MRSA has become a leading cause of skin and soft tissue infections. Its pentone valentine leucocidin (PVL) positive strain has been associated with necrotizing pneumonia[5].

Ceftaroline is a novel fifth generation cephalosporin. It exhibits broad spectrum activity against Gram-positive bacteria, including MRSA and extensively resistant strains, such as vancomycin-intermediate Staphylococcus aureus (VISA), vancomycin-resistant Staphylococcus aureus (VRSA) and heteroresistant VISA (hVISA)[6]. It is exciting new agent in the anti-MRSA arsenal. Ceftaroline is also effective against many respiratory pathogens including Streptococcus pneumoniae, Moraxella catarrhalis and Haemophilus influenzae[7].

This study was carried out with a view that, there is a need for current information on local susceptibility profile of MRSA against

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Received: 16 Jun 2017; revised received: 18 Sep 2017; accepted: 28 Sep 2018

ceftaroline which will have important therapeutic implications.

MATERIAL AND METHODS

This study was carried out at the department of Microbiology, Combined Military Hospital Peshawar, Pakistan. The study included all MRSA isolates cultured from clinical specimens of pus, body fluid, urine, tissue and blood, which were received from 1st January to 31st December 2014 in the Department of Microbiology. Repeat specimens from same patient were excluded from the study. Using WHO sample size calculator, with Confidence Interval 95% and anticipated population proportion of 98%, the sample size was calculated to be 190. It was a descriptive cross sectional study with non-probability consecutive sampling.

The clinical specimens were inoculated on recommended culture media and incubated at 37°C for 24 to 48 hrs. Identification of isolates was done by standard microbiological methods including colony morphology, Gram staining and biochemical reactions. Gram-positive cocci, positive for catalase, DNAse and slide coagulase tests were considered as S. aureus. MRSA was detected by using cefoxitin (30µg) disc on Muller-Hinton agar (MHA) as per CLSI 2014 guidelines[8]. Ceftaroline (5µg) disc was applied after swabbing the isolates of MRSA on MHA. Zone of inhibition of ceftaroline was measured after 24 hours of incubation at 370C. According to CLSI recommendations, zone of inhibition ≥24 mm was considered susceptible, 21 to 23 mm as intermediate and <20 mm as resistant. The data was analyzed by SPSS software (version 19). For qualitative variables of ceftaroline susceptibility, descriptive statistics of percentages were calculated and presented in the table.

RESULTS

In this study, a total of 190 MRSA isolates were cultured from different clinical specimens. Out of these, 183 (96.3%) MRSA isolates were susceptible to ceftaroline, 5 (2.6%) were resistant to it, whereas 2 (1.1%) were intermediate (table).

Table: MRSA susceptibility to ceftaroline.

		n	Percentage (%)
Zone of Inhibition around Ceftaroline (5µg) disc	Susceptible	183	96.3
	Resistant	5	2.6
	Intermediate	2	1.1
Total		190	100

Susceptible ≥24 mm, Intermediate 21 to 23 mm and Resistant <20 mm

DISCUSSION

The active component of prodrug ceftaroline fosamil is ceftaroline. This newer and broad spectrum cephalosporin antibiotic has demonstrated an in vitro activity against community acquired bacterial pneumonia (CABP) and typical acute bacterial skin and skin structure infections (ABSSSI) pathogens. These include resistant gram-positive pathogens such as MDR Streptococcus pneumoniae (MDRSP) and MRSA. Gram-negative pathogens include enteric gram-negative non-extended-spectrum β-lactamase (non-ESBL) producing Escherichia coli and Klebsiella pneumoniae and others such as Moraxella catarrhalis and β-lactamase–producing Haemophilus influenzae[9].

Castanheira et al assessed worldwide Antimicrobial Resistance Evaluation program in the United States from 2008 to 2010, in which surveillance for ceftaroline resistance was performed for 12062 gram-positive clinical isolates including 8469 S. aureus and 3329 S. pneumoniae in 72 US hospitals. According to his results, susceptibility of MRSA to ceftaroline was 98%[10]. Our results were comparable to what was presented by Castanheira M et al, as in this study also, the susceptibility of MRSA to ceftaroline was very high (96.3%).

Ceftaroline fosamil was approved in Nov 2010, by the US Food and Drug Administration (FDA) for the treatment of ABSSSI. Because of the extended ceftaroline activity against gram-positive organisms, including MRSA and MDRSP, this parenteral cephalosporin is considered by some to represent a new generation of cephalosporins. It has been shown to have a high in vitro affinity for PBP2a in MRSA and for MDRSP with common amino acid mutations in PBP2a, PBP2x, and PBP1a, including cefotaxime and ceftriaxone resistant strains. Ceftaroline has also been shown in vitro to be very active against emerging non-vaccine serotypes of Streptococcus pneumoniae including MDR serotype 19A[11,12]. Critchley et al compared the response of ceftaroline with that of ceftriaxone in adults with CABP. The cure rate was 84.3% and 77.7% in the patients treated with ceftaroline and ceftriaxone respectively[12].

Several studies of ceftaroline in a rabbit endocarditis model have been conducted. After a 4-day treatment regimen mimicking a human infusion of 600 mg 12 hourly, ceftaroline demonstrated excellent bactericidal activity with at least a 6-log colony-forming unit/g decrease against 2 strains of MRSA[13]. It also exhibited similar bactericidal activity in aortic valve vegetations, compared with vancomycin, against a vancomycin-sensitive strain of MRSA (ceftaroline MIC, 1 mg/L; vancomycin MIC, 1 mg/L), but a superior bactericidal activity against hVISA strain (ceftaroline MIC, 2 mg/L; vancomycin MIC, 4 mg/L). On vegetations ceftaroline exhibited a greater reduction in bacterial titers. It was demonstrated in another study when it was compared with that of vancomycin, against VRE (vancomycin resistant strains of Enterococcus faecalis) (ceftaroline MIC, 1 mg/L; vancomycin MIC, >256 mg/L) and its vancomycin-susceptible strains (ceftaroline MIC, 2 mg/L; vancomycin MIC, 2 mg/L).14 A similar bactericidal activity was observed on aortic valve vegetations when in a study the administration of ceftaroline and teicoplanin was compared against a strain of MRSA (ceftaroline MIC, 1 mg/L; teicoplanin MIC, 0.5 mg/L). It was observed that ceftaroline (Cmax 515.8 mg/L) sterilized 8 of 10 vegetations, compared with 6 of 10 vegetations that were sterilized by teicoplanin after 4 days of this dosage regimen. It was also found that a higher dose (40 mg/kg) of ceftaroline (Cmax 537.9 mg/L) was not proved to be more effective statistically[15].

After 4 days of treatment, bacterial titers were determined in joint fluid, bone marrow, and bone specimens. Against one strain of MRSA (ceftaroline MIC, 1 mg/L; vancomycin MIC, 1 mg/L; linezolid MIC, 2 mg/L), bacterial titers after vancomycin treatment were not different than in control specimens for all three tissues. Ceftaroline and linezolid demonstrated similar decreases in bacterial titers in bone marrow and bone specimens[16]. In vitro activity of ceftaroline was compared with ceftriaxone against multiple clinical MRSA and HeR-MRSA isolates. Ceftaroline was active against all HeR-MRSA isolates with MIC in the range of 0.25 µg/mL to 1 µg/mL. While MIC of ceftriaxone was between 0.5 and >32 µg/mL[17].

The rapid development of resistance and cross-resistance or co-resistance to other antimicrobial agents and classes are always of concern after the introduction of a new antimicrobial agent into clinical use. In a recent study, ceftaroline failed to induce in vitro mutational resistance and cross-resistance to other agents in both *S. aureus* (including MRSA strains) and *S. pneumoniae* (including MDRSP strains), even after 50 consecutive days of passages. This suggested that the in vivo development of mutational resistance against ceftaroline in these species is potentially low[18].

Ceftaroline has been shown to be very active in vitro against a large contemporary and geographically diverse collection of *S. aureus* (including MRSA) and *S. pneumoniae* (including MDR and ceftriaxone-resistant strains). For both ABSSSI and CABP in both adults and children, β-lactam agents are recommended as first-line therapeutic agents in developed parts of the

world if the strain causing infection is documented as being susceptible, revealing an emphasis on pathogen-directed therapy rather than an empirical therapy[19,20].

CONCLUSION

Ceftaroline can be used effectively against infections caused by MRSA, as it has shown very high in vitro activity against MRSA strains of clinical origin.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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