ICAAC 2014
K-1701

Antimicrobial Activity of Ceftaroline Tested against *Staphylococcus aureus* from Surgical Skin and Skin Structure Infections in USA Medical Centers

HS SADER, DJ FARRELL, RK FLAMM, RN JONES
JMI Laboratories, North Liberty, Iowa, USA

Helio S. Sader, MD, PhD
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
ph. 319.665.3370
fax 319.665.3371
helio-sader@jmilabs.com

Abstract

Background: Ceftaroline (CPT), the active form of CPT fosamil, is a cephalosporin approved by the United States Food and Drug Administration (USA-FDA) for treatment of acute bacterial skin and skin structure infection, including those caused by methicillin-resistant *S. aureus* (MRSA). We evaluated the activity of CPT and comparator agents tested against *S. aureus* strains isolated from surgical skin and skin structure infections (SSSI).

Methods: Clinically significant isolates (one/patient episode) were consecutively collected from surgical SSSI in 64 medical centers in the USA over a six-year period (2008-2013) and tested for susceptibility by reference CLSI broth microdilution methods against ceftaroline and several comparator agents.

Results: A total of 794 strains were tested and 50.5% were MRSA. CPT was active against oxacillin-susceptible *S. aureus* (MSSA; MIC_{90}, 0.25 µg/mL) and MRSA (MIC_{90}, 1 µg/mL). Against MSSA, CPT was 16-fold more potent than ceftriaxone (MIC_{90}, 4 µg/mL) and four- to eight-fold more potent than vancomycin (MIC_{90}, 1 µg/mL) and linezolid (MIC_{90}, 2 µg/mL). Similar to cefazolin (data not shown), the highest CPT MIC among MSSA was only 0.5 µg/mL. Among MRSA, 97.5% and 100.0% of strains were inhibited at ≤1 and ≤2 µg/mL of CPT, respectively (Table); whereas all other β-lactams exhibited very limited activity against this organism. 27.4% and 67.5% of MRSA were resistant to clindamycin and levofloxacin, respectively. Daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL), linezolid ($MIC_{50/90}$, 1/2 µg/mL), tigecycline ($MIC_{50/90}$, 0.06/0.12 µg/mL) and vancomycin ($MIC_{50/90}$, 1/2 µg/mL) were active against all *S. aureus* strains.

Conclusions: CPT exhibited potent in vitro activity against *S. aureus* causing surgical SSSI in a large number of USA hospitals, including MRSA. Based on this in vitro data, this novel cephalosporin may represent a valuable option for treatment of surgical SSSI, as well as for surgical prophylaxis since one-half of strains were MRSA.

Organism	No. of isolates (cumulative %) inhibited at ceftaroline MIC (µg/mL) of:						MIC (µg/mL)	
(no. tested)	0.06	0.12	0.25	0.5	1	2	50%	90%
S. aureus (794)	4 (0.5)	44 (6.0)	324 (46.9)	218 (74.3)	194 (98.7)	10 (100.0)	0.5	1
MSSA (393)	4 (1.0)	44 (12.2)	324 (94.7)	21 (100.0)	--	--	0.25	0.25
MRSA (401)	0 (0.0)	0 (0.0)	0 (0.0)	197 (49.1)	194 (97.5)	10 (100.0)	1	1

Abbreviations: MRSA: methicillin-resistant *S. aureus*; MSSA: methicillin-susceptible *S. aureus*.

Introduction

Ceftaroline, the active metabolite of the prodrug ceftaroline fosamil, is a broad-spectrum cephalosporin with bactericidal activity against resistant Gram-positive organisms, including methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant (MDR) strains of *Streptococcus pneumoniae*, and common Gram-negative organisms, including non-ESBL-phenotype Enterobacteriaceae. Ceftaroline fosamil is approved by the United States (USA) Food and Drug Administration (FDA) for treatment of acute bacterial skin and skin structure infection (ABSSSI), including those caused by MRSA.

Surgical SSSI causes significant patient morbidity and mortality and substantial increase in health care costs in the United States. *S. aureus* is the most common cause of surgical SSSI, and MRSA accounts for a large proportion of these infections. Furthermore, compared to infections due to methicillin-susceptible *S. aureus* (MSSA), MRSA infections have been associated with increased mortality, treatment failure, length of hospital stay and costs. We evaluated the activity of ceftaroline and comparator agents tested against *S. aureus* strains isolated from surgical skin and skin structure infections (SSSI).

Methods

Organism collection: Clinically significant isolates (one per patient) were consecutively collected from surgical SSSI in 64 medical centers in the USA over a six-year period (2008-2013), and the antimicrobial susceptibility testing results for *S. aureus* isolates from surgical SSSI (794 strains) are presented here. Isolates were sent to the coordinator laboratory (JMI Laboratories, North Liberty, Iowa, USA) for confirmatory identification and reference susceptibility testing. Species identification was confirmed when necessary by Matrix-Assisted Laser Desorption Ionization-Time Of Flight Mass Spectrometry (MALDI-TOF MS) using the Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, USA) by following the manufacturer's instructions.

Susceptibility testing: Isolates were tested for susceptibility to ceftaroline and multiple comparator agents by reference broth microdilution methods as described by Clinical and Laboratory Standards Institute (CLSI) M07-A9 (2012) and CLSI interpretations were based on CLSI (M100-S24) and EUCAST (2014) breakpoint criteria. Validated MIC panels were manufactured by ThermoFisher Scientific (Cleveland, Ohio, USA). Isolates were tested in cation-adjusted Mueller-Hinton broth. Concurrent testing of quality control strains assured proper test conditions.

Results

- MRSA accounted for 50.5% of *S. aureus* and ceftaroline was active against MSSA (MIC_{50} and MIC_{90}, 0.25 µg/mL; 100.0% susceptible) and MRSA (MIC_{50} and MIC_{90}, 1 µg/mL; 97.5% susceptible; Table 1 and Figure 1).
- Against MSSA, ceftaroline (MIC_{50} and MIC_{90}, 0.25 µg/mL) was 16-fold more potent than ceftriaxone (MIC_{50} and MIC_{90}, 4 µg/mL) and four- to eight-fold more potent than vancomycin (MIC_{50} and MIC_{90}, 1 µg/mL) and linezolid (MIC_{50}, 1 µg/mL and MIC_{90}, 2 µg/mL; Table 1).
- The highest ceftaroline MIC among MSSA was only 0.5 µg/mL and 82.4% of strains had a ceftaroline MIC of 0.25 µg/mL (Figure 1).
- Among MRSA, 97.5% and 100.0% of strains were inhibited at ≤1 and ≤2 µg/mL of ceftaroline, respectively (Table 1 and Figure 1); whereas all other β-lactams exhibited very limited activity against this organism (Table 1).
- Resistance to clindamycin (MIC_{50}, ≤0.25 µg/mL and MIC_{90}, >2 µg/mL) and levofloxacin (MIC_{50}, 4 µg/mL and MIC_{90}, >4 µg/mL) were 27.4% and 67.5% among MRSA strains, respectively (Table 1).
- Daptomycin (MIC_{50}, 0.25 µg/mL and MIC_{90}, 0.5 µg/mL), linezolid (MIC_{50}, 1 µg/mL and MIC_{90}, 2 µg/mL), tigecycline (MIC_{50}, 0.06 µg/mL and MIC_{90}, 0.12 µg/mL) and vancomycin (MIC_{50} and MIC_{90}, 1 µg/mL) were active against all *S. aureus* strains (Table 1).

Figure 1. Ceftaroline activity when tested against 793 *S. aureus* isolates from surgical skin and skin structure infections

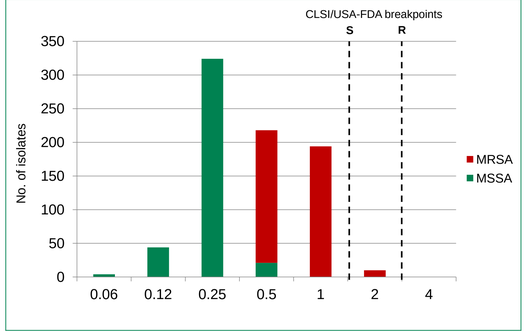

Table 1. Activity of ceftaroline and comparator antimicrobial agents when tested against 794 isolates of *S. aureus* from surgical skin and skin structure infections (USA, 2008-2013)

Antimicrobial agent	MIC (µg/mL)			%S / %I / %R	
	MIC_{50}	MIC_{90}	Range	CLSI[a]	EUCAST[a]
S. aureus (794)					
Ceftaroline	0.5	1	0.06 – 2	98.7 / 1.3 / 0.0	98.7 / 0.0 / 1.3
Oxacillin	>2	>2	≤0.25 – >2	49.5 / 0.0 / 50.5	49.5 / 0.0 / 50.5
Ceftriaxone	8	>8	0.5 – >8	49.5 / 0.0 / 50.5	49.5 / 0.0 / 50.5
Erythromycin	>2	>2	≤0.25 – >2	36.8 / 2.5 / 60.7	37.0 / 0.5 / 62.5
Clindamycin	≤0.25	>2	≤0.25 – >2	82.5 / 0.0 / 17.5	82.2 / 0.3 / 17.5
Levofloxacin	≤0.5	>4	≤0.5 – >4	58.7 / 1.1 / 40.2	58.7 / 1.1 / 40.2
TMP/SMX[b]	≤0.5	≤0.5	≤0.5 – >2	99.0 / 0.0 / 1.0	99.0 / 0.0 / 1.0
Tetracycline	≤2	≤2	≤2 – >8	96.0 / 0.9 / 3.1	94.6 / 0.4 / 5.0
Tigecycline[c]	0.06	0.12	≤0.03 – 0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Linezolid	1	2	0.5 – 2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / - / -	100.0 / 0.0 / 0.0
MSSA (393)					
Ceftaroline	0.25	0.25	0.06 – 0.5	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Ceftriaxone	4	4	0.5 – >8	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Erythromycin	≤0.25	>2	≤0.25 – >2	64.6 / 3.6 / 31.8	64.9 / 0.7 / 34.4
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	92.6 / 0.0 / 7.4	92.3 / 0.3 / 7.4
Levofloxacin	≤0.5	4	≤0.5 – >4	87.0 / 0.8 / 12.2	87.0 / 0.8 / 12.2
TMP/SMX[b]	≤0.5	≤0.5	≤0.5 – >2	99.7 / 0.0 / 0.3	99.7 / 0.0 / 0.3
Tetracycline	≤2	≤2	≤2 – >8	95.4 / 1.5 / 3.1	94.1 / 0.3 / 5.6
Tigecycline[c]	0.06	0.12	≤0.03 – 0.25	100.0 / - / -	100.0 / 0.0 / 0.0
Linezolid	1	2	0.5 – 2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Vancomycin	1	1	0.5 – 2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / - / -	100.0 / 0.0 / 0.0
MRSA (401)					
Ceftaroline	1	1	0.5 – 2	97.5 / 2.5 / 0.0	97.5 / 0.0 / 2.5
Ceftriaxone	>8	>8	8 – >8	0.0 / 0.0 / 100.0	0.0 / 0.0 / 100.0
Erythromycin	>2	>2	≤0.25 – >2	9.5 / 1.5 / 89.0	9.7 / 0.3 / 90.0
Clindamycin	≤0.25	>2	≤0.25 – >2	72.6 / 0.0 / 27.4	72.3 / 0.3 / 27.4
Levofloxacin	4	>4	≤0.5 – >4	31.0 / 1.5 / 67.5	31.0 / 1.5 / 67.5
TMP/SMX[b]	≤0.5	≤0.5	≤0.5 – >2	98.3 / 0.0 / 1.7	98.3 / 0.0 / 1.7
Tetracycline	≤2	≤2	≤2 – >8	96.5 / 0.3 / 3.2	95.0 / 0.5 / 4.5
Tigecycline[c]	0.06	0.12	≤0.03 – 0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Linezolid	1	2	0.5 – 2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / - / -	100.0 / 0.0 / 0.0

a. Criteria as published by the CLSI (2014) and EUCAST (2014).
b. TMP/SMX: trimethoprim/sulfamethoxazole.
c. In the absence of CLSI breakpoints, USA-FDA breakpoints were applied when available (Tygacil Product Insert, 2012).

Conclusions

- Ceftaroline exhibited potent in vitro activity against *S. aureus*, including MRSA, causing surgical SSSI in a large number of USA hospitals.
- Based on this in vitro data, this new cephalosporin may represent a valuable option for treatment of surgical SSSI, as well as for surgical prophylaxis since one-half of strains were MRSA.

References

1. Clinical and Laboratory Standards Institute (2012). *M07-A9. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: ninth edition.* Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute (2014). *M100-S24. Performance standards for antimicrobial susceptibility testing: 24th informational supplement.* Wayne, PA: CLSI.
3. Edmond MB, Wenzel RP (2013). Screening inpatients for MRSA--case closed. *N Engl J Med* 368: 2314-2315.
4. EUCAST (2014). Breakpoint tables for interpretation of MICs and zone diameters. Version 4.0, January 2014. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 2014.
5. Flamm RK, Farrell DJ, Sader HS, Jones RN (2014). Antimicrobial activity of ceftaroline combined with avibactam tested against bacterial organisms isolated from acute bacterial skin and skin structure infections in United States medical centers (2010-2012). *Diagn Microbiol Infect Dis* 78: 449-456.
6. Jones RN, Mendes RE, Sader HS (2010). Ceftaroline activity against pathogens associated with complicated skin and skin structure infections: Results from an international surveillance study. *J Antimicrob Chemother* 65 Suppl 4: iv17-iv31.
7. Liu C (2011). The bundled approach to MRSA surgical site infection prevention: is the whole greater than the sum of its parts?: comment on "Sustained reduction in methicillin-resistant Staphylococcus aureus wound infections after cardiothoracic surgery". *Arch Intern Med* 171: 73-74.
8. Pfaller MA, Flamm RK, Sader HS, Jones RN (2014). Ceftaroline activity against bacterial organisms isolated from acute bacterial skin and skin structure infections in United States medical centers (2009-2011). *Diagn Microbiol Infect Dis* 78: 422-428.
9. Sader HS, Flamm RK, Jones RN (2013). Antimicrobial activity of ceftaroline tested against staphylococci with reduced susceptibility to linezolid, daptomycin or vancomycin from USA hospitals (2008–2011). *Antimicrob Agents Chemother* 57: 3178-3181.
10. Teflaro® Package Insert (2012). Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/200327s009lbl.pdf. Accessed July 2014.

Acknowledgments

This study was supported by Cerexa, LLC, a wholly-owned subsidiary of Forest Laboratories, LLC. Forest Laboratories, LLC, was involved in the design and decision to present these results and JMI Laboratories received compensation fees for services in relation to preparing the abstract/poster, which was funded by the sponsor. Forest Laboratories, LLC, had no involvement in the collection, analysis, and interpretation of data.