Ceftaroline-Associated Neutropenia: Retrospective Study and Systematic Review of Incidence, Risk Factors, and Outcomes

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BACKGROUND

- *Staphylococcus aureus* remains a leading cause of bacteremia and endocarditis, with an increasing preponderance due to methicillin-resistant *S. aureus* (MRSA) strains.
- Due to the limitations of the currently available antibiotics (e.g., vancomycin) for treating MRSA infections including drug intolerance, adverse events, and/or clinical failure, new antibiotics with anti-MRSA activity have been developed.
- Ceftaroline (Teflaro®) received FDA approval in 2010 for community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI).
- Ceftaroline has been utilized off-label to treat MRSA endocarditis and orthopedic infections.
  - For these indications, ceftaroline has often been utilized for longer treatment durations (up to ≥6 weeks) and at higher doses (600 mg every 8 hours vs. 12 hours).
- Data on potential adverse events associated with ceftaroline use, especially when utilized for longer durations or at higher doses, are needed. To date, post-marketing case reports of neutropenia among patients receiving extended durations of ceftaroline have been published; however, data remains limited.

OBJECTIVES

- Describe cases of ceftaroline-associated neutropenia (ANC<1500 cells/mm^3) in a large healthcare system and to conduct a systematic review of the English literature of published cases.

METHODS

- Retrospective chart review of all inpatient ceftaroline prescriptions (January 2010-December 2017) in our healthcare system located in Southern California (i.e., four large, urban hospitals with a total of 1400 beds).
- Systematic review of the published English medical literature from 2010 to December 2017.
- **Inclusion Criteria**
  - Patients ≥ 18 years old
  - Received ceftaroline for ≥ 7 days
  - Experienced neutropenia (ANC<1500 cells/mm^3)
- **Exclusion Criteria**
  - Neutropenia pre-existed initiation of ceftaroline
  - Alternate cause for neutropenia
  - No or limited individualized data could be obtained (for systematic review)

RESULTS

- Within our healthcare system, a total of 61 patients received ceftaroline for ≥7 days; 56 met inclusion criteria and 7% (n=4) developed neutropenia without another identifiable cause. All four patients were being treated for MRSA infections and had favorable outcomes (Table 1).
- For the systematic review, 37 cases were identified including our 4 cases (Table 2).
- Overall incidence of ceftaroline-associated neutropenia was 12% (range 7-18%) for studies with case:control data (Table 3).

Table 1: Details of Current Cases of Ceftaroline-Associated Neutropenia

Age/ Sex	Indication	Dose	Duration (days)	Nadir ANC (cells/mm^3)	Days of Neutropenia
66 M	Prosthetic knee infection	300 mg IV q8 hr	8	1205	2
59 F	Bacteremia, endocarditis, diskitis/osteomyelitis	400 mg IV q8 hr	20	20	10
26 F	Bacteremia, endocarditis	600 mg/400 mg IV q8 hr	21	5	7
44 M	Osteomyelitis, endocarditis	600 mg IV q12 hr	23	1472	2

Table 2:Summary Characteristics of Patients in the Systematic Review Receiving Ceftaroline who Developed Neutropenia, 2010-2017, n=37

Age, median, years	44 (range 20-90)
Sex, female	22/37 (59%)
Organism treated	
S. aureus	31/37 (83%)
Neutropenia	
Median time to development, days	25 (range 8-125)
Nadir ANC<100 cells/mm^3	18/37 (49%)
Mean duration of neutropenia, days	4 days (range 1-16)
Concurrent antibiotic, yes	12/30 (40%)
Concurrent renal insufficiency (CrCl < 60 ml/min)	7/27 (26%)
Concurrent hematologic effects	
New-onset anemia (hemoglobin decline of ≥2 mg/dl)	6/25 (24%)
New-onset thrombocytopenia (drop of >100 cells/mm^3)	8/26 (31%)
Eosinophilia	9/26 (35%)
Neutropenic complications: Fever or Bacteremia	6/37 (16%) / 1 (3%)
Receipt of G-CSF for neutropenia	11/37 (30%)

RESULTS

Table 2 Continued

Ceftaroline Dosage	
CrCl > 50 ml/min: 600 mg q12 hr / 600 mg q8 hr	15/22 (68%) / 7/22 (32%)
CrCl 31- 50 ml/min: 600 mg q12 hr / 400 mg q8 hr	1/3 (33%) / 2/3 (67%)
CrCl 15-30 ml/min: 400 mg q12 hr / 300 mg q8 hr	1/2 (50%) / 1/2 (50%)
CrCl Not Reported: 600 mg q12 hr / 600 mg q8 hr	5/7 (71%) / 2/7 (29%)
Dose Not Reported	3/3 (100%)
Favorable Outcome	37/37 (100%)

Table 3: Summary of Ceftaroline-Associated Neutropenia in Studies with Control Group

Study	Ceftaroline Use	Risk Factors	Incidence of Neutropenia
Furtek KJ et al.[1]	≥7 days	Duration of ceftaroline	7% (5/67)
LaVie KW et al.[4]	≥7 days	Female sex & low BMI	18% (7/39)
Turner RB et al.[8]	≥14 days	None identified	17% (9/53)
Current Study	≥7 days	None identified	7% (4/56)
All Studies	**≥7-14 days**	**------**	**12% (25/215)**

CONCLUSIONS

- Neutropenia was common during long-term use of ceftaroline
  - Median time of occurrence was 25 days
  - Overall incidence of neutropenia was 12% (25/215 total patients; range 7%-18%) when ceftaroline was utilized for ≥7-14 days
- Risk factors remain unclear. Previous studies have suggested antibiotic duration[1], female sex[4], and low BMI[4] to be factors, but these have not been consistent among studies.
- Recommend baseline and at least weekly CBC/diff monitoring and more frequent if a decline in ANC is observed while receiving ceftaroline.

REFERENCES

(1) Furtek KJ, et al. J Antimicrob Chemother 2016. (2) Jain R, et al. Pharmacotherapy 2014. (3) Khan U, et al. BMJ Case Rep Published online 2017. (4) LaVie KW, et al. Antimicrob Agents Chemother 2015. (5) Phull P, et al. J Hematol 2016. (6) Rimawi RH, et al. J Clin Pharm Ther 2013. (7) Sahar N et al. J Med Cases 2016. (8) Turner RB, et al. J Antimicrob Chemother 2018. (9) Varada NL, et al. Pharmacotherapy 2015. (10) Yam FK, et al. Am J Health Syst Pharm 2014.