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REVIEW ARTICLE

Risk of Neutropenia with the Use of Ceftaroline: A Review

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Abstract

Objective: Ceftaroline is a fifth-generation cephalosporin with activity against methicillin-resistant *Staphylococcus aureus* (MRSA), which is a clinically distinct feature for a member of this class. Cephalosporins have previously been associated with neutropenia, a serious hematologic condition with an absolute neutrophil count (ANC) falling below 1500-1800 cells/µL. Since its FDA approval in 2010, ceftaroline has been associated with neutropenia in several studies. In this review, our aim is to examine these reports and evaluate their findings.

Data sources: A systematic search was conducted using PubMED, Embase, and Web of Science databases. Keywords utilized in the search were "ceftaroline, or Teflaro, or Zinforo" and "neutropenia."

Study selection: Case reports, case series, observational, and experimental studies in the English language of human participants were included. For inclusion, neutropenia was defined as an ANC of no more than 1800 cells/µL. Studies reporting concurrent exposure to chemotherapy were excluded.

Data extraction/synthesis: Search results produced eight published articles that underwent review by the authors. Two case studies and six observational studies highlighted a common theme and outcome: Extended use of ceftaroline with exposure greater than two consecutive weeks is associated with an increased risk of neutropenia.

Conclusions: To our knowledge, this is the first review to explore the risk of neutropenia with ceftaroline use. Despite the limited amount of relevant published research, existing results suggest a potential association. Large well-designed observational studies are needed to delineate the impact and implications of this serious adverse event.

Keywords

Ceftaroline, Cephalosporins, Neutropenia, Adverse drug reaction, Pharmacoepidemiology

Introduction

Neutrophils are a type of white blood cells (WBCs) that maintain a vital role in defending the human body from bacteria, fungi, and other infectious organisms [1]. In clinical practice, the ANC is oftentimes reported as a laboratory result, but it can also be easily derived by multiplying total WBCs by the percentage of neutrophils. In most healthy individuals, the ANC ranges between 2,500 cells/µL and 6,000 cells/µL [2]. While neutropenia is generally defined as an ANC of less than 1,500 cells/µL [3], a less widely used cutoff of less than 1,800 cells/µL has been used by the World Health Organization (WHO) [4]. Neutropenia can be further classified based on the severity into three categories, including, mild (1,000 to 1,500 cells/µL), moderate (500 to 1,000 cells/µL) and severe (< 500 cells/µL) [5]. Common etiologies of neutropenia include infection, myeloid suppression, immune-mediated conditions, and certain medications [1]. Nonchemotherapy drug-induced neutropenia is commonly referred to as idiosyncratic drug-induced neutropenia (IDIN), as its exact mechanism has not been fully elucidated [1]. While the incidence of IDIN is relatively uncommon, ranging from 2 to 15 cases per million in the United States (U.S); [6] it is strongly attributed to approximately 70% of severe cases of neutropenia [1]. Severe neutropenia is associated with an increased risk of morbidity and mortality, which is even more pronounced in patients over 65 years of age, and those with renal disease, sepsis, or shock [1]. A number of anti-infective agents have been associated with IDIN. Notably, beta-lactam antibiotics, including penicillin derivatives, cephalosporins, carbapenems and monobactams, account for 48% of antibiotic-

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associated IDIN [7]. In particular, cephalosporins have been associated with IDIN in several reports during the last several decades [8-15]. Moreover, a number of 3rd generation cephalosporins have contributed to 43% of beta-lactam-associated severe neutropenia in one retrospective cohort study (Vial T, 2019).

Ceftaroline, the first 5th generation cephalosporin, is unique in being the only FDA-approved cephalosporin with antimicrobial activity against MRSA [16]. It is currently FDA-approved for acute bacterial skin and skin structure infections (SSTIs) and bacterial community acquired pneumonia (CAP) [16]. Due to the limited available therapeutic options for MRSA, off-label use of ceftaroline is not uncommon [17]. High daily doses and long duration of therapy, ranging from several weeks to months, are oftentimes used to treat complicated MRSA-related osteomyelitis, endocarditis and bacteremia [14,17]. Since beta-lactam associated IDIN has been shown to be dose- and/or duration-dependent, it becomes a challenge when used clinically for these off-label indications [7]. A number of reports have signaled a potential link between ceftaroline and neutropenia [17-24]. Therefore, we aim to review available studies of ceftaroline and its potential association with neutropenia to better understand the risk of this serious adverse event with its use.

Literature Search Strategy

A literature search was conducted on PubMed, Embase, and Web of Science to identify all studies examining the association between ceftaroline use and neutropenia. A search string was developed using the terms “ceftaroline”, “Teflaro”, and “Zinforo”, to indicate the exposure, and “neutropenia” to indicate the adverse event of interest. Teflaro and Zinforo are the two brand name formulations in the U.S. and Europe, respectively [25,26]. We included studies from all years, as ceftaroline was approved by the FDA first in 2010, and there has not been a prior review of the association with neutropenia [25]. For inclusion, neutropenia was defined as an ANC of no more than 1800 cells/µL. Results were limited to articles written in English and conducted with human subjects. Studies with reported concurrent exposure to chemotherapy or immunosuppressive agents were excluded as they pose independent risk factors for neutropenia [3]. Furthermore, reports of agranulocytosis, defined as an ANC of 0 cells/µL [27], were excluded. Two authors conducted the literature search independently and articles were included based on meeting the criteria of the search string and consensus between authors.

Results

Utilizing the search terms and limits previously outlined, the search generated 16 articles on PubMed, 80 on Embase, and 18 on Web of Science. After examining the titles and abstracts, there were eight articles that met inclusion. A number of studies were excluded for reviewing the clinical efficacy of ceftaroline, use of non-English language, or use of *in vivo/in vitro* research methods. Of the eight included, two articles were case studies and six were observational studies. Of the six observational studies, five were retrospective chart reviews and one was a retrospective cohort study. Three of the studies were multi-center reviews and three were single center reviews, including the one cohort study. The primary outcomes of these studies were either development of neutropenia or discontinuation of ceftaroline therapy, with the exception of one study that examined the clinical efficacy of MRSA bloodstream infection clearance. The latter study by Zasowski, et al. (2017) reported on the incidence of neutropenia during ceftaroline therapy; therefore, it was included in our review (Table 1).

Among the majority of chart reviews, a relatively small number of participants were included (median n = 67, range: 12-211). Only one study had a sample of over 100 participants, which was the retrospective review conducted by Zasowski, et al. encompassing 211 MRSA infected patients treated with ceftaroline [24]. Overall, participants who received ceftaroline were mostly male, and neutropenia onset consistently occurred after prolonged ceftaroline therapy of greater than 13 days. In all studies, discontinuation of ceftaroline therapy led to increased ANC within approximately one month during follow-up. The chart reviews were conducted in various locations across the U.S., including the Southeast, Midwest, and the Pacific Northwest.

Furthermore, these studies encompassed diverse patient populations, including participants from the Veterans Administration and academic teaching hospitals [17-24]. In the review by LaVie, et al. 39 patients were studied after receiving ceftaroline for more than seven days. Of the seven patients that developed neutropenia in the study, six were on the typical dose of ceftaroline (600 mg intravenously every 12 hours). In this study, participants who developed neutropenia were more likely to be female, with five out of seven cases occurring in females. Additionally, a trend of normal-low body mass index (BMI) was observed in patients that developed neutropenia, with a median BMI 23.9 kg/m^2 compared to 31.55 kg/m^2 in nonneutropenic patients ($p < 0.024$).

While one of the neutropenic patients had a BMI of 34.1 kg/m^2, the BMI for remaining six neutropenic participants was 26.2 kg/m^2 or less. Neutropenia resolved rapidly upon discontinuation. Among patients that had ANC drop below 2,500 cells/µL, 70% (N = 10) went on to develop neutropenia. Therefore, the authors recommended obtaining a complete blood count (CBC) with differential semiweekly instead of weekly to closely monitor ANC if it falls below 2,500 cells/µL [17]. Another chart review by Furtek, et al. showed an incidence of

Table 1: Summary of literature found describing the relationship between ceftaroline use and neutropenia.

Authors	Year	Study Design	Population	Exposure	Neutropenia Development (%)	Time to Neutropenia	Time to Normal ANC
Turner, et al.	2017	Retrospective multi-center cohort study	Adult patients admitted to a 6-hospital health system in Portland, Oregon from 2011-2017 (n = 753)	Ceftaroline therapy for ≥ 14 days	36 (4.8%)	Mean 20 days (25^{th}-75^{th} percentile, 15-29)	Mean 3 days (range 2-23)[b]
Jain, et al.	2014	Retrospective multi-center chart review	Adult patients at University of Washington and Harborview Medical Centers from 2011 to 2012 (n = 12)	600 mg IV ceftaroline every 8 or 12 hours	4 (33%)	Mean 31 days. (Range 22-40)[c]	-
Furtek, et al.	2016	Retrospective multi-center chart review	Adult patients from Massachusetts General Hospital and Brigham and Women's Hospital from 2010 to 2015 (n = 67)	Ceftaroline therapy for ≥ 7 days	7 (10%)	Mean 29 days (range 13-64)	Mean 9 days (range 3-14)
Zasowski, et al.	2017	Retrospective multi-center chart review	Adult patients from 2011-2015 at Detroit Medical Center, UF Health-Shands Hospital, or Henry Ford Hospital (n = 211)	Ceftaroline treatment	3 (1.4%)	Mean 16 days (range 13-20)	-
Lavie, et al.	2016	Retrospective single-center chart review	Adult patients admitted to an 800-bed academic medical center from 2012 to 2014 (n = 39)	Ceftaroline therapy for ≥ 7 days	7 (18%)	Median first neutropenic day was day 17	Within 1 month
Jansen, et al.	2017	Retrospective single-center chart-review	Patients at VA St. Louis Health Care System (n = 75)	At least one dose of ceftaroline from 2010-2017	3 (4%)	Mean 40 days (range 37-42)	-
Rimawi, et al.	2013	Case Study	90-year-old female (n = 1)	600 mg IV ceftaroline every 12 hours	1 (100%)	25 days	1 week
Yam, et al.	2014	Case Study	67-year-old Caucasian man (n = 1)	600 mg IV ceftaroline every 8 hours	1 (100%)	3 weeks	9 days

a) In patients developing neutropenia

b) In those with consecutive days of neutropenia (19 out of 36 patients)

c) Time to discontinuation due to development of neutropenia

neutropenia of 10-14% (N = 67) with two weeks or more of continuous ceftaroline therapy. Furthermore, 21% of participants developed neutropenia with 3 weeks or more of ceftaroline exposure, which is a higher incidence rate than that reported in other studies. The median duration of ceftaroline exposure in patients who developed neutropenia was 26 days versus 15 days in patients who did not develop incident neutropenia (p-value = 0.048) [21]. Of note, this is the only study that defined neutropenia using the WHO's reference range of an ANC < 1,800 cells/mm^3 [21]. All the other studies included in the review defined neutropenia as an ANC < 1500 cells/µL. Studies that had shorter duration of ceftaroline therapy had lower incidence of neutropenia. For example, Zasowski, et al. reported that the average length of inpatient stay was only 11 days. Only three of the 211 patients in their study developed neutropenia, and all neutropenic patients had above average length of stay (13, 20, and 15 days) [24]. Due to this phenomenon, neutropenia could be underrepresented in this study because a longer exposure period to ceftaroline therapy is needed. In order to determine potential cofounders, the study by Jansen and Moenstar compared baseline allergies of participants who developed neutropenia

to those who did not but found no clinical difference [23]. The retrospective cohort study was the largest of the included studies with 753 participants. The study compared patients who received ceftaroline (n = 53) to patients that received a comparable antibiotic (n = 700) from April 2011 to September 2017. Comparable antibiotics were defined as cefazolin, daptomycin, linezolid, nafcillin, or vancomycin. A significantly higher incidence of developing neutropenia was found in ceftaroline patients compared with those who received one of the comparable antibiotics (17.0% vs. 3.9%, $p < 0.001$).

After controlling for other covariates, ceftaroline therapy continued to remain a risk factor for developing neutropenia (adjusted OR: 3.97, 95% CI: 1.61-9.78) compared to therapy with other antibiotics. Of note, patients who received ceftaroline were treated for more consecutive days compared to the patients on comparable antibiotics (median: 27 days, IQR: 18-39 vs. median: 18 days, IQR: 15-26) [20]. The two case reports mirror the chart reviews and case control study. Both case reports were of elderly patients (65+ years-old), one male and one female that underwent ceftaroline therapy for 21 and 34 days, respectively. Both patients showed an ANC of zero and significantly decreased WBC after two weeks of treatment. The patients discontinued treatment as a result, and ANC and WBC remained elevated several days after discontinuation. Both patients suffered from multiple chronic conditions and claimed no changes in their medications before or after starting ceftaroline [18,19].

Discussion

Relevance to previously published literature

Prior to the submission of the new drug application (NDA) in December 2009, Forest Laboratories Inc. appended the results of two sets of double-blind, randomized clinical trials (RCTs) investigating the efficacy and safety of ceftaroline for each of CAP and SSSIs [16,28-31]. Neutropenia was not reported as an adverse event in either FOCUS 1 or FOCUS 2 trials, which compared ceftaroline to ceftriaxone for CAP in over 1200 patients [28,29]. Furthermore, a combined safety analysis of the FOCUS trials did not reveal neutropenia as an adverse effect [32]. Similarly, the CANVAS 1 and 2 trials, which compared ceftaroline to the combination of vancomycin and aztreonam for SSTIs in 1396 patients, showed no neutropenia cases [30,31]. Additionally, the COVERS trial, which compared ceftaroline to the same combination used in the CANVAS trials in 761 patients with complicated SSTIs, reported no cases of neutropenia [33]. At the conclusion of the RCTs, ceftaroline was found to be well-tolerated, with a safety profile similar to the comparator agents used in these phase 3 trials. The associated risk of neutropenia and ceftaroline therapy was not first identified in published literature until post marketing studies demonstrated the association.

Evaluation of included evidence

The evidence in the literature for support of the association between ceftaroline and neutropenia is minimal. Although the variety in location and patient population across the literature makes a case for more generalizable conclusions to be made regarding this association, the quantity of the studies is small. A larger pool of literature would strengthen the validity of the review. Additionally, better quality literature with more robust study designs would lend itself to causal inference. With the majority of the literature being case reports or chart reviews with small samples, which are low levels of evidence, there is the possibility of making a spurious association due to unmeasured confounding. The one cohort study, though relatively large, has concerns of selection bias with significant differences between their study groups, which could have biased their estimates. The study was adequately powered to detect a difference between the exposed and control group, adding strength to the review.

Recommendations for researchers

Given that less than ten years have lapsed since its approval, available post marketing data is limited. Due to the inherent drawbacks of clinical trials, including limited duration and number of participants; they are deemed to lack the capacity for detecting rare side effects such as IDIN [34]. Furthermore, clinical trials usually under represent patients with complex health problems, especially the elderly, a population that is typically vulnerable to adverse events due to polypharmacy [3,34]. Therefore, more observational pharmacoepidemiologic studies should be considered to further evaluate the relationship between ceftaroline and neutropenia as that is a preferable research design to further understand the magnitude and impact of this uncommon adverse effect.

Recommendations for practitioners

Prolonged ceftaroline use for non-FDA approved indications is likely to continue due to the limited number of available options for treatment of MRSA [17]. A key recommendation for practitioners is more frequent monitoring of CBC with differential to obtain an ANC, especially for those with an ANC level trending to fall below 2500 cells/μL [17]. Factors other than prolonged duration of therapy that tended to be associated with an increased risk of neutropenia include female gender, low-normal BMI, and older age [17,19]. Of note, older age is a known risk factor for reduced kidney function and chronic kidney disease [35]. Therefore, it is important to be diligent when dosing ceftaroline in patients with these characteristics to avoid unwanted adverse events as it is primarily renally cleared. Ceftaroline renal dose

adjustment is warranted for patients with compromised kidney function as its area under the curve (AUC) can drastically increase 52-115%, depending on the level of renal impairment [27].

Conclusions

After consideration of the reviewed literature, it is clear that the association between ceftaroline and neutropenia warrants additional research to fully elucidate the risk of ceftaroline and the development of neutropenia. Our research indicates that across the United States and in varying patient populations the use of ceftaroline is positively associated with the development of neutropenia after prolonged use both on and off label. Since the first case report of neutropenia associated with ceftaroline use was published in 2013, three years after FDA approval, these chart reviews have continued to demonstrate this association with the culmination of a large multi-center retrospective cohort study in 2017. Despite the limitations of this literature, the cross-study agreement regarding prolonged therapy and the recovery of ANC within one month of therapy discontinuation suggests that this is not a spurious association and deserves more rigorous research.

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Authors Declaration

All authors participated in collection, organization, and writing of the following manuscript.

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