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Real life experience with Ceftobiprole in a tertiary care hospital

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Short title: Ceftobiprole in real life

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Highlights

- Data on the use of Ceftobiprole in real life, severely ill patients, are limited.
- A favorable clinical outcome was observed in 20 of 29 patients receiving Ceftobiprole.
- 3 patients had Ceftobiprole-related toxicity, including 2 cases of myoclonus.
- No major adverse effects on bone marrow, kidney and liver function were observed.

- Ceftobiprole is a safe and effective treatment for bacterial infections.

Abstract

Objectives: Ceftobiprole is a new therapeutic option for bacterial pneumonia, with activity against most antimicrobial resistant gram-positive cocci, including methicillin-resistant Staphylococcus aureus. Data on the use of Ceftobiprole in real life are limited. We evaluated the efficacy and safety of Ceftobiprole in a context of real life hospital practice.

Methods: In a single center, observational, retrospective clinical study, we collected data of 29 patients undergoing Ceftobiprole therapy, with a focus on clinical outcomes and adverse events.

Results: There was a high burden of comorbidities in the study cohort, including kidney dysfunction (38%) and cancer (24%), and high proportion of patients with sepsis/septic shock (72%), a central line (41%) or on mechanical ventilation (21%). Most infections were nosocomial (24, 82.8%). Ceftobiprole was mostly prescribed because of pneumonia (17 patients, 58.6%), and bloodstream infection (10 patients, 34.5%), both empirically (9 cases, 31%) and as targeted therapy (20, 69%, with Staphylococci as the dominant pathogens). It was the first-line drug in 15 cases (51.7%). Overall, a favorable clinical outcome was observed in the majority of cases (68.9%), with clinical cure in 3 (10.3%) and clinical improvement in 17 (58.6%). Failure of treatment occurred in 7 cases (24.1%). Three patients experienced a definite Ceftobiprole-related adverse event, with 2 cases of myoclonus. No major adverse effects on bone marrow, kidney and liver function were observed.

Conclusions: Ceftobiprole, even outside current indications, may be a safe and effective treatment for resistant gram-positive cocci infections where other molecules are inactive or poorly tolerated and for salvage therapy.

Key words: Ceftobiprole; Effectiveness; Safety; Adverse events; Outcomes; Bloodstream infection;

1. Introduction

The global increase in resistance to multiple antimicrobials continues to involve Gram-positive bacteria, particularly staphylococci, enterococci and streptococci (1), translating into rising costs in terms of morbidity, mortality and health care resource utilization (2). In recent years, a limited number of new effective antibiotics have been approved against resistant Gram-positive cocci, including Ceftobiprole (3), a new intravenous fifth-generation cephalosporin.

Ceftobiprole shows in vitro activity against a large number of Gram-positive and Gram-negative pathogens (4-6) causing hospital- and community-acquired pneumonia (HAP/CAP) as well as bloodstream infections (BSI). Its most relevant feature is activity against methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci and penicillin-resistant Streptococcus pneumoniae (7-11).

As a result of its spectrum of activity, Ceftobiprole can be administered as monotherapy in the empirical treatment of HAP. Furthermore, its use in infectious syndromes other than pneumonia has been described by case reports (12-15). When compared to other broad-spectrum cephalosporins, Ceftobiprole appears to have a lower effect on gut flora (16) and, in animal models, it does not promote growth of or toxin production by *Clostridioides difficile* (17).

To date, there are limited literature data on the use of Ceftobiprole in *real life*, i.e. for patients who more closely reflect daily clinical practice compared to those included in registration trials.

Therefore, the objective of this study was to describe, in a context of real life hospital practice, the efficacy and safety of Ceftobiprole in a single center.

2. Patients and Methods

2.1 Study design

This was a single center, observational, retrospective clinical study that collected data regarding the use in clinical practice of Ceftobiprole in the Monaldi Hospital, Naples, Italy, between November 2017 and October 2019. The diagnostic and therapeutic approach used in individual cases was not influenced by the decision to include patient clinical data in this study. Data retrieval was approved by our Institution Ethics Committee (Judgement protocol N. 314/2018).

2.2 Patients included in the study

All patients undergoing Ceftobiprole therapy, alone or in combination with other antimicrobials, within the accrual time, and who received at least three doses of the drug, were included in this study. There were no exclusion criteria.

2.3 Variables analyzed

Through a dedicated Case Report Form, the following variables were collected: clinical and hematochemical data, comorbidities (including Charlson comorbidity index) (18), severity of illness (19), infection data (20), indications for, doses and duration of Ceftobiprole administration, outcomes of treatment and hospitalization, occurrence of adverse events. Renal function was measured as estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI), based on the actual creatinine serum levels.

2.4 Clinical Outcomes

Clinical cure was defined as disappearance of signs and symptoms and normalization of biochemical infection markers coupled with the lack of need for further antibiotic therapy.

Clinical improvement was defined as reduction of the intensity of signs and symptoms as well as improvement of laboratory parameters, associated with transition to oral therapy/step down regimens.

Microbiological eradication was defined as clearance of the initial pathogen from the primary infection source.

Clinical failure was defined as persistence or relapse of the same infection, associated with withdrawal of Ceftobiprole and switch to another antimicrobial regimen.

Toxicity was defined as occurrence of any adverse event, as described below.

2.5 Safety assessment

No a priori or prospective search for adverse events was performed. We scrutinized patient files in order to detect adverse drug reactions most commonly observed with Ceftobiprole in clinical trials. These included fungal infections, skin rashes, altered consciousness, seizures/epilepsy, muscle spasms, diarrhea (including *Clostridioides difficile*), elevation of liver enzymes (AST, ALT, LDH, phosphatase alkaline), reactions at the infusion site, leukopenia, anemia, thrombocytosis, thrombocytopenia, dyspnea, asthma, and elevation of the blood levels of other routinely monitored parameters (triglycerides, creatinine, glucose, uric acid).

3. Results

The study included 29 patients, whose main clinical features are presented in Table 1.

Ceftobiprole was mostly administered in medical wards (n=18 pts, 62.1%), with a lower proportion of cases treated in surgical wards (n=6 pts, 20.7%, mostly Cardiac surgery) or an intensive care unit (n=5 pts, 17.2%).

A high burden of comorbidities was evident in the study cohort, as also shown by a median Charlson comorbidity index of 7. A large proportion of patients had ischemic heart disease (44.8%), heart failure (41.4%), and peripheral arterial disease (27.6%). The prevalence of chronic obstructive pulmonary disease and diabetes mellitus was also substantial (27.6% for both). Among diabetics, 75% of patients had overt target organ damage. Although Ceftobiprole does not show any hepatic metabolism or specific liver toxicity, it is noteworthy that our cohort also included 3 patients (10.3%) with moderate or severe liver disease. Seven patients (24.1%) had a solid or an hematological neoplasia.

The baseline renal functional profile of treated patients was also assessed. Based on the eGFR, all patients were classified into stages of chronic kidney disease (Table 1). A moderate or severe kidney disease (defined as an eGFR <30 ml/min or being on dialysis) was present in 11 patients (37.9%) and there were 7 patients on hemodialysis or other forms of renal replacement therapy.

Twelve (41.4%) patients carried a central venous line at the time of Ceftobiprole initiation and 6 patients (20.7%) started this drug while on mechanical ventilation. Of these, one had ventilator-associated pneumonia (VAP). A condition of sepsis was present in 17 of the 29 patients (58.6%), with a median SOFA score at diagnosis of 5 (range 2-15), whereas septic shock was evident in 4 patients (13.8%). Of note, in the treated cohort, SOFA increased by a median of 3 points (range 2-7) compared to admission when Ceftobiprole therapy was started.

There were hematological abnormalities at baseline, with a substantial proportion of patients showing significant anemia (Hgb <9 gr/dL; n=11 [37.9%]), and a 10.3% prevalence of leukopenia or thrombocytopenia.

Ceftobiprole was prescribed in 17 patients (58.6%) because of pneumonia, including HAP in 13 (81.2%) and CAP in 3 (18.8%) cases. One patient (3.4%) was treated because of VAP. Less common indications for Ceftobiprole use were BSI in 10 patients (34.5%), including infective endocarditis in 3 (10.3%), and skin and skin structure infection in 2 (6.9%). Accordingly, Ceftobiprole was used both in-label and off-label, with a propensity to use in nosocomial pneumonia (in-label) and bacteremia (off-label). Overall, Ceftobiprole-treated infections were nosocomial in 24 (82.8%) and community acquired in 5 (17.2%) patients. Ceftobiprole was used in an empirical antimicrobial regimen in 9 cases (31%) and as a targeted therapy in 20 (69%). Among the latter, causative agents of infection were methicillin-resistant *Staphylococcus aureus* in 7 (35%) patients, methicillin-sensitive *Staphylococcus aureus* in 2 (10%), coagulase-negative Staphylococci in 7 (35%, of which 6 were methicillin-resistant), and other pathogens in 4 (2 *Escherichia coli*, 1 *Moraxella catarrhalis*, 1 *Haemophilus influenzae*).

Details of treatment regimen are shown in Table 1. Most patients received a dose of 500 mg every 8h, with dose adjustments in a minority of cases. Indeed, only 9 of 13 patients with eGFR <50 ml/min had an upfront dose reduction according to the label. On-treatment modification of Ceftobiprole dosage due to on-therapy worsening of kidney function was needed in only 1 patient. Ceftobiprole was used alone in 11 patients (37.9%), and combined to other antimicrobials in the remaining 18 (62.1%), with the most common partners being daptomycin (5 pts), piperacillin-tazobactam (4 pts), meropenem (4 pts). Ceftobiprole was used as first-line drug in 15 cases (51.7%), while in 14 (48.3%) it took over as a second treatment line.

Outcomes of Ceftobiprole treatment are shown in Table 1. Overall, a favorable clinical outcome was observed in the majority of cases (20 patients, 68.9%). In the single patient with VAP treated with Ceftobiprole, therapeutic failure occurred. Table 2 provides details on the 7 patients who experienced Ceftobiprole treatment failure.

Only sparse data regarding microbiological eradication or incidence of relapse could be obtained due to lack of systematic follow up microbiological assays. One case of definite infection relapse

occurred within 30 days, whereas in other 8 patients longer term absence of recurrence was documented.

Survival status at 30 days after Ceftobiprole completion was available for all 29 patients. Of these, 8 (27.5%) had died. None of these deaths had occurred while on Ceftobiprole treatment. Death could be attributable to infection in 4 of the 8 deceased patients, whereas the remaining 4 patients died for non-infectious causes.

Three patients experienced a definite Ceftobiprole-related adverse event (Table 3): 2 had significant myoclonuses and 1 an erythematous skin rash. One patient with myoclonus completed treatment and resolved the adverse event thereafter, whereas the other stopped Ceftobiprole after 7 days when the electroencephalography showed abnormal activity. All of these 3 patients had received a renal-adjusted dose of Ceftobiprole. There were no cases of *Clostridioides difficile* infection. The dynamics of the most important hemato-chemical parameters is shown in Figure 1. In one patient a severe increase in bilirubin occurred in the context of advanced heart failure with liver congestion. Overall, our analysis did not show major adverse effects of Ceftobiprole on bone marrow, kidney and liver function, in the short-term and on a small study sample.

Discussion

Ceftobiprole is a novel treatment option for infections due to multidrug resistant gram-positive organisms. Despite of its broad in vitro activity, it has limited indications and its use, outside of clinical trials, has been seldom described. Thus, the question arises as to whether Ceftobiprole is safe and effective for real life, more severely ill and complex patients.

Data from our single center experience suggest Ceftobiprole may be a valuable treatment option for sick, comorbid and aged subjects with both pneumonia and BSI due to resistant organisms. Indeed, a favorable outcome of the infection was observed in the majority of cases, despite the substantial proportion of patients with sepsis or septic shock, and with a very limited burden of adverse events.

This translated into satisfactory patient outcomes, especially when the high baseline Charlson comorbidity indexes and Sequential Organ Failure Assessment scores are considered.

Renal function was often compromised and did not negatively impact Ceftobiprole treatment. Dose adjustments were infrequent and there were no signs of drug accumulation or worsening filtration rate. This is of particular value in light of the negative renal effects or challenging use of many antimicrobials for gram-positive infections, including glycopeptides, aminoglycosides, and daptomycin. Indeed, fewer patients than expected had a dose reduction according to the label, suggesting the feasibility of a more aggressive use of the drug in selected real life patients compared to clinical trials. Hematological abnormalities were also prevalent among treated patients and there was no evidence of adverse effects on blood cells, suggesting Ceftobiprole is a viable alternative to less bone marrow-friendly antimicrobials, including linezolid and cotrimoxazole. Moreover, among liver disease patients no dose modification or treatment interruption was necessary. Overall, Ceftobiprole safety was in line with literature data, including the low propensity to induce *Clostridioides difficile* infections, that did not occur in our experience.

Interestingly, Ceftobiprole was often used empirically in our series. This confirms it can also be of value pending microbiological tests, allowing appropriate treatment to be carried out based on the broad Ceftobiprole spectrum of activity.

Beyond tolerability, Ceftobiprole showed in our experience an overall clinical effectiveness somewhat lower than that observed in prior studies (21, 22), although in patients with a higher median age and a higher burden of comorbidities. A review of Ceftobiprole use in pneumonia by Syed et al. (23) showed results similar to those observed by us, but in a cohort characterized by additional comorbidities. One clinical feature of our patients was a high prevalence of central venous lines and ICU admission. Central catheters are frequently implanted in elderly or ill patients and are a sign of weakness and severity *per se*. Thus, treated patients were at substantial risk of complications, including superinfection with drug-resistant microorganism. The high prevalence of

these clinical features in our study should be taken into consideration when considering rates of clinical success.

Our study adds to current evidence on off label use of Ceftobiprole, that was reported for BSI/infective endocarditis (12), mediastinitis (15) and osteomyelitis (14), infectious syndromes commonly caused by gram-positive cocci.

In patients experiencing Ceftobiprole-related toxicity, its dose was chosen according to Ceftobiprole renal impairment dose adjustment protocol. Therefore, no correlation was seen between renal impairment, dosage and toxicity.

Our results must be interpreted with caution and certain limitations should be considered, including the relatively small number of patients analysed, and the retrospective collection of information.

In conclusion, Ceftobiprole use, even outside of current indications, could be an option in specific scenarios, including: (i) resistant gram-positive cocci infections, when other options are inactive in vitro; (ii) when there has been or there's a high risk of toxicity with other molecules; (iii) for salvage monotherapy or combination therapy.

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Figure legends

Figure 1: Dynamics of several laboratory parameters during Ceftobiprole treatment. BL, baseline; EoT, end of treatment.

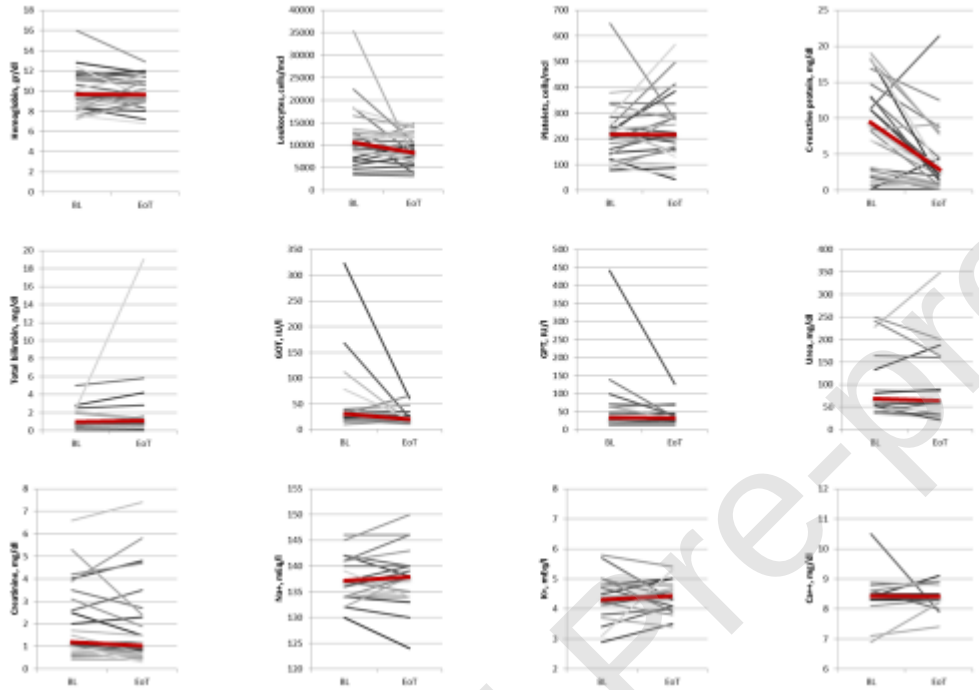

Table 1. General patient features at baseline (start of Ceftobiprole administration), infection characteristics and treatment outcomes

N	29
Sex, M/F	20/9
Age, yrs	70.5 (16 – 85)
Weight, kg	75 (42 – 98)
Body mass index, kg/m^2	27.2 (16 – 31.2)
Sepsis	17 (58.6%)
Septic shock	4 (13.8%)
Sequential Organ Failure Assessment score	5 (2 – 15)
Charlson comorbidity index	7 (1 – 12)
Hemoglobin, gr/mcl	9.8 (7.3 – 16)
Leukocytes, cells/mcl	10435 (3530 – 35280)
Platelets, cells/mcl	221000 (79000 – 647000)
Creatinine, mg/dl	1.3 (0.4 – 6.6)
Estimated GFR, ml/min	49 (6 – 154.2)
Total bilirubin, mg/dl	1.01 (0.15 – 5.2)
AST, IU/L	30 (10 – 323)
ALT, IU/L	30.5 (12 – 442)
Na+, mEq/L	137 (130 – 146)
K+, mEq/L	4.30 (2.9 – 5.8)
Ca+, mEq/L	8.45 (6.9 – 10.5)
Albumin, gr/dl	2.6 (2.1 – 3.9)
Urea, mg/dl	68.5 (36 – 250)

C-reactive protein, mg/dl	9.7 (0.8 – 19)
Chronic kidney disease stages	
Stage 1	6 (20.7%)
Stage 2	5 (17.2%)
Stage 3A	4 (13.8%)
Stage 3B	3 (10.3%)
Stage 4	3 (10.3%)
Stage5	8 (27.6%)
Source of Infection	
Hospital Acquired Pneumonia	13 (44.8%)
Community Acquired Pneumonia	3 (19.3%)
Ventilator Associated Pneumonia	1 (3%)
Bloodstream infection	10 (34%)
Modes of Ceptobiprole use	
Monotherapy	11 (37.9%)
Combination therapy	18 (62.1%)
Empirical treatment	9 (31.1%)
Targeted treatment	20 (68.9%)
Doses administered	
500 mg q8h	20 (68.9%)
500 mg q12h	6 (20.6%)
250mg q24h	3 (10.3%)
Outcomes of Ceptobiprole treatment	
Clinical cure	3 (10.3%)
Clinical improvement	17 (58.6%)
Clinical failure	7 (24.1%)
Toxicity requiring withdrawal	2 (6.8%)

Data are median (range) or mean ± standard deviation or number (percent)

Table 2. Characteristics of patients who failed Ceftobiprole treatment

Nr	Age (years)	Infection	Days from infection diagnosis to Ceftobiprole prescription	Isolated microorganism	Mortality
1.	66	Hospital acquired pneumonia	6	Culture negative	No
2.	85	Community acquired pneumonia	7	*E.coli, E. faecalis, St. hominis*	Yes
3.	60	Bacteremia	0	*E.coli*	No
4.	80	Bacteremia	0		No
5.	82	Ventilator associated pneumonia	0		Yes
6.	76	Bacteremia	0		Yes
7.	61	Endocarditis	0	*St. haemolyticus MR*	Yes

Table 3. Adverse drug reactions observed during Ceftobiprole treatment

Ceftobiprole-treatment emergent Adverse Events	N (%)
Skin rashes	1 (3.4)
Seizures/epilepsy	1 (3.4)
Myoclonus	2 (6.9)
Altered consciousness	0
Dyspnea	0
Asthma	0
Diarrhea (including C. difficile)	0
Fungal infections	0
Reactions at the infusion site	0
Hemoglobin reduction (>1 gr/dl)	10 (34)
De novo thrombocytosis	3 (10.3)
De novo thrombocytopenia	1 (3.4)
De novo leukopenia	1 (3.4)
Elevation of liver transaminases / bilirubin	1 (3.4) / 2 (6.9)