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Letter to the Editor

Real-life experience in the use of ceftobiprole for the treatment of nosocomial pneumonia: a case series

Editor: S. Stefani

Sir,

Hospital-acquired pneumonia (HAP) stands out as the second leading type of hospital-acquired infection in adults and is associated with substantial clinical and economic burden, with a mortality rate of 13% [1].

In the context of an increasing frail population, with its underlying multimorbidity and therefore polypharmacy, together with alarming antibiotic resistance rates, it appears mandatory to assess the available treatment strategies and their tolerability. Older age, immunocompromised status, admission to and prolonged stay in the intensive care unit (ICU), chronic obstructive pulmonary disease (COPD) and other co-morbidities are underlying conditions often associated not only with the development of HAP but also with an adverse outcome [1].

In this context, ceftobiprole, a fifth-generation cephalosporin approved for the treatment of HAP (excluding ventilator-associated pneumonia) with broad bactericidal activity, including methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* and non-extended-spectrum β-lactamase (ESBL)-producing Gram-negative bacteria, might represent a viable and useful antibiotic in this ageing clinical setting, combining the possible ease of monotherapy with an acceptable safety profile, few drug interactions and an emerging low risk of *Clostridioides difficile* infection (CDI) [2].

Here we present a case series of patients diagnosed with non-ventilator-associated HAP treated with ceftobiprole over a 1-year period (September 2019 to September 2020) at our 1200-bed tertiary-care teaching hospital (Policlinico Umberto I, Rome, Italy). Adult patients (age >18 years) diagnosed with HAP receiving ≥24 h of ceftobiprole therapy in a non-ICU setting were included. The study was approved by the local Ethics Committee and informed consent was waived due to the retrospective nature of the research. Results were expressed as the median and interquartile range (IQR) for continuous variables and as number (percentage) for categorical variables.

The median age of the 25 included patients was 71 years (IQR, 47–83 years), with a majority of males (15/25; 60%). Moreover, 22 patients (88%) presented at least one co-morbidity and 17 (68%) presented two or more co-morbidities, with a median Charlson co-morbidity index (CCI) of 5 (IQR, 3–6). The median time from hospital admission to HAP onset was 7 days (IQR, 3–21 days). Although the rate of pathogen detection was low (5/25; 20%), MRSA was predominant (3/5; 60%). Clinical cure, defined as resolution of signs and symptoms of pneumonia or sufficient improvement such that no further antibacterial therapy was needed and improvement (or no worsening) on chest radiography, was recorded in 80% of patients (20/25), while the overall mortality rate was 16% (4/25). In the subgroups of patients at risk of a non-favourable outcome, similar clinical cure rates were observed, being 80% and 82% in patients with COPD and those with at least two co-morbidities, respectively, which are slightly higher than those for patients aged ≥75 years (72.7%), immunosuppressed (71.4%) and with a CCI >5 (70%). Two patients experienced mild skin rash during drug infusion, requiring drug discontinuation in one patient after 5 days of therapy. No cases of CDI were observed during or after therapy, underlining its low impact on the gut microbial flora. Overall patient characteristics and the differences between cured and non-cured subjects are summarised in Table 1. A shorter duration of ceftobiprole therapy and a trend towards male sex, as well as an apparently higher mortality, were observed in non-cured patients. However, a generalisation of these results could not be performed owing to the small number of patients.

In our real-life experience, ceftobiprole showed a high percentage of cure in the treatment of non-ventilator-associated HAP, which was comparable in older patients as well as those presenting COPD, multiple co-morbidities and immunosuppression. This is consistent with a 2019 post-hoc retrospective analysis of the two major phase III registrative clinical trials for HAP and community-acquired pneumonia (CAP), where overall early clinical improvement and cure were recorded in 86.9% and 77.8%, respectively [3].

Although the extremely small sample of patients cannot offer a generalisation, our real-life experience could represent a crucial field for further research since data on ceftobiprole in the clinical setting are still limited. Compared with Durante-Mangoni et al., who described their real-life experience in the use of ceftobiprole for pneumonia and conditions other than CAP/HAP [4], our case series registered a higher rate of favourable outcome. Despite similar age and rate of co-morbidities, this difference might be explained by the absence in our series of patients recording sepsis/septic shock, ICU admission and infections other than pneumonia, widely present in the abovementioned report. In an additional retrospective study evaluating the use of ceftobiprole for the treatment of 48 patients with severe pneumonia (either CAP or HAP) in the emergency department, the authors found a clinical cure rate of 85.4% [5], similar to that observed in our series. Again, the study population comprised mostly elderly and frail subjects.

In conclusion, putting together our case series with other similar available real-life experiences found in the literature, ceftobiprole could represent a viable and useful antibiotic for the treatment of HAP in an ageing clinical setting, often dealing with co-morbidities and polypharmacy, through the combination of monotherapy with its wide spectrum of activity and acceptable safety profile.

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Table 1
General characteristics of the study population.

Characteristic	Total (n = 25)	Cure (n = 20)	Non-cure (n = 5)	P-value [a]
Age (years) [median (IQR)]	71 (47–83)	71 (50–83)	83 (31–87)	0.85
Sex (M/F) [n (%)]	15/10 (60/40)	10/10 (50/50)	5/0 (100/0)	0.06
Presence of ≥1 co-morbidity [n (%)]	22 (88)	17 (85)	5 (100)	0.90
Presence of ≥2 co-morbidities [n (%)]	17 (68)	14 (70)	3 (60)	0.90
Type of co-morbidities [n (%)]				
COPD	5 (20)	4 (20)	1 (20)	0.90
Cardiovascular disease	9 (36)	7 (35)	2 (40)	0.90
Dementia	6 (24)	4 (20)	2 (40)	0.56
Chronic renal failure	7 (28)	7 (35)	0 (0)	0.27
Immunosuppression [b]	7 (28)	5 (25)	2 (40)	0.59
Haematological disorders [c]	3 (12)	3 (15)	0 (0)	0.90
Diabetes mellitus	3 (12)	3 (15)	0 (0)	0.90
Cancer	3 (12)	2 (10)	1 (20)	0.50
Liver disease	2 (8)	2 (10)	0 (0)	0.90
CCI [median (IQR)]	5 (3–6)	4.5 (2.5–6)	6 (2.5–7)	0.56
SARS-CoV-2 infection [n (%)]	4 (16)	4 (20)	0 (0)	0.54
Length of stay (days) [median (IQR)]	24 (17–36)	24 (16–41)	23 (19–27)	0.78
Time from hospital admission to infection onset (days) [median (IQR)]	7 (3–21)	7 (3–21)	7 (3–18)	0.80
Pathogen detection [n (%)]	5 (20)	4 (20)	1 (20)	0.90
Type of pathogen [n (%)]				
MRSA	3/5 (60)	3/4 (75)	0 (0)	0.90
MSSA	1/5 (20)	1/4 (25)	0 (0)	0.90
Escherichia coli	1/5 (20)	0 (0)	1/1 (100)	0.20
Length of ceftobiprole therapy (days) [median (IQR)]	7 (7–9.5)	8 (7–10)	4 (3–6.5)	0.006
Cure [n (%)]	20 (80)	–	–	
In-hospital mortality [n (%)]	4 (16)	2 (10)	2 (40)	0.16
Mortality related to HAP	0 (0)	0 (0)	0 (0)	
Mortality related to non-HAP infection	2/4 (50)	1/2 (50)	1/2 (50)	0.9
Mortality related to non-infective cause	2/4 (50)	1/2 (50)	1/2 (50)	0.9
Dosage of ceftobiprole [n (%)]				
500 mg t.i.d.	17 (68)	13 (65)	4 (80)	0.90
500 mg b.i.d.	7 (28)	6 (30)	1 (20)	0.90
250 mg b.i.d.	1 (4)	1 (5)	0 (0)	0.90
Ceftobiprole adverse reactions [n (%)]	2 (8)	0 (0)	2 (40)	0.90
Type of adverse reaction [n (%)]				
Shock	0 (0)	0 (0)	0 (0)	–
Gastrointestinal symptoms	0 (0)	0 (0)	0 (0)	–
Skin rash	2/2 (100)	0 (0)	2/2 (100)	0.90
Other	0 (0)	0 (0)	0 (0)	–

IQR, interquartile range; COPD, chronic obstructive pulmonary disease; CCI, Charlson comorbidity index; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; HAP, hospital-acquired pneumonia; t.i.d., three times daily; b.i.d., twice daily.

[a] Categorical variables were compared by χ^2 or Fisher's exact test, as appropriate, whereas continuous data were analysed by Student's t-test and non-parametric Mann–Whitney test. Statistical analyses were performed using GraphPad Prism v.8 for Windows (GraphPad Software MacKiev), as appropriate.

[b] Immunosuppression includes solid-organ transplantation (n = 4; 3 kidney and 1 liver), acquired immune deficiency syndrome (AIDS) (n = 2) and congenital immunodeficiency (n = 1).

[c] Haematological disorders include leukaemia/lymphoma (n = 2) and myelofibrosis (n = 1).

Data availability

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

None declared.

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Ethical approval

The study was approved by the local Ethics Committee and informed consent was waived due to the retrospective nature of the research

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