ABSTRACT

Ceftobiprole is a new cephalosporin with an extended spectrum activity against the majority of microorganisms isolated in bacteraemia including methicillin-susceptible (MSSA) and -resistant *S. aureus* (MRSA). This antibiotic has demonstrated a potent activity against MRSA in animal models of endocarditis in monotherapy but particularly in combination with daptomycin, suggesting that this combination could be a future option to improve the outcome of staphylococcal endovascular infections. In addition, the extended-spectrum ceftobiprole activity, including coagulase-negative staphylococci, *Enterococcus faecalis*, *Enterobacteriaceae* and *Pseudomonas aeruginosa* represents an advantage for use as empirical therapy in bacteraemia potentially caused by a broad spectrum of microorganisms, such as in catheter-related bacteraemia.

INTRODUCTION

*Staphylococcus aureus* is one of the leading causes of bloodstream infections [1] and in the recent years the most common microorganism causing endocarditis [2]. Despite therapeutic advances, a recent study on 3395 consecutive adult patients with *S. aureus* bacteraemia (SAB) from 20 care centers in Europe and the United States reported a crude 14 and 90-day mortality rate of 14.6% and 29.2%, respectively [3]. Source control (catheter removal, abscess drainage) and early administration of an adequate antibiotic treatment are factors independently associated with success [4], however, randomized control trials to determine the best antibiotic treatment in SAB are scarce and new data mainly arise from observational studies. The major advances can be summarized as follows:

1) The *in vitro* synergy between beta-lactams and aminoglycosides has not been translated into a clinical benefit probably due to the unacceptable risk of nephrotoxicity [5] and it is no longer recommended [6].

2) Vancomycin is associated with a higher failure rate than beta-lactams against methicillin-susceptible *S. aureus* (MSSA), even when vancomycin is given empirically and switched to a beta-lactam within 72h after the first blood culture [7].

3) For the treatment of methicillin-resistant *S. aureus* (MRSA) bacteremia, vancomycin should be dosed to achieve an AUC/MIC ≥ 400. To obtain this goal, a minimum serum concentration of 15-20 mg/L is necessary, and the recommended dose is 15-20 mg/kg/12h. In critically ill patients, a loading dose of 30-35 mg/kg is suggested to early achieve the pharmacodynamic goal [8].

4) Vancomycin MIC of 2 mg/L has been associated with a higher mortality rate in MRSA bacteremia probably due to the low probability to attain the pharmacodynamic target [9, 10], and the higher prevalence of hetero-resistance to vancomycin in those strains with a MIC ≥ 2 mg/L [11].

5) The therapeutic range of vancomycin (serum concentration between 15 and 20 mg/L) overlaps with the nephrotoxic range [12].

6) A randomized clinical trial in *S. aureus* bacteremia comparing daptomycin vs. anti-staphylococcal penicillin (for MSSA) or vancomycin (for MRSA) plus gentamicin for the first 4 days showed that daptomycin is a suitable alternative but still associated with a high failure rate for high-inoculum infections like left-sided endocarditis because of a risk of selecting strains with reduced susceptibility [13]. In addition, a loss of daptomycin susceptibility in the absence of any administered antibiotic has been recently observed in an experimental model of prosthetic joint infection, probably as a result of *in vivo* selection pressure from cationic host peptides [14, 15].

In the last guidelines from the Infectious Diseases Society of America (IDSA) [6], vancomycin is still the first line choice...
but daptomycin is considered an alternative. Recent recommendations from Spanish experts support the use of high dose daptomycin (8-10 mg/kg/24h), and for high-inoculum infections, combination therapy with a second active antibiotic [16, 17]. These findings clearly point out 1) the need of alternative treatments for S. aureus bacteremia and 2) the major efficacy issues of beta-lactams over any alternative.

**ACTIVITY OF CEFTOBIROLE AGAINST STAPHYLOCOCCI**

Ceftobiprole medocaril is a new cephalosporin with *in vitro* activity against *S. aureus* and coagulase-negative staphylococci (CoNS). In a recent study, 99.5% of 15,426 *S. aureus* isolates were susceptible to ceftobiprole at the EUCAST breakpoint of 2 mg/L. The minimum inhibitory concentrations of 90% (MIC<sub>90</sub>) for methicillin susceptible and resistant isolates were 0.5 and 2 mg/L, respectively. Against CoNS, the ceftobiprole MIC<sub>90</sub> was 0.25 and 2 mg/L against methicillin susceptible and -resistant isolates, respectively [18]. Ceftobiprole's activity was not affected by vancomycin MIC and it remained active against isolates with a high vancomycin MIC (2 mg/L). Ceftobiprole has a time-dependent bactericidal activity that is optimal at 2 to 8 times the MIC [19]. In the rabbit endocarditis model using MRSA strains with a MIC of 2 mg/L, ceftobiprole was as effective as vancomycin [20, 21] and even superior to vancomycin, daptomycin and linezolid using the same model but a different strain with a ceftobiprole MIC of 4 mg/L [22]. In a rat model of endocarditis the efficacy of a continuous infusion of ceftobiprole to maintain serum concentrations about 6, 12 or 25 mg/L was evaluated [23]. The highest concentration sterilized 100% of the vegetations and the other two >90%, supporting the *in vitro* pharmacodynamic models showing a bactericidal activity against MRSA when T>MIC is 100% [24]. In these animal models, no selection of ceftobiprole resistant strains was detected in line with *in vitro* data showing very low frequency of resistance development after single-passage selection [19]. These studies also demonstrated a high stability of ceftobiprole, after 24h exposure to a high inoculum (10<sup>6</sup> CFU) of a penicillinase-producing *S. aureus* strain, being even more stable than methicillin. This is of interest since a high failure rate in high inoculum infections (endocarditis) has been observed with cephalosporins like cefazolin when the causative strain is producing type A beta-lactamase [25]. The activity of ceftobiprole against type A, B, and C beta-lactamase producing MSSA has been tested and a slight increase in the MIC was documented when comparing standard and high inoculum of type A, B and C producing MSSA beta-lactamase positive strains but the MIC remained ≤2 mg/L in all cases [26].

**CLINICAL EXPERIENCE WITH CEFTOBIROLE IN BACTERAEMIC PATIENTS**

The clinical experience is scarce but there were bacteremic patients within the 4 pivotal phase 3 clinical trials comparing ceftobiprole with other alternatives for community (CAP), hospital (HAP) acquired pneumonia, and for complicated skin and soft tissue infections (cSSTI) [27-30]. A pooled analysis of these 4 trials assessed the efficacy of ceftobiprole and comparators against staphylococcal bacteraemia in cSSTI, CAP, and HAP. Comparators included vancomycin (cSSTI), vancomycin plus ceftazidime (cSSTI), ceftriaxone (with linezolid in cases of suspected MRSA) (CAP) and ceftazidime plus linezolid (HAP) (Rello J, Rahav, Scheeren T, Saulay M, Engelhardt M, Weite T. Pooled analysis of clinical cure and mortality with ceftobiprole medocaril versus comparators in staphylococcal bacteremia in complicated skin infections, community- and hospital-acquired pneumonia. ECCMID 2016: 0-318). The outcomes showed that clinical responses were similar with ceftobiprole and standard-of-care comparators (table 1). In patients with MRSA, there was a trend towards improved clinical cure rates at test of cure (55.6% vs. 22.2%) and all-cause mortality at day 30 (0 vs. 22.2%) with ceftobiprole compared with other regimens (table 1). A double-blind, randomised, non-inferiority study to compare ceftobiprole (500 mg/8h) and daptomycin (6 mg/kg/24h) in adult patients with *S. aureus* bacteremia, including right-sided infective endocarditis, is ongoing (https://clinicaltrials.gov/ct2/show/NCT03138733).

| Outcome | Ceftobiprole, n/N (%) | Comparator, n/N (%) |
|---------|----------------------|---------------------|
| Any staphylococcal bacteremia | 22/45 (48.9) | 22/50 (44) |
| Coagulase-negative staphylococci | 10/22 (45.5) | 10/22 (45.5) |
| *S. aureus* | 12/23 (52.2) | 12/28 (42.9) |
| MSSA | 4/9 (44.4) | 7/15 (46.7) |
| MRSA | 5/9 (55.6) | 2/9 (22.2) |

The high mortality associated with particular pathologies such as endovascular infections deserves a particular attention since several *in vitro* antibiotic combinations have shown synergism but clinical trials to test these new therapeutic alternatives are scarce [3]. For instance, beta-lactams have shown *in vitro* synergy with vancomycin against MRSA [31-34] and a subsequent clinical trial randomized 60 patients with MRSA bacteremia to receive vancomycin alone or in combination with fluclouxilin for 7 days [35]. The mean time to resolution of bacteremia in the combination group was 1.94 days compared with 3 days in the vancomycin group (P = 0.06). In line with this, ceftobiprole has also demonstrated *in vitro* synergism with vancomycin and in a rat model.
of endocarditis, the combination of sub-therapeutic dose of ceftobiprole and vancomycin was as effective as monotherapy with standard ceftobiprole dose against MRSA and VISA strains [36, 37]. However, the combination with vancomycin does not avoid the potential risk of nephrotoxicity, therefore, other alternatives are required. The most promising approach is the association of daptomycin with a β-lactam since 1) the in vitro synergy has been described [38-41], 2) the ability of β-lactams to avoid the selection of daptomycin resistant mutants, 3) the dual effect of β-lactams, potentiating the activity of cationic host peptides against MSSA and MRSA [42], and 4) two retrospective case series exist showing good clinical results [43, 44]. Sub-inhibitory concentrations of ceftobiprole reduced daptomycin MICs 4-fold which was confirmed in time-kill studies [45]. Interestingly, a recent case report of a patient with a prosthetic valve endocarditis due to MRSA, who failed on daptomycin monotherapy and to daptomycin plus piperacillin-tazobactam, was switched to daptomycin plus ceftobiprole due to persistent bacteremia and fever. After 48h, under the new combination, the patient became afebrile and he was operated with good outcome afterwards [46].

A potential concern is the adequate dose of ceftobiprole for bacteremia and endocarditis. The pharmacodynamic target derived from skin and soft tissue infections is a free concentration over the MIC for 50% of the interval between 2 consecutive doses (>50% ft>MIC). The probability of achieving this target, with the current approved dose (500 mg/8h in 2h infusion), is >90% for MICs 4 mg/L [47]. However, a higher exposure (100% ft>MIC) is associated with a potent bactericidal activity [24] and it would be the preferred target for severe and high inoculum infections. Using the current dose, the probability of obtaining a 100% of ft>MIC for MRSA strains is lower but it can be significantly improved by giving 500 mg/6h or 1 g/8h both infused in 4h or any dose in continuous infusion. A recent open-label study carried out in 33 adults treated in the ICU examined the pharmacokinetics of high-dose ceftobiprole administered over a longer infusion period (1000 mg over 4 h/12h for patients with a CrCl 50-79 mL/min and 8h for CrCl 80 mL/min) for 1 day [48]. Ceftobiprole was well tolerated and a 100% of ft>MIC of 4 mg/L was obtained regardless of the CrCl.

On the other hand, catheters are the leading cause of nosocomial bacteremia and according to recent experience; although Gram-positives are still the most frequent microorganisms, Gram-negative pathogens including Enterobacteriaceae and P. aeruginosa are significantly increasing [49, 50]. The extended-spectrum activity, including methicillin-resistant coagulase-negative staphylococci, Enterococcus faecalis and Gram-negatives including P. aeruginosa, of ceftobiprole is an advantage for a monotherapy as empirical treatment for catheter related bacteremia.

In conclusion, ceftobiprole is a new anti-MRSA β-lactam with a time-dependent bactericidal activity and strong data in animal models of endocarditis showing that this monotherapy is more effective than vancomycin and that the combination with daptomycin has a potent synergistic activity. Therefore, ceftobiprole should be considered as a potential empirical option when MRSA bacteremia is suspected and in combination with daptomycin for the treatment of endovascular infections as a primary option or as a salvage therapy. In the future, it is necessary to collect more clinical experience with this antibiotic and to evaluate the most adequate dosage particularly for more severe infections.

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