DRUG EVALUATION

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Ceftobiprole medocaril in the treatment of hospital-acquired pneumonia

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Ceftobiprole medocaril is a fifth-generation cephalosporin approved in Europe as single-agent therapy for hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP). It is rapidly converted to the active metabolite ceftobiprole following intravenous administration. Ceftobiprole has a broad spectrum of activity, notably against methicillin-resistant *Staphylococcus aureus*, ampicillin-susceptible enterococci, penicillin-resistant pneumococci and *Enterobacteriaceae* not producing extended-spectrum β -lactamase. Ceftobiprole is primarily excreted renally by glomerular filtration, with minimal propensity for interaction with co-administered drugs. Normal dose is ceftobiprole 500 mg, administered by 2-h intravenous infusion every 8 h, with dose adjustment according to renal function. In a pivotal Phase III trial in patients with HAP, ceftobiprole monotherapy was as efficacious as ceftazidime/linezolid for clinical and microbiological cure and was noninferior to ceftazidime/linezolid in the subgroup of patients with HAP excluding VAP. Ceftobiprole and ceftazidime/linezolid were similarly well tolerated. Ceftobiprole is an efficacious and well-tolerated option for empirical treatment of patients with HAP (excluding VAP).

Hospital-acquired pneumonia (HAP) is one of the most common nosocomial infections, with an incidence of 5–10 cases per 1000 hospital admissions in the USA, approximately one-quarter of which are acquired in intensive care units (ICUs) [1–3]. Higher rates of HAP occur in elderly people, patients who are immunocompromised or have undergone surgery, and those being fed via a nasogastric tube [2]. HAP is associated with high mortality and morbidity, and consequently increases the burden on healthcare resources. HAP prolongs hospital stay by 7–9 days on average, and is associated with excess costs of more than US\$40,000 per patient [2]. The crude death rate among patients with HAP is 30–70% [2].

The most common bacterial pathogens involved in HAP are *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]), *Pseudomonas aeruginosa*, *Acinetobacter* spp. and some *Enterobacteriaceae* spp. (such as *Klebsiella* spp., *Enterobacter* spp. and *Escherichia coli*) and less frequently, *Serratia* spp., *Stenotrophomonas maltophilia*, *Streptococcus pneumoniae* and *Haemophilus influenzae* [4].

Initial empirical antimicrobial therapy for HAP needs to target a broad spectrum of Gram-positive and Gram-negative pathogens. The choice of therapeutic agent should take into consideration the types and susceptibility patterns of local pathogens (including those within a particular hospital), as well as other variables such as the duration of previous hospital stay (e.g., for differentiation between early- and late-onset HAP), recent use of antibiotic therapy and the presence of comorbidities [2,5–7]. Appropriate empirical therapy should be implemented rapidly (within 4 h) following the initial diagnosis [7,8]; guidelines list a range of treatment options including β -lactams/ β -lactamase inhibitors

KEYWORDS

- antimicrobial
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- hospital-acquired pneumonia

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(e.g., piperacillin/tazobactam), cephalosporins (e.g., cefuroxime, cefotaxime, ceftriazone and ceftazidime), carbapenems (e.g., imipenem and meropenem) and fluoroquinolones (e.g., levofloxacin, moxifloxacin and ciprofloxacin) [2,6]. Suspicion of the involvement of 'hard-to-treat' pathogens, such as *P. aeruginosa*, *Acinetobacter* spp. or MRSA, further directs the treatment (e.g., suspicion of MRSA requires the use of vancomycin, linezolid or teicoplanin) [6]. There remains a need for additional antibiotics that provide well-tolerated broad-spectrum activity against multidrug-resistant (MDR) pathogens to simplify initial empirical therapy for HAP.

A range of new antibiotics that might have potential in the treatment of HAP include novel glycopeptides (e.g., dalbavancin, oritavancin and telavancin), iclaprim, temocillin and new-generation cephalosporins (e.g., ceftobiprole and ceftaroline) [3]. Among these, ceftobiprole is approved in Europe for use as a single-agent therapy for HAP (excluding ventilator-associated pneumonia [VAP]). The aim of this review is to provide an overview of the clinical pharmacology and clinical use of ceftobiprole in patients with HAP. Ceftobiprole is also indicated for use in community-acquired pneumonia (CAP; for reviews, see Syed [9] and Liapikou *et al.* [10]) and has also been investigated in the treatment of complicated skin and soft-tissue infections (cSSTI; for review, see Zhanel *et al.* [11]). However, these indications are outside the scope of this review and any information relating to these conditions is included only when it provides supporting evidence.

Introduction to ceftobiprole medocaril

Ceftobiprole medocaril (Zevtera® or Mabelio®; Basilea Pharmaceutica Ltd, Basel, Switzerland) is a prodrug that is rapidly and almost completely metabolized to the active drug, ceftobiprole, following intravenous (iv.) administration (Figure 1). The dose of the drug is reported and measured as the active principal (ceftobiprole 500 mg is administered as ceftobiprole medocaril sodium 666.6 mg). Ceftobiprole is a member of the pyrrolidinone-3-ylidenemethyl cephem series of cephalosporins [12]. It has been described as a fifth-generation cephalosporin because of its broad spectrum of activity, including against MRSA, ampicillin-susceptible enterococci, penicillin-resistant pneumococci and *Enterobacteriaceae* strains not producing extended-spectrum β -lactamase (ESBL) [13]. The recommended

dose for patients with normal renal function is ceftobiprole 500 mg by iv. infusion over 2 h every 8 h (q8h) in adults; dose adjustment is required in certain patient groups (see later for details).

The antibacterial activity of ceftobiprole results from binding to penicillin-binding proteins (PBPs), blocking their transpeptidase activity and thus disrupting the synthesis of the peptidoglycan layer of bacterial cell walls. Ceftobiprole binds with strong affinity to important PBPs (e.g., PBP2 and PBP3) in Gram-negative bacteria including *E. coli* and *P. aeruginosa*, but not to PBP5 in *E. coli*, or to PBP5 or PBP6 in *P. aeruginosa* [14]. This may be of relevance because PBP5 plays a role in intrinsic resistance to β -lactam antibiotics in *E. coli*, as well as playing a key role in maintaining cell shape [15]. In *P. aeruginosa*, the β -lactamase activity of PBP5 contributes to β -lactam resistance [16,17]. For Gram-positive bacteria, ceftobiprole has high affinity for PBP2a (encoded by *mecA*), which confers methicillin resistance in MRSA isolates [14]. This activity against MRSA is maintained in strains expressing *mecC* and *mecALGA251* [18]. Ceftobiprole has high affinity for PBP1a and PBP2x, but low affinity for PBP2b (these three PBPs confer β -lactam resistance in *S. pneumoniae* [14]). In addition, ceftobiprole lacks affinity for mutated PBP5 (overexpression of which confers penicillin resistance in *Enterococcus* spp.) [12], although it shows good affinity for the unmutated form, which is overexpressed in some penicillin-resistant strains [19]. The range of PBP binding seen with ceftobiprole implies a broad spectrum of antimicrobial activity in a single agent for important pathogens encountered in patients with HAP.

The activity of ceftobiprole against clinically relevant pathogens has been extensively reviewed elsewhere [9,11]. Table 1 summarizes the *in vitro* antimicrobial activity of ceftobiprole and comparator agents against pathogens frequently associated with HAP [20]. *In vitro*, ceftobiprole exhibits activity against major Gram-positive pathogens similar to that of linezolid, teicoplanin and vancomycin [9]. Ceftobiprole has potent activity against *S. aureus*, including MRSA and *S. aureus* strains resistant to linezolid or daptomycin, vancomycin-intermediate *S. aureus* (VISA), heterogeneous VISA and vancomycin-resistant *S. aureus* (VRSA) [21]. Susceptibility to ceftobiprole was generally maintained across *S. aureus* strains with different staphylococcal cassette chromosome *mec* and/or multilocus sequence

Figure 1. Chemical structures of the prodrug ceftobiprole medocaryl and the active metabolite ceftobiprole.

types [21,22]. Ceftobiprole is also active against *S. pneumoniae*, including penicillin-susceptible and penicillin-resistant strains, and β -hemolytic or viridans streptococci, and *Enterococcus faecalis*, but not against *Enterococcus faecium* [9].

With respect to Gram-negative pathogens, ceftobiprole shows good activity against *Enterobacteriaceae* spp., *E. coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* strains not producing ESBL (Table 1) [20]. However, ceftobiprole was generally inactive against ESBL-producing strains, as were ceftazidime and ceftriaxone [9]. Although *Enterobacter* spp. and *Citrobacter* spp. are generally susceptible to ceftobiprole, strains overproducing AmpC β -lactamase tend to be resistant; ceftazidime and ceftriaxone show more limited activity against these organisms and are also inactive against strains overproducing AmpC β -lactamase [9,23]. In addition, ceftobiprole shows good activity against ceftazidime-susceptible strains of *Serratia* spp., including *Serratia marcescens* [9], and approximately two-thirds of *P. aeruginosa* isolates are susceptible to ceftobiprole (Table 1). Ceftobiprole has limited activity against *Acinetobacter* spp. (Table 1), but exhibits good activity against Gram-negative fastidious respiratory pathogens such as *H. influenzae* and *Moraxella catarrhalis* irrespective of β -lactamase production or ampicillin resistance [9].

For anaerobic bacteria, ceftobiprole is generally active against *Clostridium* spp. and *Fusobacterium* spp., but inactive against *Bacteroides* spp., *Prevotella* spp. and *Veillonella*

spp. [11]. Bacteria causing atypical pneumonia (*Chlamydophila pneumoniae*, *Burkholderia cepacia* complex, *Mycoplasma pneumoniae*, *Mycobacterium* spp., *Nocardia* spp. and *Stenotrophomonas maltophilia*) are not generally susceptible to ceftobiprole [18].

Ceftobiprole has demonstrated *in vitro* bactericidal activity toward all or most MRSA clinical isolates, including heterogeneous VISA, VISA, VRSA and coagulase-negative strains [22,24–28]. Moreover, ceftobiprole is effective in the prevention of intracellular MRSA growth in macrophages and keratinocytes compared with other cephalosporins, such as ceftriaxone, cefoxitin, cephalexin or cefuroxime; the increased activity of ceftobiprole compared with the other cephalosporins was at least partly related to its greater ability to bind to PBP2a under acidic conditions [29]. Ceftobiprole is generally bactericidal *in vitro* against *S. pneumoniae* (including strains resistant to penicillin, macrolides and/or fluoroquinolones), vancomycin-resistant *E. faecalis*, *H. influenzae* (including β -lactamase-positive strains), β -lactamase-positive *M. catarrhalis* and ESBL-negative *Enterobacter cloacae* [30–33]. Ceftobiprole has also demonstrated *in vitro* bactericidal activity against *P. aeruginosa* [30,34]. In addition, it exhibits a modest postantibiotic effect against 12 pneumococcal, staphylococcal and enterococcal isolates *in vitro* [35], and against an MRSA strain, but minimal postantibiotic effects were observed against a penicillin-resistant *S. pneumoniae* strain *in vivo* [36].

Table 1. *In vitro* activities of ceftobiprole and comparator agents against key bacterial isolates from European, Turkish and Israeli medical centers (2005–2010).

Organism	MIC range	MIC ₅₀	MIC ₉₀	Susceptible isolates, % (EUCAST)
All <i>Staphylococcus aureus</i> (n = 15,426)				
Ceftobiprole	≤0.06–4	0.5	1	>99
Ceftriaxone	≤0.25–>8	4	>8	73
Linezolid	≤0.12–>8	1	2	>99
Vancomycin	≤0.12–2	1	1	100
Methicillin/oxacillin-susceptible <i>S. aureus</i> (n = 11,279)				
Ceftobiprole	≤0.06–2	0.25	0.5	100
Ceftriaxone	≤0.25–>8	4	4	100
Linezolid	≤0.12–2	1	2	100
Vancomycin	≤0.12–2	1	1	100
Methicillin/oxacillin-resistant <i>S. aureus</i> (n = 4147)				
Ceftobiprole	0.12–4	1	2	98
Linezolid	0.25–>8	1	2	>99
Vancomycin	≤0.12–2	1	1	100
<i>Streptococcus pneumoniae</i> (n = 4443)				
Ceftobiprole	≤0.06–2	≤0.06	0.5	99
Ceftriaxone	≤0.25–32	≤0.25	1	84
Linezolid	≤0.12–2	1	1	100
Vancomycin	≤1–1	1	1	100
<i>Enterobacteriaceae</i> spp. (n = 17,480)				
Ceftobiprole	≤0.06–>8	≤0.06	>8	83
Ceftazidime	≤1–>16	≤1	16	84
<i>Pseudomonas aeruginosa</i> (n = 3434)				
Ceftobiprole	≤0.06–>8	2	>8	65 [†]
Ceftazidime	≤1–>16	2	>16	75
<i>Acinetobacter</i> spp. (n = 1146)				
Ceftobiprole	≤0.06–>8	>8	>8	–
Ceftazidime	≤1–>16	>16	>16	–

[†]EUCAST nonspecies-specific breakpoint.
 EUCAST: European Committee on Antimicrobial Susceptibility Testing; MIC: Minimum inhibitory concentration; MIC₅₀: MIC required to inhibit 50% of isolates; MIC₉₀: MIC required to inhibit 90% of isolates.
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Ceftobiprole has demonstrated synergistic activity in combination with vancomycin against MRSA and glycopeptide-intermediate *S. aureus* both *in vitro* [37] and *in vivo* [38], and against VISA *in vivo* [39]. Ceftobiprole has also shown *in vitro* synergy in time–kill studies in combination with daptomycin against daptomycin-nonsusceptible MRSA strains [40], and some daptomycin-susceptible and daptomycin-resistant/vancomycin-resistant enterococci [41]; ceftobiprole has also shown *in vitro* synergy in combination with plazomicin against some MRSA strains [42], and in combination with amikacin or levofloxacin against *P. aeruginosa* [34]. Ceftobiprole exhibits bactericidal and curative activity in murine

pneumonia models of infection by *S. aureus* including MRSA [43,44], *S. pneumoniae* including MDR strains [45], *H. influenzae* [46], *E. cloacae* [46] and ESBL-negative but not ESBL-positive *K. pneumoniae* [46].

Pharmacokinetics & pharmacokinetic/pharmacodynamic considerations

The pharmacokinetics of ceftobiprole have been extensively reviewed elsewhere [47]. The principal pharmacokinetic parameters of ceftobiprole in healthy individuals are summarized in Table 2 [48,49]. Following iv. administration, ceftobiprole medocaril is rapidly (<1 min) and almost completely converted to active ceftobiprole [47].

Peak plasma concentrations ($C_{\max}$) are reached at the end of infusion and show a biphasic decline as a result of initial rapid distribution to other body compartments, principally the extracellular fluid, followed by a relatively slow elimination [48,49]. The pharmacokinetics of ceftobiprole are linear after single and multiple doses of 125–1000 mg [48,49]. Steady-state drug concentrations are reached on the first day using a q8h regimen [47]. Following administration of the approved dose regimen (500 mg iv. q8h administered over 2 h) in healthy individuals, at Day 5 the mean ceftobiprole $C_{\max}$ was 33 mg/l, the area under the plasma concentration–time curve (AUC) over the dosing interval was 102 mg h/l, the volume of distribution at steady state (V_{ss}) was 15.5 l (equating to the volume of the extracellular fluid) [47] and the AUC in epithelial lining fluid versus that for plasma was approximately 25% [44].

Ceftobiprole has limited potential to interact with other drugs during co-administration. Active ceftobiprole undergoes minimal metabolism to form a microbiologically inactive open-ring metabolite, which accounts for approximately 4% of ceftobiprole exposure in individuals with normal renal function [47]. Ceftobiprole shows minimal (16%) binding to plasma protein (primarily albumin but also α_1 -acidic glycoprotein), which is independent of drug and protein concentrations [47]. *In vitro*, ceftobiprole is not an inhibitor of and/or substrate for the cytochrome P450 system or the P-glycoprotein transporter system. Moreover, ceftobiprole is not an inhibitor of the breast cancer resistance protein, multidrug resistance protein 1, multidrug resistance-associated protein 2, organic anion transporters (OAT) 1 or OAT 3, or organic cation transporters 1 and 2 [9]. Ceftobiprole is an inhibitor of hepatocyte uptake transporters, organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3, and may therefore increase plasma concentrations of drugs that are metabolized by these pathways (e.g., statins, glyburide and bosentan) [9].

Ceftobiprole is almost exclusively eliminated through renal (glomerular filtration) excretion, with a mean elimination half-life ($t_{1/2}$) of 3.3 h, a total systemic clearance (CL) of 5.0 l/h and a total renal clearance (CL_R) of 4.3 l/h [47]. About 88% of the dose administered is recovered in urine, of which 80–90% is active ceftobiprole [9]. The risk of renal drug–drug interactions is low given that ceftobiprole does not

undergo active tubular excretion and undergoes minimal reabsorption [9].

Ceftobiprole undergoes minimal hepatic metabolism; it is slowly converted to the inactive open-ring metabolite in hepatocytes [47]. Fecal excretion of active ceftobiprole is also minimal, with no measurable concentrations of ceftobiprole detected in feces from healthy volunteers who received iv. ceftobiprole 500 mg q8h for 7 days [50]. The minimal hepatic metabolism and fecal excretion of active ceftobiprole may indicate that the drug is likely to have a negligible impact on intestinal microflora. Indeed, ceftobiprole did not promote *C. difficile* growth and toxin production in murine cecal contents, unlike ceftazidime, cefoxitin, ceftriaxone, cefotaxime and ertapenem, which did undergo at least some degree of hepatic metabolism and fecal excretion [51]. Furthermore, administration of ceftobiprole 500 mg q8h for 1 week had no significant effect on normal intestinal microflora in healthy humans [50]. Taken together, these properties may help minimize the potential for ceftobiprole to be associated with *Clostridium difficile* infection, which can be driven by broad-spectrum antimicrobials undergoing hepatic metabolism and subsequent biliary excretion [52].

Given the predominantly renal elimination, ceftobiprole disposition is affected by renal impairment. In a study of 20 otherwise healthy volunteers, systemic ceftobiprole exposure increased with decreasing renal function [18,53,54]. Ceftobiprole AUC increased by approximately 30%, 250% and 330% in individuals with mild (creatinine clearance [CL_{CR}] 50–80 ml/min), moderate (CL_{CR} 30–<50 ml/min) and severe (CL_{CR} <30 ml/min) renal impairment, respectively, compared with those with normal renal function [18,53,54]. In addition, patients with moderate or severe renal impairment had reduced renal clearance of ceftobiprole compared with individuals with normal renal function (78 and 91%, respectively) [9]. The $t_{1/2}$ of ceftobiprole was longest in patients with severe renal impairment (11 vs 3.5 h in those with normal renal function) [53]. Exposure to ceftobiprole was also shown to be substantially increased in patients with end-stage renal disease (ESRD) [9]. In patients treated in an ICU, pathophysiological changes such as increased cardiac output in sepsis may enhance renal function, increasing CL_{CR} to supranormal levels (>150 ml/min) [55]. Ceftobiprole CL and V_{ss} are increased by about 40 and 30%, respectively, in patients

Table 2. Principal pharmacokinetic parameters for ceftobiprole following single- or multiple-dose administration of intravenous ceftobiprole over 30 min.

	Single dose					Multiple doses (q24h on days 1 and 8; q12h on days 2–7)			
	125 mg	250 mg	500 mg	750 mg	1000 mg	Day 1		Day 8	
						500 mg	750 mg	500 mg	750 mg
C_{max} (mg/l)	9.87 ± 0.78	19.5 ± 2.75	35.5 ± 6.79	59.6 ± 10.7	72.2 ± 8.78	40.6 ± 7.38	60.7 ± 4.55	44.2 ± 10.8	60.6 ± 9.99
$AUC_{0-\infty}$ (mg h/l)	20.3 ± 2.82	43.7 ± 5.99	76.6 ± 3.88	135 ± 27.6	151 ± 9.04	101 ± 9.04	156 ± 19.3	108 ± 22.2	165 ± 12.8
$t_{1/2}$ (h)	2.84 ± 0.21	3.42 ± 0.29	3.44 ± 0.30	3.47 ± 0.37	3.25 ± 0.20	3.63 ± 0.48	3.64 ± 0.32	4.04 ± 0.31	4.11 ± 0.41
CL (l/h)	6.27 ± 0.97	5.81 ± 0.84	6.54 ± 0.34	5.74 ± 1.13	6.64 ± 0.41	4.99 ± 0.46	4.85 ± 0.57	5.05 ± 0.95	4.84 ± 0.34
CL_R (l/h)	4.60 ± 0.38	4.35 ± 0.57	5.07 ± 0.22	4.08 ± 0.75	4.16 ± 0.57	4.12 ± 0.75	4.05 ± 0.47	4.47 ± 1.07	4.09 ± 0.60
V_{ss} (l)	17.9 ± 2.00	17.8 ± 3.11	19.8 ± 1.95	18.4 ± 2.63	18.9 ± 2.31	16.4 ± 2.11	16.3 ± 1.82	16.7 ± 3.58	16.1 ± 2.20
Urinary recovery (%)	74.2 ± 8.14	76.1 ± 14.4	77.5 ± 3.27	71.3 ± 1.48	62.5 ± 6.33	82.2 ± 9.11	83.7 ± 3.91	87.8 ± 9.30	84.4 ± 9.23

Data are shown as mean ± standard deviation.

$AUC_{0-\infty}$: Area under the plasma concentration–time curve from time zero extrapolated to infinity; C_{max} : Maximum plasma concentration; CL: Total systemic clearance; CL_R : Total renal clearance; q12h: Every 12 h; q24h: Every 24 h; $t_{1/2}$: Elimination half-life; V_{ss} : Volume of distribution at steady state.

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with augmented renal function compared with values in patients with normal renal function [9]. Similar results have been reported with high-dose ceftobiprole (1000 mg) administered by iv. infusion over 4 h q8h in patients in an ICU [56].

Systemic exposure to ceftobiprole is slightly higher (by approximately 20%) in women compared with men after administration of the same dose, although this is almost exclusively accounted for by difference in body weight [47]. Importantly, the percentage of the dosing interval during which the free drug concentration remained above the minimum inhibitory concentration (MIC; % $fT > MIC$), assuming an MIC of 4 mg/l, is not affected by gender [57]. The pharmacokinetics of ceftobiprole have not yet been determined in adolescents or children (<18 years of age).

The probability of achieving specific percentage targets for $fT > MIC$ with ceftobiprole has been determined using population pharmacokinetic modeling and Monte Carlo simulations for different dose regimens [58,59]. For a MIC cutoff of 4 mg/l for Gram-positive bacteria, the probability of reaching 40%, 50% and 60% $fT > MIC$ targets was 100%, 99% and 79%, respectively, for ceftobiprole 500 mg iv. q8h administered over 30 min [58]. In a second set of analyses, ceftobiprole 500 mg iv. q8h administered over 2 h was associated with an 80% probability of achieving a 50% $fT > MIC$ target [59]. The probabilities of achieving a 50% $fT > MIC$ target were 99% and 100% for MRSA (MIC₉₀ 1 mg/l) and methicillin-sensitive *S. aureus* (MIC₉₀ 0.5 mg/l), respectively, and the probabilities of attaining a

60% $fT > MIC$ target were 88%, 94% and 62% for AmpC-producing bacilli (MIC₉₀ 16 mg/l), AmpC-nonproducing bacilli (MIC₉₀ ≤0.25 mg/l) and *P. aeruginosa* (MIC₉₀ 32 mg/l), respectively. Based on these analyses, the ceftobiprole dosing regimen of 500 mg iv. q8h administered over 2 h was selected for the Phase III studies in patients with Gram-positive and Gram-negative pathogens. In a validation study [60], the probability of $fT > MIC$ target attainment determined from the Monte Carlo simulations adequately predicted the ceftobiprole plasma concentrations achieved in the Phase III study in patients with HAP.

Clinical efficacy

The efficacy of ceftobiprole has been investigated in Phase III clinical trials in patients with HAP [61], CAP [62] and cSSTIs [11]. This current review centers on the pivotal Phase III trial in patients with HAP, which compared the efficacy and safety of single-agent therapy with ceftobiprole and the combination of ceftazidime/linezolid [61].

The pivotal Phase III trial was a multinational, randomized, double-blind, noninferiority study comparing ceftobiprole with ceftazidime/linezolid in 781 adults with HAP (defined as a diagnosis of pneumonia after >72 h of hospitalization or stay in a chronic care unit). Key inclusion criteria were: clinical signs or symptoms of pneumonia (at least two of purulent respiratory secretion, tachypnea or hypoxemia); fever or leukocytosis/leukopenia; new or persistent radiographic infiltrates; and an Acute Physiology and Chronic

Health Evaluation II (APACHE II) score of 8–25. Key exclusion criteria were: severe renal or hepatic impairment; evidence of infection with ceftobiprole- or ceftazidime-resistant pathogens; clinical conditions likely to interfere with efficacy assessment (e.g., sustained shock, active tuberculosis, lung abscess and postobstructive pneumonia); and systemic antibiotic treatment for >24 h in the 48 h before enrollment. Patients were stratified across treatment arms according to the presence of VAP (defined as a diagnosis of pneumonia developing >48 h after mechanical ventilation [yes/no]) and APACHE II score (8–19/20–25); those with VAP were further stratified according to ventilation duration (</≥5 days).

Patients were randomly assigned (1:1) to receive ceftobiprole (500 mg iv. q8h administered over 2 h [n = 391]) or ceftazidime plus linezolid (2 g iv. . every 8 h [q8h] administered over 2 h plus 600 mg iv. q12h administered over 1 h [n = 390]) for 7–14 days. Patients in the ceftobiprole group also received placebo q12h administered by iv. infusion over 1 h to maintain the double-blind conditions. Additional open-label treatment with a fluoroquinolone or an aminoglycoside was permitted for patients at risk of pseudomonal infection (the addition of anti-pseudomonal therapy in each treatment group was prespecified for ethical reasons because this was the first Phase III study of ceftobiprole in which patients infected with *pseudomonas* were to be recruited). The primary efficacy end point was clinical cure rate at the test of cure (TOC) visit (7–14 days after the last dose of study drug or early termination) in the intent-to-treat (ITT) and clinically evaluable populations, with non-inferiority defined using a 15% margin for 95% CIs. The . The main secondary end points were microbiological eradication at the TOC visit in the ITT and microbiologically evaluable populations with a valid pathogen at baseline, and 30-day all-cause mortality in the ITT population, as well as safety and tolerability.

The baseline demographic and clinical characteristics of the ITT population were generally similar in the two treatment groups. In the ceftobiprole and ceftazidime/linezolid arms, there were similar proportions of patients aged >65 years (45% vs 47%), and those with APACHE II score ≥15 (41% vs 41%), systemic inflammatory response syndrome (72% vs 73%), bacteremia (10% vs 12%), prior antibiotic use within 24 h of enrollment (58% vs 62%) and a valid baseline pathogen (69% vs 68%), although there was a

higher proportion of men than women among those receiving ceftobiprole (71% vs 62%). Furthermore, the demographics and baseline characteristics of the ITT population and the most frequently isolated baseline pathogens in the microbiologically evaluable population remained similar in both treatment groups for the subgroups of patients with HAP excluding VAP and those with VAP alone. In the overall ITT population, 69% of patients had a valid pathogen (Gram-positive, 36%; Gram-negative, 48%; polymicrobial, 24%; *Pseudomonas* spp., 13%; and MRSA, 11%). In the overall microbiologically evaluable population, the most frequently (>5.0%) isolated baseline pathogens were: *S. aureus* (42%), including MRSA (17%); *Enterobacteriaceae* (38%), including *K. pneumoniae* (12%), *E. coli* (10%), *Enterobacter* spp. (6.3%) and *Proteus* spp. (5.1%); *P. aeruginosa* (18%); *A. baumannii* (9.3%); *S. pneumoniae* (7.8%); and *Haemophilus* spp. (5.4%).

Results for the primary efficacy end point, clinical cure at the TOC visit, are presented for the ITT and clinically evaluable populations in **Figure 2**. Ceftobiprole was noninferior to ceftazidime/linezolid for patients with HAP (non-VAP and VAP). Additional efficacy end point analyses were performed on subpopulations with HAP (excluding VAP) and VAP according to regulatory guidance [63]. Ceftobiprole was noninferior to ceftazidime/linezolid in patients with HAP (excluding VAP), but not in those with VAP (**Figure 2**).

For secondary efficacy end points, microbiological eradication rates at the TOC visit in patients with HAP (excluding VAP) were similar in the ceftobiprole and ceftazidime/linezolid groups in the ITT (49% vs 54%; difference -5.0; 95% CI: -15.3–5.3) and microbiologically evaluable (63% vs 68%; difference -4.6; 95% CI: -16.7–7.6) populations. Clinical cure and microbiological eradication rates by pathogen for patients with HAP (excluding VAP) were similar in both treatment groups (**Table 3**). Patients with HAP (excluding VAP) in the ITT population also had similar 30-day all-cause mortality (16.7% vs 18.0%; difference -1.2; 95% CI: -7.4–5.0) and pneumonia-specific 30-day mortality (5.9% vs 5.6%; difference 0.3; 95% CI: -3.5–4.1) with ceftobiprole and ceftazidime/linezolid.

Noninferiority of ceftobiprole relative to ceftazidime/linezolid was not demonstrated in the subgroup of patients with VAP (clinical cure rate at the TOC visit: 23% vs 37%; **Figure 2**). Therefore, ceftobiprole is not approved for the

Figure 2. Clinical cure rates with ceftobiprole and ceftazidime/linezolid in the (A) intent-to-treat and (B) clinically evaluable populations.
[†]Difference ceftobiprole minus ceftazidime/linezolid.
 HAP: Hospital-acquired pneumonia; TOC: Test of cure; VAP: Ventilator-associated pneumonia.
 Data taken from [61].

treatment of patients with VAP. However, analysis of the subgroup of patients who required mechanical ventilation during treatment or developed pneumonia within the 48 h after the start of ventilation (i.e., who were not defined as having VAP) showed that clinical cure rates were higher with ceftobiprole than with ceftazidime/linezolid (55% vs 41%; difference 14.7%; 95% CI: -7.6–37.1). Thus, it appears that mechanical ventilation itself does not explain the results seen in patients with VAP, and ceftobiprole

can be used in patients with HAP who require ventilation. Multivariate logistic regression analysis did not identify any of 37 factors (e.g., baseline pathogens, gender, age, comorbidities and vasopressor use) that could explain the outcome in patients with VAP. Moreover, there were no differences between the pharmacokinetic/pharmacodynamic profile of ceftobiprole in the VAP and in the non-VAP subgroups [64]. Modelling data also showed that ceftobiprole plasma concentrations were sufficient for a target MIC

of 4 mg/l in 92% of patients, suggesting that plasma concentrations of ceftobiprole were adequate in patients with VAP [61]. Unfortunately, however, further data exploring the efficacy of ceftobiprole in patients with VAP are not available, and this could be an area for future studies. Consequently, there was no clear explanation for the failure to demonstrate noninferiority in the VAP patients, although a baseline demographic imbalance may have occurred as a result of the relatively small patient numbers enrolled.

Clinical cure rates were further analyzed by baseline demographic and clinical characteristics among patients with HAP (excluding VAP) [61]. Clinical cure rates at the TOC visit in the clinically evaluable population were similar for both treatments in subgroups analyzed by age, gender, patient geographic region, APACHE II score, care facility, prestudy antibiotic use and antipseudomonal antibiotic use (Table 4). The marked difference between treatments in the subgroup of patients in the USA likely reflects the small numbers of patients in each group (ceftobiprole, n = 27; ceftazidime/linezolid, n = 24).

A *post hoc* analysis of the Phase III trial data was conducted to assess rates of early clinical improvement in patients with HAP (excluding VAP) [65]. Early clinical improvement was defined as improvement of symptoms (including purulent sputum, rales, tachypnea, hypoxemia,

pleuritic chest pain, rigor and cough) or cure 4 days after starting treatment, based on an assessment of symptoms by the investigator using standardized criteria. Patients treated with ceftobiprole had a numerically higher early clinical improvement rate than those receiving ceftazidime/linezolid (87% vs 78%; difference 8.5%; 95% CI: 0.9–16.1), with more pronounced differences seen in those treated for Gram-positive infections (87% vs 74%; difference 13.0%; 95% CI: -0.4–26.4), particularly MRSA (95% vs 53%; difference 42.1%; 95% CI: 17.5–66.7). Clinical cure rates at the TOC visit were similar in both treatment groups for the overall population and in the subgroups with Gram-positive or MRSA infections. The higher early clinical improvement rates among patients treated with ceftobiprole than among those receiving ceftazidime/linezolid may be related to the rapid bactericidal profile of ceftobiprole (particularly against Gram-positive organisms) [65].

Ceftobiprole also provides similar efficacy to ceftazidime/linezolid in early- and late-onset HAP (excluding VAP), according to a *post hoc* analysis of the Phase III trial data [66]. The time of HAP onset is often regarded as an important variable in HAP management, with late-onset disease being more likely to involve MDR pathogens and to be associated with increased morbidity and mortality [2,67]. Demographics and clinical

Table 3. Clinical cure rates and microbiological eradication rates with ceftobiprole and ceftriaxone/linezolid at the test of cure visit by pathogen in the microbiologically evaluable population for patients with hospital-acquired pneumonia (excluding ventilator-associated pneumonia).

	Clinical cure		Microbiological eradication	
	Ceftobiprole (n = 116)	Ceftazidime/linezolid (n = 120)	Ceftobiprole (n = 116)	Ceftazidime/linezolid (n = 120)
<i>Staphylococcus aureus</i>	28/39 (72)	36/49 (73)	23/39 (59)	31/49 (63)
MSSA	15/20 (75)	24/30 (80)	15/20 (75)	21/30 (70)
MRSA	13/19 (68)	12/19 (63)	8/19 (42)	10/19 (53)
<i>Streptococcus pneumoniae</i>	7/7 (100)	13/14 (93)	7/7 (100)	13/14 (93)
<i>Enterobacteriaceae</i>	33/46 (72)	32/45 (71)	29/46 (63)	32/45 (71)
<i>Escherichia coli</i>	8/14 (57)	7/11 (64)	8/14 (57)	7/11 (64)
<i>Klebsiella pneumoniae</i>	11/12 (92)	15/19 (79)	10/12 (83)	15/19 (79)
<i>Enterobacter</i> spp.	7/9 (78)	3/7 (43)	6/9 (67)	3/7 (43)
<i>Proteus</i> spp.	4/5 (80)	2/5 (40)	3/5 (60)	2/5 (40)
<i>Serratia</i> spp.	3/5 (60)	2/4 (50)	2/5 (40)	2/4 (50)
<i>Pseudomonas aeruginosa</i>	12/16 (75)	14/20 (70)	9/16 (56)	11/20 (55)
<i>Acinetobacter baumannii</i>	4/8 (50)	9/12 (75)	4/8 (50)	9/12 (75)
<i>Haemophilus</i> spp.	2/5 (40)	9/9 (100)	2/5 (40)	9/9 (100)

Data are shown as the number of patients achieving clinical cure or microbiological eradication/total number of patients (%).

HAP: Hospital-acquired pneumonia; MRSA: Methicillin-resistant *S. aureus*; MSSA: Methicillin-susceptible *S. aureus*; VAP: Ventilator-associated pneumonia.

Data taken from [61], with permission from Oxford University Press on behalf of the Infectious Diseases Society of America.

Table 4. Clinical cure rates with ceftobiprole or ceftazidime/linezolid at the test of cure visit in the clinically evaluable population for patients with hospital-acquired pneumonia (excluding ventilator-associated pneumonia).

	Ceftobiprole	Ceftazidime/linezolid	Percent difference (95% CI)
All patients	154/198 (78)	141/185 (76)	1.6 (-6.9–10.0)
Age (years)			
18–44	24/27 (89)	18/22 (82)	7.1 (-12.9–27.1)
45–64	48/60 (80)	52/66 (79)	1.2 (-12.9–15.3)
≥65	82/111 (74)	71/97 (73)	0.7 (-11.3–12.7)
Sex			
Male	107/139 (77)	86/112 (77)	0.2 (-10.3–10.7)
Female	47/59 (80)	55/73 (75)	4.3 (-9.9–18.6)
Geographic region			
USA	20/27 (74)	14/24 (58)	15.7 (-10.0–41.5)
Europe	93/112 (83)	90/104 (87)	-3.5 (-13.1–6.1)
Other	41/59 (69)	37/57 (65)	4.6 (-12.5–21.7)
APACHE II score			
8–19	146/185 (79)	134/171 (78)	0.6 (-8.0–9.1)
20–25	8/13 (62)	7/14 (50)	11.5 (-25.7–48.8)
Care facility			
ICU	51/73 (70)	39/59 (66)	3.8 (-12.3–19.8)
Non-ICU	103/125 (82)	102/126 (81)	1.4 (-8.1–11.0)
Pre-study antibiotics[†]			
None	44/53 (83)	49/59 (83)	0.0 (-14.0–13.9)
Usage ≤24 h	52/65 (80)	45/59 (76)	3.7 (-10.8–18.3)
Usage >24 h	58/80 (73)	47/67 (70)	2.4 (-12.3–17.0)
Antipseudomonal antibiotics[‡]			
Yes	15/27 (56)	10/19 (53)	2.9 (-26.3–32.2)
No	139/171 (81)	131/166 (79)	2.4 (-6.2–10.9)

[†]The window for prestudy antibiotics was limited to 72 h prior to baseline.

[‡]Empirical antibiotic treatment was added to the study drug regimen for 48 h in patients with a suspected *Pseudomonas aeruginosa* infection or for 5–7 days for those with a proven *P. aeruginosa* infection.

Data taken from [61], with permission from Oxford University Press on behalf of the Infectious Diseases Society of America.

characteristics as well as baseline pathogens were generally similar in patients with early-onset HAP and those with late-onset disease (<5 and ≥5 days after hospitalization), although patients with early-onset HAP tended to be older and were more likely to have received ventilation at baseline. Ceftobiprole was as effective as ceftazidime/linezolid as assessed by clinical cure rates at the TOC visit in both early-onset HAP (75% vs 67%; difference 7.7%; 95% CI: -8.6–24.0) and late-onset HAP (79% vs 80%; difference -0.9%; 95% CI: -10.6–8.8), for the clinically evaluable population. The 30-day all-cause mortality was also similar between treatments in early- (16% vs 18%) and late-onset (17% vs 18%) HAP. Interestingly, the similarity of the baseline pathogen profiles in the early- and late-onset HAP subgroups indicates that time to HAP onset is not a strong predictor of pathogen distribution, and this is consistent with the findings of previous studies [67,68].

Safety & tolerability

Ceftobiprole is generally well tolerated in patients with HAP. Treatment-related adverse events (AEs) reported in the Phase III study of ceftobiprole in patients with HAP are summarized in **Table 5**. The AE profile for ceftobiprole was broadly similar to that for ceftazidime/linezolid. The incidences of hyponatremia, phlebitis, vomiting and hypokalemia were higher with ceftobiprole, while those of diarrhea, rash and elevations in levels of aspartate aminotransferase and alanine aminotransferase were higher with ceftazidime/linezolid; dysgeusia was reported only for patients receiving ceftobiprole. Treatment-related serious AEs occurred at a similar rate with ceftobiprole and ceftazidime/linezolid (3.9 vs 3.1%). There were no clinically relevant between-group differences in other laboratory values, vital signs, results of physical examinations or electrocardiograms. These findings are similar to those

reported in the Phase III ceftobiprole study in patients with CAP [62] and in a summary of clinical safety from Phase II and III studies in a total of 1668 participants [69]. Within these studies, 1239 patients (696 with HAP or CAP and 543 with cSSTI) received 500 mg q8h, 389 patients with cSSTI received 500 mg q12h and 40 patients with cSSTI received 750 mg q12h [18]. The most common AEs (occurring in $\geq 3\%$ of patients) were nausea, vomiting, diarrhea, infusion site reactions, hypersensitivity (including urticaria, pruritic rash and drug hypersensitivity) and dysgeusia [18]. No unexpected safety and tolerability findings were reported in a pharmacokinetic study of high-dose ceftobiprole (1000 mg iv., administered over 4 h) in patients treated in an ICU [56]; note that this dose of ceftobiprole is not approved for use.

Ceftobiprole administration

The dosing regimen for ceftobiprole was determined based on the result of the Monte-Carlo simulations discussed earlier, and was validated in the Phase III studies in HAP [61] and CAP [62]. The recommended dose regimen for patients with normal renal function is ceftobiprole 500 mg iv. q8h, administered over 2 h. An infusion period of 2 h in patients with normal renal function is important as data from the cSSTIs studies (in which ceftobiprole was administered as 500 mg q12h over 1 h) suggest that shorter administration was associated with a higher incidence of

nausea [11,69]. Dose adjustment is required in those with moderately or severely impaired renal function [18]: dosing should be reduced to 500 mg q12h in patients with moderate renal impairment (CL_{CR} 30–<50 ml/min) and to 250 mg q12h in those with severe renal impairment (CL_{CR} <30 ml/min). In patients with ESRD, the dose should be 250 mg every 24 h. Dose adjustment is not necessary in patients with mild renal impairment (CL_{CR} 50–80 ml/min). In patients with augmented renal function (CL_{CR} >150 ml/min), the dose should remain at 500 mg q8h, but the duration of infusion should be increased to 4 h. No dose adjustment is needed based on gender, age, body weight or hepatic impairment.

Conclusion

Ceftobiprole medocaril is a fifth-generation iv. cephalosporin that offers broad-spectrum antimicrobial activity. It is rapidly and almost completely converted to the active metabolite ceftobiprole following administration. Ceftobiprole exhibits potent *in vitro* antimicrobial activity against Gram-positive and Gram-negative pathogens that are frequently associated with HAP, such as *S. aureus* (including MRSA), *S. pneumoniae* (including penicillin-resistant strains), *P. aeruginosa*, *Enterobacteriaceae* (non-ESBL-producing strains) and *Acinetobacter* spp. Ceftobiprole undergoes minimal metabolism to form an inactive metabolite and is primarily excreted renally by glomerular filtration. *In vitro*

Table 5. Treatment-related adverse events with ceftobiprole or ceftriaxone/linezolid for patients with hospital-associated pneumonia.

	Ceftobiprole (n = 386)	Ceftazidime/linezolid (n = 386)
Number of patients with at least one treatment-related AE	96 (24.9)	98 (25.4)
Hyponatremia	17 (4.4)	10 (2.6)
Diarrhea	12 (3.1)	25 (6.5)
Nausea	8 (2.1)	8 (2.1)
Phlebitis	8 (2.1)	5 (1.3)
Oral candidiasis	6 (1.6)	4 (1.0)
Hypokalemia	6 (1.6)	3 (0.8)
Vomiting	6 (1.6)	3 (0.8)
Rash	3 (0.8)	6 (1.6)
Elevated ALT	3 (0.8)	6 (1.6)
Elevated AST	3 (0.8)	4 (1.0)
Pyrexia	4 (1.0)	2 (0.5)
Dysgeusia	5 (1.3)	0

Data are shown as the number of individuals (%) for patients with HAP (non-VAP and VAP).

AE: Adverse event; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HAP: Hospital-acquired pneumonia; VAP: Ventilator-associated pneumonia.

Data taken from [61], with permission from Oxford University Press on behalf of the Infectious Diseases Society of America.

EXECUTIVE SUMMARY

Mechanism of action

- Ceftobiprole binds to penicillin-binding proteins (PBPs), blocking their transpeptidase activity and thus disrupting the synthesis of the peptidoglycan layer of bacterial cell walls.
- Ceftobiprole binds with strong affinity to important PBPs (e.g., PBP2 and PBP3) in Gram-negative bacteria including *Escherichia coli* and *Pseudomonas aeruginosa*, but not to PBP5 in *E. coli*, or to PBP5 or PBP6 in *P. aeruginosa*.
- For Gram-positive bacteria, ceftobiprole has high affinity for PBP2a (encoded by *mecA*), which confers methicillin resistance in methicillin-resistant *Staphylococcus aureus* (MRSA) isolates.
- Ceftobiprole has high affinity for PBP1a and PBP2x, but low affinity for PBP2b (these three PBPs confer β -lactam resistance in *Streptococcus pneumoniae*) and mutated PBP5 (which confers penicillin-resistance in *Enterococcus* spp.).

Microbiology & spectrum of activity

- Ceftobiprole exhibits antimicrobial activity *in vitro* against major Gram-positive pathogens, similar to that of linezolid, teicoplanin and vancomycin.
- Ceftobiprole has potent activity against *S. aureus*, including MRSA; notably, it maintains activity against *S. aureus* strains resistant to linezolid or daptomycin, vancomycin-intermediate *S. aureus*, heterogeneous vancomycin-intermediate *S. aureus* and vancomycin-resistant *S. aureus*.
- With respect to Gram-negative pathogens, a high proportion of *Enterobacteriaceae* clinical isolates are susceptible to ceftobiprole. Ceftobiprole shows good activity against *E. coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* strains not producing extended-spectrum β -lactamase (ESBL). However, it is generally inactive against ESBL-producing strains (as are other cephalosporins).
- *Citrobacter* spp. and *Enterobacter* spp. are generally susceptible to ceftobiprole; however, strains overproducing AmpC β -lactamase tend to be resistant.
- For anaerobic bacteria, ceftobiprole is generally active against *Clostridium* spp. and *Fusobacterium* spp., but inactive against *Bacteroides* spp., *Prevotella* spp. and *Veillonella* spp.; bacteria causing atypical pneumonia are not generally susceptible to ceftobiprole.

Pharmacokinetic properties

- Ceftobiprole medocaril is administered by intravenous infusion, and is rapidly (<1 min) and almost completely converted to active ceftobiprole.
- The pharmacokinetics of ceftobiprole are linear after single and multiple doses over the 125–1000 mg dose range.
- Ceftobiprole undergoes minimal metabolism to form an inactive metabolite and shows minimal (16%) binding to plasma protein.
- Ceftobiprole is almost exclusively eliminated through renal (glomerular filtration) excretion, with about 88% of the administered dose recovered in urine; dose adjustments may be required depending on renal function.
- The results of *in vitro* inhibitor/substrate studies indicate a minimal propensity for interaction with co-administered drugs.

Clinical efficacy

- A pivotal Phase III trial has demonstrated the efficacy of single-agent therapy with ceftobiprole 500 mg iv. every 8 h (q8h) administered over 2 h in patients with hospital-acquired pneumonia (HAP) compared with a combination of ceftazidime/linezolid.
- Ceftobiprole showed noninferiority to ceftazidime/linezolid for clinical cure rates at the test of cure visit in the intent-to-treat (50 vs 53%, respectively) and clinically evaluable (69 vs 71%, respectively) populations.
- Ceftobiprole was noninferior to ceftazidime/linezolid for clinical cure rates in the subgroup of patients with HAP (excluding ventilator-associated pneumonia [VAP]), but not in those with VAP.
- Clinical cure and microbiological eradication rates by pathogen for patients with HAP (excluding VAP) were similar in both treatment groups.

EXECUTIVE SUMMARY (CONT.)**Safety & tolerability**

- Ceftobiprole is generally well tolerated in patients with HAP.
- The adverse event profile for ceftobiprole was broadly similar to that for ceftazidime/linezolid in the Phase III study in patients with HAP.
- The most common adverse events with ceftobiprole in clinical trials (occurring in $\geq 3\%$ of patients) were nausea, vomiting, diarrhea, infusion site reactions, hypersensitivity and dysgeusia.

Dosage & administration

- The recommended dose regimen for patients with normal renal function is ceftobiprole 500 mg iv. q8h, administered over 2 h in adults.
- Dose adjustment may be necessary depending on renal function; doses need to be reduced in patients with moderate or severe renal impairment and in those with end-stage renal disease.
- No dose adjustment is needed based on gender, age, body weight or hepatic impairment.

inhibitor/substrate studies indicate minimal propensity for interaction with co-administered drugs. Early-phase clinical studies have established a ceftobiprole regimen of 500 mg iv. q8h administered over 2 h. Dose adjustment may be necessary depending on renal function.

A range of new antibiotics is being investigated that might have potential in the treatment of HAP, including novel glycopeptides (e.g., dalbavancin, oritavancin and telavancin), iclaprim, temocillin and new-generation cephalosporins (e.g., ceftaroline) [3]. Among these agents, ceftaroline also has anti-MRSA activity [70]. Ceftaroline has been approved for the treatment of CAP, but not HAP. There are currently no registered clinical trials of ceftaroline underway, although there has been a report on clinical experience with ceftaroline in a limited number of patients with HAP or VAP [71]. The availability of additional antibiotics that provide well-tolerated broad-spectrum activity against MDR pathogens will help to simplify initial empirical therapy for HAP.

In a pivotal Phase III trial in patients with HAP, empirical therapy with single-agent ceftobiprole showed similar efficacy to the ceftazidime/linezolid combination with respect to clinical and microbiological cure rates. Ceftobiprole was also noninferior to ceftazidime/linezolid in the subgroup of patients with HAP excluding VAP, although noninferiority was not demonstrated in individuals with VAP. Thus, ceftobiprole has been approved in the EU for the treatment of HAP (excluding VAP) and can be used in patients with HAP who require ventilation. It is also approved in the EU for the treatment

of CAP. Ceftobiprole and ceftazidime/linezolid were similarly well tolerated in the Phase III trial in patients with HAP. The most common treatment-related AEs across all clinical studies included nausea, vomiting, diarrhea, infusion site reactions, hypersensitivity and dysgeusia.

In conclusion, ceftobiprole is an effective and well-tolerated option for the empirical treatment of patients with HAP (excluding VAP). Its broad spectrum of activity against bacterial pathogens commonly encountered in patients with HAP, including MRSA, offers the potential for a simplified monotherapy regimen compared with the usual combination therapy. It would be important for future studies to explore in more detail the activity of ceftobiprole against hard-to-treat HAP pathogens; in particular, a study assessing the efficacy of ceftobiprole compared with vancomycin or linezolid in MRSA HAP would help further characterize the role of ceftobiprole.

Disclaimer

The author takes full responsibility for the content of the article.

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