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REVIEW

Resistance and the management of complicated skin and skin structure infections: the role of ceftobiprole

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Abstract: Antimicrobial resistant bacteria are an increasing concern due to the resulting increase in morbidity, mortality, and health-care costs associated with the administration of inadequate or delayed antimicrobial therapy. The implications of inadequate antimicrobial therapy in complicated skin and skin structure infections (cSSSIs) have gained more attention recently, most likely due to the recent emergence of community-acquired methicillin resistant *Staphylococcus aureus* (MRSA) and the already high prevalence of MRSA in the nosocomial setting. Due to the continuous threat of resistance arising and the limitations of currently available agents for the treatment of cSSSIs, it is necessary to develop new antimicrobials for this indication. Ceftobiprole medocaril, the prodrug of ceftobiprole, is a parental investigational cephalosporin for the treatment of cSSSIs displaying a wide-spectrum of activity against both Gram-positive and Gram-negative species, including MRSA. Ceftobiprole displays noncomplex linear pharmacokinetics, is eliminated primarily by glomerular filtration, and distributes to extracellular fluid. Additionally, it has been shown that the extent of distribution to the site of action with regard to cSSSIs, ie, the extracellular space fluid of subcutaneous adipose tissue and skeletal muscle, is expected to be efficacious, as free concentrations meet efficacy targets for most pathogens. Similar to other beta-lactams, it displays an excellent safety and tolerability profile with the primary adverse events being dysgeusia in healthy volunteers, resulting from the conversion of the prodrug to the active, and nausea in patients. Ceftobiprole has demonstrated noninferiority in two large-scale pivotal studies comparing it to vancomycin, clinical cure rates 93.3% vs 93.5%, respectively, or vancomycin plus ceftazidime, clinical cure rates 90.5% vs 90.2%, respectively. Given the pharmacokinetic and pharmacodynamic properties, ceftobiprole is a promising new agent for the treatment of cSSSIs and has the potential to be used as a single agent for empiric treatment.

Keywords: cSSSIs, resistance, MRSA, cephalosporins

Introduction

Antimicrobial resistant bacteria are an increasing concern due to the resulting increase in morbidity, mortality, and health-care costs associated with the administration of inadequate or delayed antimicrobial therapy.[1–9] Proper guidelines should be followed to efficiently manage skin and skin structure infections and avoid the over usage of available antibiotics, which could possibly facilitate resistance development. The management of skin and skin structure infections is dependent on several factors. One factor is whether the infection is complicated or uncomplicated, as this dictates the need for antibiotics. Complicated infections are defined as infections involving deep soft tissues and usually require antimicrobial therapy and possibly surgical

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intervention. Infections occurring in patients with significant comorbidities, eg, diabetes or eczema, or in certain anatomical locations, eg, perianal, may also be considered complicated.[10–13] Uncomplicated infections, however, are more superficial and less serious, eg, impetigo, cellulitis, and folliculitis.[10,12,13] Typically, uncomplicated skin and soft tissue infections are effectively managed with incision and drainage.[14,15] The management of complicated infections is more complex and it is recommend that in addition to possible incision and drainage, the following be performed in order to optimize antimicrobial therapy; a detailed history, examination of the lesions as part of a physical exam, and administration of empiric antimicrobial therapy with adjustment after microbiological identification of the pathogen(s).[16] These guidelines attempt to provide as much information as possible to health care providers so that optimal therapy can be started and treatment may be adjusted as additional information becomes available.

The selection of an empiric antibiotic with activity against the causative pathogen(s) is nevertheless, difficult due to resistance and the wide-range of possible pathogens. For example, *Staphylococcus aureus* and *Pseudomonas aeruginosa* respectively, account for approximately 45% and 11% of skin and soft tissue infections in North America.[17] Despite these difficulties, selection of an appropriate antibiotic in a timely fashion is imperative due to the negative outcomes associated with inadequate antimicrobial therapy (IAT). The impact of IAT has been extensively studied in pneumonia and bloodstream infections due to the more severe clinical outcomes associated with these infections, ie, higher mortality rates.[18] While there are some previous data that suggest that IAT results in negative outcomes in skin and soft tissue infections,[7] the implications of IAT in complicated skin and skin structure infections (cSSSIs), including surgical site infections, have gained more attention recently.[3,4,8]

The high prevalence of methicillin resistant *S. aureus* in the nosocomial setting, or hospital-acquired MRSA (HA-MRSA), and the emergence of community-acquired methicillin-resistant *S. aureus* (CA-MRSA)[19–21] is certainly a cause for concern and numerous studies have been conducted to evaluate the impact of CA-MRSA in particular. Studies have examined whether or not there has been a correlation between physician visits and the emergence of CA-MRSA. The literature on the effect of CA-MRSA on overall ambulatory visits is controversial and therefore difficult to interpret. However, numerous studies do in fact show a correlation between the emergence of CA-MRSA and an increase in emergency department visits and/or visit rates due to skin and soft tissue infections.[22–24] Subsequently, there may also be an increase in prescriptions for antibiotics with activity against CA-MRSA.[22,25] However, this literature is also controversial.[23,24] Despite contradictory reports, it can be definitively stated that with the emergence and prevalence of resistant species, particularly resistance in *Staphylococcus* species (Figure 1),[12] and the negative impacts of IAT, there is a need to develop new antimicrobial therapeutic options.

Antimicrobial therapies for the treatment of cSSSIs

When selecting empiric therapeutic options for the treatment of cSSSIs, it is necessary to consider regional resistance patterns to make an appropriate treatment recommendation. It has been recommended that for patients with skin and soft tissue infections (SSTIs) in regions where CA-MRSA prevalence is greater than 10%–15%, alternatives to the commonly prescribed beta-lactams should be used.[25,26] Additionally, it has been suggested that due to resistance, ciprofloxacin, levofloxacin, and clindamycin, are no longer viable empirical treatment options.[27] Vancomycin has long been the standard empirical therapy for patients with serious cSSSIs, as it displays good activity against MRSA and other Gram-positive organisms commonly implicated in these infections. However, resistance to vancomycin is seen in *Enterococcus* species, >10%,[17,28] and in a few case reports with *S. aureus*.[29–31] In view of the problem of resistance, several new therapeutic options have been recently developed. However, many of these new treatments have serious limitations

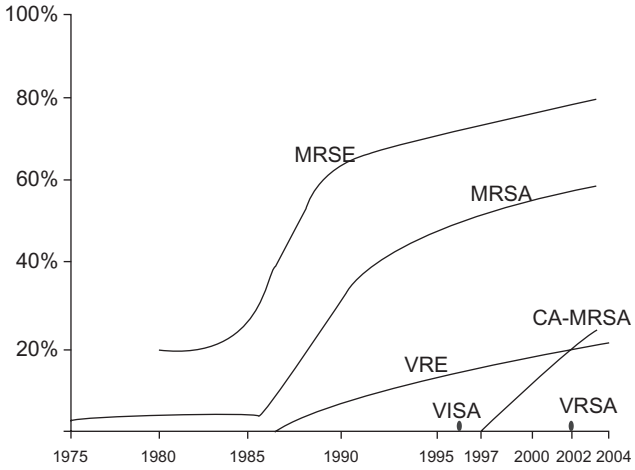

Figure 1 Trends in resistance among Gram-positive pathogens (1975–2004). MRSE: methicillin-resistant *S. epidermidis*. VRE: vancomycin-resistant *Enterococcus*. VISA: vancomycin-intermediate *S. aureus*. VRSA: vancomycin-resistant *S. aureus*. Reprinted with permission from Lee SY, Kuti JL, Nicolau DP. Antimicrobial management of complicated skin and skin structure infections in the era of emerging resistance. *Surg Infect (Larchmt)*. 2005;6:283–295.[12] Copyright © 2005 Mary Ann Liebert, Inc. publishers.

including a narrow activity profile, eg, Gram-positive organisms only, and/or serious side effects.

Quinupristin–dalfopristin has been approved for the treatment of bacteremia due to vancomycin-resistant *Enterococcus faecium* and cSSSIs due to methicillin-susceptible *S. aureus* (MSSA) and *Streptococcus pyogenes.*[32] However, it is not active against vancomycin-resistant *Enterococcus faecalis.*[32] Additionally, it is not indicated in infections against MRSA, although it has been suggested to be an acceptable treatment option[33,34] and displays an *in vitro* $MIC_{90} \leq 1$ mg/L.[35–37] Finally, quinupristin–dalfopristin also bears a significant probability of myalgia as a side effect and requires a central venous catheter for administration, which limits its use.[34,38] Linezolid is another available agent for the treatment of Gram-positive infections, including MRSA. Like vancomycin, resistance to linezolid has occurred but is rare.[39] A more detrimental limitation for selection of this agent is the cost; $1,677 for a 10-day treatment regimen.[27] Additionally, this option does not have an optimal adverse event profile as a considerable frequency of serious adverse events is observed, eg, thrombocytopenia, peripheral neuropathy, and lactic acidosis.[40] Daptomycin has also been proven efficacious in cSSSIs but, like other previously mentioned agents, is not active against Gram-negative organisms.[41] Myopathy may result due to treatment with daptomycin[42] and, subsequently, alternative treatments may be better options in patients concomitantly on statins.[27] Tigecycline is approved for the treatment of cSSSIs and has a wide-spectrum of activity including many resistant Gram-positive and Gram-negative pathogens, with the exception of *P. aeruginosa.*[43–45] Trials comparing tigecycline to vancomycin-aztreonam in patients with cSSSIs revealed that tigecycline has a significantly higher incidence of gastrointestinal events, including nausea and vomiting.[46] However, most events were mild to moderate and did not lead to discontinuation of therapy. Tigecycline is contraindicated in children and pregnant women as it has a tendency to accumulate in bone[47,48] and cause bone and teeth discoloration.[49] The above examples describe some available treatment options for cSSSIs. To describe the pharmacokinetic and pharmacodynamic profile of each in full and evaluate the numerous additional therapeutic options, is beyond the scope of this paper and the reader is referred to several reviews.[11,12,16,27,38,50,51]

In view of the above examples, it is evident that there is a need to develop new antimicrobials for the treatment of cSSSIs which have activity against resistant Gram-positive and Gram-negative species with acceptable safety and tolerability. One promising new treatment option is ceftobiprole, a parental cephalosporin antibiotic with a wide-spectrum of activity including several resistant species such as MRSA. This compound has finished phase III trials for the indication cSSSIs but has not yet been FDA approved. This paper reviews the pharmacokinetic/pharmacodynamic (PK/PD) profile of ceftobiprole with respect to its potential role in cSSSIs.

Ceftobiprole pharmacokinetics

Plasma concentrations

Ceftobiprole is available only as a parental agent and is delivered as the water-soluble prodrug ceftobiprole medocaril. It is supplied in single use vials as lyophilized powder corresponding to 500 mg of ceftobiprole, 666.6 mg of the prodrug, and is reconstituted in water or 5% dextrose for injection. After reconstitution it is further diluted in 0.9% sodium chloride, 5% dextrose, or Lactated Ringer's solution for infusion. The stability and recommended storage conditions of ceftobiprole in each of these solutions varies and should be referenced.[52] Once infused, the prodrug is converted to the active within seconds by type A esterases.[53] The protein binding of ceftobiprole has been cited as 16%–38%.[53–55] Dose proportionality is displayed as clearance, volume of distribution, and dose normalized AUC and C_{max} are consistent in doses ranging from 125–1000 mg.[55,56] The currently recommended empirical dosing regimen of ceftobiprole for the treatment of cSSSIs is 500 mg every 8 hours as a 2-hour i.v. infusion for 7–14 days. In patients without diabetic foot infection and where gram-positive pathogens only have been documented, the recommended treatment regimen is 500 mg every 12 hours as a 1-hour i.v. infusion for 7–14 days.[52] Following empirical dosing, the C_{max} is 33.0 mg/L and the $AUC_{0\text{-}tau}$ is 102 mg*hr/L.[52,53,57] After a single 500 mg dose as a 1-hour infusion, the C_{max} is 34.2 mg/L and the $AUC_{0-\infty}$ is 116 mg*hr/L.[53] In a multiple dose study the accumulation of ceftobiprole was found to be negligible with a 12-hour dosing interval.[55] Similarly, no significant accumulation occurs during an 8-hour dosing interval.[52] The pharmacokinetics in patients with cSSSI were similar to healthy volunteers as after dosing 750 mg every 12 hours the $AUC_{0-\infty}$ was 143 mg*hr/L compared to 165 mg*hr/L, respectively.[53] In this study the half-life was somewhat lower in patients, 3.06 hours, compared to in healthy volunteers, 4.11 hours.[53,58] However, in a separate study in healthy volunteers, half-life was reported as 2.61 hours.[54] It was

also found that gender does not affect systemic exposure of ceftobiprole if normalized for body weight.[53]

Volume of distribution/tissue distribution

Ceftobiprole is similar to other beta-lactams in that it distributes primarily to extracellular fluid. The volume of distribution of ceftobiprole is approximately 18L, reported range of V_{ss} 11L to 21.7L.[56] Therefore, it would be assumed that ceftobiprole reaches the site of action to a significant degree, as most bacterial pathogens reside in the extracellular space fluid. To more accurately determine ceftobiprole's concentration at the site of action, a microdialysis study was conducted. In this study, concentrations were measured in subcutaneous soft tissues, ie, adipose tissue and skeletal muscle. Concentrations in these tissues are particularly important to define the PK/PD relationship with regard to cSSSIs. It was found that the AUC ratios of free tissue/free plasma were 0.69 and 0.49 for skeletal muscle and s.c. adipose tissue, respectively, demonstrating that ceftobiprole has the ability to penetrate into these tissues[54] (Figure 2). Additionally, a study using radiolabeled ceftobiprole was conducted in mice and rats to determine the tissue distribution. It was shown that ceftobiprole distributed rapidly into tissues with the highest tissue/plasma ratio occurring in the kidney, 1:3, and did not penetrate into the brain, tissue/plasma ratio 0:01.[52] However, the results from radiolabelled studies should be interpreted cautiously as only free drug at the site of action is active and this technique fails to differentiate between central and peripheral compartments.

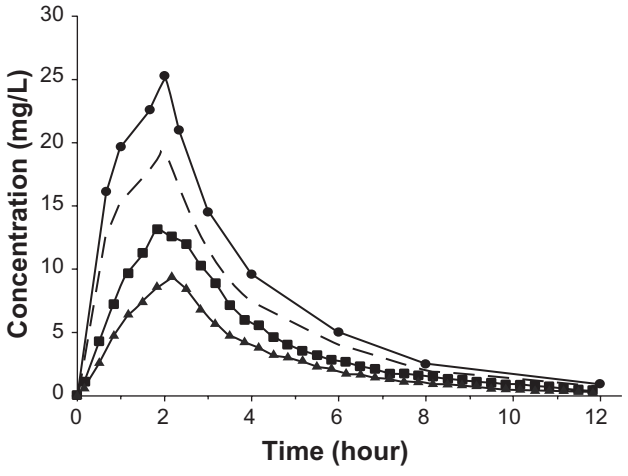

Figure 2 Mean ceftobiprole concentration in plasma (circles), free plasma (dashed line), skeletal muscle (squares), and s.c. adipose tissue (triangles) over 12 h. Reprinted with permission from Barbour A, Schmidt S, Sabarinath SN, et al. Soft-tissue penetration of ceftobiprole in healthy volunteers determined by *in vivo* microdialysis. *Antimicrob Agents Chemother*. 2009;53:2773–2776.[54] Copyright © 2009 American Society for Microbiology.

Clearance

Ceftobiprole is primarily eliminated by glomerular filtration as clearance, range 4.46–5.99L/hr,[56] is highly correlated to creatinine clearance[53] and approximately equal to the glomerular filtration rate multiplied by the unbound fraction of ceftobiprole. The recovery of unchanged drug in the urine was measured in a single ascending dose study, dose range 125–1000 mg delivered as 0.5-hour infusions. It was determined that 62% to 78% of unchanged drug is recovered in urine of healthy volunteers over 24 hours.[55] After administration of ceftobiprole, 500 mg 2hr infusion q8hr, in healthy volunteers, ≥83% of the drug was found unchanged in the urine, while the primary metabolite, ie, the open-ring metabolite, represented <7%.[57] Ceftobiprole is not thought to be eliminated by active tubular secretion as demonstrated by a probenecid study or metabolism as preclinical and *in vitro* experiments showed no potential for CYP interactions.[53] A dosing adjustment is recommended in patients with impaired renal function. Patients with a creatinine clearance (Cl_{cr}) of 30 < 50 mL/min should have the dosing interval adjusted to every 12 hours. In patients with a Cl_{cr} < 30 mL/min, the dosing regimen should be 250 mg every 12 hours as a 2 hour i.v. infusion.[52]

Population pharmacokinetics

Several population PK models have been developed for ceftobiprole. Many of these models were developed for use in Monte Carlo simulations to aid in selection of the optimal dosing regimen. Additionally, these models allow identification of significant covariates and show how these covariates affect the pharmacokinetics and, subsequently, safety and efficacy. In terms of resistance development, theses models can be used to predict the target attainment rate as susceptibility changes, eg, at increased MICs. Phase I data was fit to a two-compartment model to perform Monte Carlo simulations and identify an appropriate dosing regimen for phase II.[59] Data from phase I and II studies were used to develop a three-compartment model with first-order elimination from the central compartment.[60] In this model, a hydrolysis compartment was included as the prodrug was infused at a constant rate into this compartment and then hydrolyzed to the active compound. The active drug entered the central compartment via a first-order process. The clearance was dependent on the creatinine clearance in this model. Later the predicted distribution of renal function was used to calculate the target attainment rate and determine the appropriate dosing regimen in patients with various degrees of renal function. Data from phase I, II, and III studies were modeled using a three

compartment model which included a central compartment and deep and shallow peripheral compartments. In this model, sex, body weight, creatinine clearance, and health status were identified as covariates.[61] Finally, epithelial lining fluid (ELF) concentrations from healthy volunteers were used to develop a four-compartment model where ELF represented a separate compartment.[62] This model was more directed at identifying the target concentration at the site of action, ie, ELF, for the indication of nosocomial pneumonia. The application of these models will be discussed in a later section.

Adverse events

In pivotal phase III trials, ceftobiprole had a safety and tolerability profile similar to competitors. In a study comparing ceftobiprole to vancomycin plus ceftazidime, 56% of patients in the ceftobiprole arm and 57% of patients in the comparator arm, experienced at least one adverse event (AE).[63] Similarly, 7% of patients in the ceftobiprole arm and 9% in the competitor arm had at least one serious AE. Four percent of patients from both arms had to discontinue treatment due to an AE. In a study comparing ceftobiprole to vancomycin, only 52% of patients in the ceftobiprole arm had at least one AE, compared to 51% in the vancomycin arm.[64] Four percent of patients in the ceftobiprole arm and 6% in the vancomycin arm discontinued treatment due to an AE. Six percent of subjects in either arm experienced an AE. Interestingly, dysgeusia was a common AE in the comparator trial with vancomycin and in trials with healthy volunteers but was not listed in the vancomycin plus ceftazidime trial. The most common AEs for ceftobiprole from single and multiple dose studies in healthy volunteers and comparator studies in patients are nausea, headache, dysgeusia, vomiting, diarrhea, constipation, hypersensitivity, and infusion site reaction. Dysgeusia is directly related to ceftobiprole dosing and is thought to be due to the conversion of ceftobiprole medocaril to the active, ceftobiprole, and diacetyl, which is known to produce a caramel-like odor.[53,55,65] The most common AEs in healthy volunteers and patients with cSSSIs are summarized in Table 1.[55,63,64,66]

Table 1 Most common adverse events (AEs) in healthy volunteers and patients.[55,63,64,66]

	Healthy volunteers	Patients
Total No. of subjects	42	932
Total No. of subjects with at least one AE	21	507
Total No. of subjects with at least one serious AE	0	63
Dysgeusia	17	30
Nausea	10	113
Headache	10	68
Abdominal pain	2	*
Vomiting	1	61
Diarrhea	1	62
Constipation	0	33
Hypersensitivity[a]	0	49
Infusion-site reaction	1	48

[a]Including rash and pruritus.

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Ceftobiprole pharmacodynamics

In vitro

Ceftobiprole, like other beta-lactams, binds to penicillin binding proteins (PBPs) and inhibits cell-wall synthesis. It has a wide-range of activity against gram-positive pathogens, including MRSA, and a pharmacodynamic profile similar to cefepime and ceftazidime against Gram-negative pathogens.[67] The *in vitro* activity of ceftobiprole against isolates collected from cSSSIs during the phase III pivotal studies is presented in Table 2.[68] One feature of ceftobiprole that makes it a more attractive therapeutic option over many other antibiotics is its activity against several resistant species including MRSA. Ceftobiprole's activity against MRSA is due to its strong affinity for PBP2a (PBP2'), the major cause of resistance to other beta-lactams.[69,70] Additionally, ceftobiprole has been determined to be primarily bactericidal from *in vitro* time-kill studies[71] and by demonstrating MBC/MIC ratios of <4 for a large majority of tested isolates.[72] Ceftobiprole, however, shows poor affinity for PBP5 and is therefore not active against *E. faecium*.[70] Also, ceftobiprole is susceptible to some beta-lactamases which explains the wide range of MICs for *P. aeruginosa, Klebsiella pneumo-*

Table 2 *In vitro* susceptibility determined from isolates collected from cSSSIs from phase III trials with ceftobiprole[68]

	MIC_{90} (mg/L)	MIC range (mg/L)
MSSA	0.5	0.12–1
MRSA	2	0.25–4
*Pseudomonas aeruginosa**	>64	0.25–>64
Enterococcus faecalis	0.5	0.12–0.5
Enterococcus faecium#	#	2–>64
Escherichia coli	0.12	0.015–>64
Enterobacter cloacae	>64	0.03–>64
Klebsiella pneumonia	32	0.03–>64
Streptococcus pyogenes	0.015	0.008–0.25
Streptococcus agalactiae	0.12	0.015–0.12
CoNS methicillin susceptible	0.5	0.015–1
CoNS methicillin-resistant	2	0.06–4
Proteus mirabilis	0.12	0.015–>64

Pseudomonas aeruginosa ceftazidime-susceptible MIC_{90}-16.[70] #Three isolates collected.

nia, and *Escherichia coli*. For example, 38.7% of *P. aeruginosa* are inhibited at an MIC ≤ 1 mg/L, while 85.2% are inhibited at an MIC ≤ 8 mg/L.[73] Ceftobiprole is resistant to hydrolysis by the TEM-1 and SHV-1 beta-lactamases, similar to the competitors cefepime and ceftazidime. However, it is susceptible to hydrolysis by *P. aeruginosa* displaying high expression of AmpC beta-lactamases or the VIM-2 carbapenemase and *E. coli* expressing KPC-2 carbapenemase or the CTX-M-15 extended-spectrum beta-lactamase (ESBL).[74] The MIC_{90} against *Klebsiella* species and *E. coli* for ceftobiprole was >8 mg/L, while the MIC_{90} of the carbapenems ertapenem, imipenem, and meropenem were ≤0.5 mg/L in isolates confirmed as ESBL producing.[73]

The post-antibiotic effect (PAE), is a pharmacodynamic measurement that determines if there is any residual effect once the antimicrobial agent has been removed from the system after exposure to suprainhibitory antimicrobial concentrations. For ceftobiprole, PAEs for *S. pneumoniae*, *S. aureus*, and *E. faecalis* were 1.4–3.1 hours, 0–1.7 hours, and 0–0.9 hours, respectively.[75] Perhaps a more useful *in vitro* pharmacodynamic measurement is the post-antibiotic sub-MIC effect (PA-SME) as it measures the effect of subinhibitory concentrations after initial exposure to suprainhibitory concentrations. This situation more closely mimics the *in vivo* situation where there is fluctuation between doses. The PA-SME for *S. pneumoniae*, *S. aureus*, and *E. faecalis* were 4.8 > 10.3 hours, 1.5–9.6 hours, and 3.8 > 10.7 hours, respectively.[75] Comparatively, *in vivo* PAEs were found to be 0–0.8 hours and 3.8–4.8 hours for *S. pneumonia* and *S. aureus*, respectively.[76]

Serial passage studies

Serial passage studies are often performed with investigational antimicrobials to evaluate the potential for resistance development. When compared to imipenem, ciprofloxacin, and linezolid, ceftobiprole displayed no resistance development using an initial inoculum of 10^5 CFU/mL of *S. aureus* (3 MRSA and 1 MSSA) or against *S. aureus* 745 with an initial inoculum of 2×10^8 CFU/plate after six to eight passages.[70] In a separate study, it was shown that after 50 passages resistance to ceftobiprole did not develop in 10 strains of *S. aureus*, including strains with methicillin and/or vancomycin resistance and coagulase negative strains with or without methicillin and/or vancomycin resistance.[77] The highest observed MIC occurred in the vancomycin-intermediate *S. aureus* (VISA) strain, 8 mg/L, and was four times the original MIC. Similarly, after 50 passages, resistance to ceftobiprole was also not observed in *Haemophilus influenzae*, six beta-lactamase positive and two negative strains, or *Moraxella catarrhalis*, two beta-lactamase positive strains.[78] The highest increase in MIC was four times the original MIC which occurred in one strain of beta-lactamase positive *H. influenzae*, 0.06 mg/L to 0.25 mg/L. One group was able to demonstrate the occurrence of resistance due to mutations in the *mecA* gene by transforming a *mecA* negative strain with a plasmid that carries the mutated gene or by the induction of mutations in the *mecA* transformed strain through serial passages with ceftobiprole.[79] However, the high inoculum used to induce the mutations after serial passage is not likely to occur in a single patient for a sustained period of time. Surprisingly, in this study, resistance also developed in the *mecA* negative strain, suggesting a chromosomal mechanism of resistance.

Animal models

The efficacy of ceftobiprole has also been evaluated in several animal models, the most relevant for the indication of cSSSIs being the mouse abscess model and the murine skin infection model. The peritonitis model will be briefly discussed as peritonitis is often related to, or caused by, surgical site infections, a subclass of cSSSIs. Also noteworthy is the thigh infection model which will be discussed further in the PK/PD section. Animal models which support possible other indications including septicemia,[70] endocarditis,[80] and pneumonia/lung infections[81,82] will not be discussed here. In the mouse abscess model, mice were inoculated with *S. aureus* I-6, a MRSA strain, or Mu50, a MRSA/VISA strain, under the skin of the groin with abscess developing within 3 days in control animals.[70] Treatment was administered up to 3 hours after inoculation. Compared to vancomycin (10 mg/kg) and linezolid (20 mg/kg), ceftobiprole (10 mg/kg) treatment resulted in a greater decrease in bacterial counts of MRSA I-6 from untreated controls, 3.42, 0.80, and 5.12 log decreases, respectively. Similarly, with VISA, ceftobiprole (10 mg/kg) demonstrated a larger decrease in log bacterial counts compared to vancomycin (40 mg/kg) and linezolid (20 mg/kg), >4.79, 0.13, and 0.64, respectively, displaying the efficacy of ceftobiprole compared to competitors currently used to treat serious MRSA cSSSIs.

The murine skin infection model compared the activity of ceftobiprole to cefazolin, vancomycin, and linezolid against an MSSA and an MRSA strain in immunocompetent mice.[83] The activity of ceftobiprole was also compared to cefepime and meropenem-cilastatin against two *P. aeruginosa* strains, an inducible AmpC beta-lactamase strain (OC4351) and an overproducing AmpC beta-lactamase strain (OC4354), in immunocompromised

mice.[83] The mice were inoculated with 6.7–7.0 $\log_{10}$ CFU/mouse of *S. aureus* or 5.9 to 6.8 $\log_{10}$ CFU/mouse of *P. aeruginosa*. After inoculation to the right (MRSA) and left (MSSA) flank, animals were treated with 1.6–100 mg/kg/day at 1, 3, 25, and 27 hours post infection with ceftobiprole medocaril, cefazolin, vancomycin, or linezolid. One, 2, 25, and 27 hours after inoculation to the left (OC 4351) and right (OC 4354) flanks with *P. aeruginosa*, animals were treated with ceftobiprole medocaril, cefepime, or meropenem-cilastatin with 1.6–100 mg/kg/day. The reduction of CFU/g of infected skin with MSSA and MRSA was greatest with ceftobiprole compared to comparators linezolid and cefazolin across all doses tested. Compared to vancomycin, ceftobiprole treatment resulted in a greater reduction in CFU/g for MSSA and MRSA at all doses, except the 100 mg/kg/day dose at which the decrease in CFU of MRSA/g was equivalent (−1.4 $\log_{10}$ change from inoculum). Similarly, ceftobiprole had a greater relative decrease in lesion volume compared to competitors for MSSA and MRSA at all doses, except MSSA with vancomycin at the 100 mg/kg/day dose, lesion volumes of 555, 437, 567, and 1181 mm^3 for ceftobiprole, vancomycin, linezolid, and untreated controls respectively. Against both *P. aeruginosa* strains, ceftobiprole was as efficacious as meropenem-cilastatin and better than cefepime when comparing change in $\log_{10}$ CFU/g at doses of 25 and 100 mg/kg/day. The $\log_{10}$ change in CFU/g at a dose of 100 mg/kg/day was −1.4, 1.7, −1.1 for ceftobiprole, cefepime, and meropenem-cilastatin, respectively, against OC4354. In terms of lesion size, ceftobiprole displayed a greater decrease from untreated controls than cefepime but displayed similar efficacy to meropenem-cilastatin. It should be noted that AmpC levels did not affect ceftobiprole efficacy. This study displayed the potential of ceftobiprole to be used as an empiric agent as it displayed efficacy against two of the most common cSSSI pathogens.

The efficacy of ceftobiprole was also compared to ampicillin, in the mouse *Enterococcal* peritonitis model.[84] Infections were induced using an initial inoculum that was 10 × the inoculum that caused death in half the population (LD_{50}). The strains used included four *E. faecalis* strains; one beta-lactamase producing (BLA^+), two VRE, and one laboratory strain OG1RF. It was found that ceftobiprole displayed similar activity to ampicillin with a 50% protective dose (PD_{50}) for ceftobiprole of 7.7 mg/kg, 5.2 mg/kg, and 4.2 mg/kg compared to 12.5 mg/kg, 16.4 mg/kg, and 8 mg/kg for ampicillin, against the two VRE strains and the OG1RF strain, respectively. Notably, ceftobiprole displayed a much lower PD_{50} compared to ampicillin against the Bla^+ strain, 2 mg/kg compared to >100 mg/kg.

Comparator studies

Two large scale phase III pivotal studies have been conducted in patients with complicated skin and skin structure infections for ceftobiprole. Ceftobiprole was compared to vancomycin in patients with cSSSIs caused by Gram-positive pathogens.[64] In this study, 500 mg ceftobiprole or 1000 mg vancomycin were administered as 60 minute i.v. infusions ever 12 hours for 7 to 14 days. It was found that ceftobiprole is noninferior to vancomycin with clinical cure rates of 93.3% and 93.5%, respectively. In a separate study, the efficacy of ceftobiprole was compared to vancomycin plus ceftazidime in patients with cSSSI. In this study, patients in the ceftobiprole arm received 500 mg of ceftobiprole administered as a 120-minute i.v. infusion every 8 hours plus a 60-minute i.v. infusion of placebo. Patients in the vancomycin plus ceftazidime arm received 1000 mg vancomycin over 60 minutes every 12 hours plus 1000 mg of ceftazidime over 120 minutes every 8 hours.[63] It was found that ceftobiprole is noninferior to vancomycin plus ceftazidime as the clinical cure rates were 90.5% and 90.2%, respectively.

While the role of PVL as a virulence factor in MRSA infections is controversial, it is agreed that PVL is associated with community-acquired infections and, as previously mentioned, the increasing frequency of CA-MRSA infections is correlated to a subsequent increase in ED visits. Therefore, it is interesting to note that ceftobiprole had a higher clinical cure rate compared to vancomycin in MRSA PVL-positive infections, 93.1% (27/29) compared to 84.6% (22/26), although this finding was not statistically significant.[64] Similarly, ceftobiprole had a higher clinical cure rate for PVL-positive isolates compared to vancomycin plus ceftazidime, 92.1% (35/38) compared to 84.2% (16/19).[63]

Ceftobiprole pharmacokinetics/pharmacodynamics

Establishing pharmacokinetic/pharmacodynamic targets

The PK/PD relationship has been established in the mouse thigh and lung infection models.[82] The more relevant targets for cSSSI would be those established from the thigh infection model and, therefore, the results from these experiments will be the main focus. Dose fractionation studies in neutropenic mice,

with doses ranging from 0.01 mg/kg to 160 mg/kg administered every 3, 4, 6, 8, 12 and/or 24 hours 2 to 10 hours after infection, were used to determine the best correlated PK/PD index and the magnitude of that index resulting in bacterial stasis or a 2-log kill. These studies were performed using 19 bacterial strains including *S. aureus* (MSSA and MRSA), *S. pneumoniae* (PSSP, PRSP, and one ciprofloxacin-resistant strain), *E. coli*, *K. pneumoniae*, *Enterobacter cloacae*, and *P. aeruginosa.* From the dose-response curves of the thigh infection model, it was found that the T > MIC needed to produce a static effect and 2-log were 19.8% and 31.9%, respectively, for *S. aureus*, and 15.9% and 25.1%, respectively, for *S. pneumoniae*. As typical, a larger magnitude of the PK/PD target was needed to produce stasis and 2-log kill with Gram-negative species, 36.5% and 54.3%, respectively. These identified targets are in good agreement with the targets currently known to produce efficacy for beta-lactams in both animal models and in the clinic.[85–87] Additionally, a CART analysis showed that patients with a T > MIC of 25% had a higher probability of therapeutic success, further validating the identified efficacy targets.[88]

Dose selection/evaluation

The targets identified from dose fractionation studies are often used to predict efficacy using Monte Carlo simulations to find the target attainment rate (TAR). Monte Carlo simulations take variability of the PK, such as inter-patient variability, and PD, ie, the MIC distribution, into account when calculating the TAR. This technique has been used numerous times for the dose selection and dose evaluation for ceftobiprole. In addition to the targets set by dose fractionation experiments, empirical targets are also used as antibiotics in the same class often have approximately the same target. For example, a general PK/PD target for beta-lactams is approximately 40% $fT_{>MIC}$. However, even among beta-lactam antibiotics the efficacy target varies between subgroups, ie, cephalosporins, penicillins, and carbapenems, and specific pathogens.[85–87] Monte Carlo simulations were performed first using PK data from 12 healthy volunteers, where the TAR for the PK/PD targets of $fT_{>MIC}$ 30%–60% were calculated for numerous doses, 250–1000 mg administered every 12 or 8 hours.[59] From these simulations it was concluded that a 750 mg dose given every 12 hours had a high probability of efficacy for organisms with MICs up to 4 mg/L. Monte Carlo simulations were later performed using a larger and more diverse patient population.[89] In these simulations, the PK was characterized using data from 150 subjects from both phase I and phase II trials. Doses of 500 mg every 8 hours delivered as 0.5-, 1-, or 2-hour i.v. infusions and 500 mg every 12 delivered as a 1-hour i.v. infusion were simulated to determine the TAR for targets of 30%–60% $fT_{>MIC}$. Additionally, the TAR was calculated in patients with renal impairment, Cl_{cr} = 30 mL/min dosed with 250 mg every 8 hours as a 2-hour i.v. infusion, and Cl_{cr} = 50 mL/min dosed with 500 mg every 12 hours as a 2-hour i.v. infusion. Based on these simulations, 500 mg administered as a 1-hour i.v. infusion every 12 hours was recommended for the indication of cSSSIs. Also, a dosing regimen of 500 mg as a 2-hour i.v. infusion every 8 hours was deemed an appropriate dose in patients with mild to moderate renal impairment, ie, a Cl_{cr}~50 mL/min. Finally, simulations were done using a model that was developed using data from phase I, II, and III trials and the individual patient demographics from patients in the phase III trials using a dosing regimen of 500 mg every 8 hours as a 2-hour i.v. infusion.[61] It was found that the overall TAR for targets of $fT_{>MIC}$ 30% and 50% were 94.6% and 93.7%, respectively, based on the MIC distribution and a creatinine clearance of ≥80 mL/min.[88] The dose of 500 mg delivered as a 2-hour infusion was also validated in the microdialysis study where it was found that concentrations in the extracellular fluid of s.c. adipose tissue and skeletal muscle met the PK/PD target of $fT_{>MIC}$ 40% for organisms with a MIC ≤ 2 mg/L.[54]

Discussion

In North America, 44.6% of SSTIs are caused by *S. aureus*, of which 35.9% are methicillin-resistant.[17] The second most commonly identified pathogen, *P. aeruginosa*, accounts for 11.1% of SSTIs, while the third and fourth most commonly isolated pathogens were *Enterococcus* species (9.3%) and *E. coli* (7.2%), respectively. Additionally, cSSSIs can be polymicrobial and include both Gram-positive and Gram-negative pathogens, eg, diabetic foot infections. Therefore, due to the wide-spectrum of causative pathogens and various resistance mechanisms, an obvious challenge arises in identifying a first-line single agent or even combination therapy for empiric treatment prior to microbial identification. Based on its activity profile, ceftobiprole has the potential to serve as a single agent for the empiric treatment of cSSSIs. However, pathogen identification and characterization is still needed as ceftobiprole is susceptible to some beta-lactamases. For example, while activity is observed against *E. coli*, MIC_{90} 0.12 mg/L, in species producing ESBLs (~6%),[17,67] the MIC_{90} is reported as >8 mg/L.[67] Additionally, ceftobiprole does not display good activity against *E. faecium.*[70] Another minor limitation of ceftobiprole, is that the mechanism of action does not inhibit protein synthesis as some competitors. Down regulating PVL, a possible virulence factor, could be advantageous in CA-MRSA infections.[27]

In conclusion, ceftobiprole has several characteristics that make it a promising single agent for use empirically to treat cSSSIs including its spectrum of activity,

distributional properties, and excellent safety and tolerability profile.

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