Review Article

Ceftobiprole-A novel cephalosporin to combat MRSA

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Abstract. Gram positive cocci are responsible for a large number of infections, involving the skin and skin structures, respiratory tract, bloodstream etc., both in the community as well as in the hospital settings. However, the recent emergence of multidrug resistant strains has compromised therapeutic options as well as made therapy less effective and costlier. As medicine continues to evolve to combat these pathogens, they always seem to be a step ahead of us. Vancomycin, the drug of choice for resistant strains of gram positive cocci, has also seen the development of bacteria resistant to it. The introduction of ceftobiprole, a novel fifth-generation cephalosporin, has brought with it new hope for combating these pathogens. It exerts its antibacterial effect by binding to the PBP (penicillin-binding protein), blocking formation of the bacterial cell wall and ultimately leading to cell lysis and death. It has also got a wide antibacterial spectrum covering many gram negative bacteria as well as anaerobes. Ceftobiprole has been evaluated in various clinical trials including the multicentric STRAUSS 1 and 2 trials, and the results have demonstrated favourable efficacy of ceftobiprole against gram positive cocci. Thus, although ceftobiprole provides us with another option in our battle against the microbes, its judicious use is imperative so that we do not run out of therapeutic options in the near future.

Key words: ceftobiprole, MRSA, cephalosporin, cocci.

1. Introduction

Antimicrobial resistance has become a global concern. Gram positive cocci, in particular, are responsible for many severe infections, like skin and skin structure infections (SSSIs), bacteraemia, respiratory infections etc. in community and hospital settings. Furthermore, multidrug resistance of these organisms is alarming because this resistance compromises therapeutic options (1).

The introduction of methicillin in 1959 was a ground-breaking achievement in the war against penicillin-resistant *Staphylococcus aureus.* However, during the past three decades methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a cause of infection in the community and healthcare settings. Centers for Disease Control (CDC) reports that MRSA currently causes 1% of all *Staphylococcus* infections, and >50% of healthcare associated *Staphylococcus* infections. As such, it has proved to be a major cause of mortality and morbidity (2).

In India, the incidence of MRSA is also increasing (3-7). In a study by Mehta *et al* (3), 32% of *S.aureus* isolates were found to be multiply resistant, with the individual figures for resistance being 20% (Bombay), 42.5% (Delhi) and 47% (Bangalore). Worldwide also, there has been a dramatic trend of increasing reports of outbreaks and increased prevalence of community-acquired MRSA during the past few years (8-11). The increasing incidence of MRSA has also been documented from southern and eastern Mediterranean countries including Egypt, Turkey, and Jordan (40). There have also been recently published reports of increasing resistance in the African subcontinent (41).

Vancomycin is considered to be the drug of choice for the treatment of MRSA infection. However, its widespread use has led to the emergence of strains with increasing MIC

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concentrations, and on occasions, clinical resistance. Vancomycin intermediate *Staphylococcus aureus* (VISA) (Vancomycin MIC 4-8 µg/ml) and vancomycin resistant *Staphylococcus aureus* (VRSA) (Vancomycin MIC>=16 µg/ml) are rare, but have been documented globally (1). In India, vancomycin resistance has recently been reported from various centres (14,15).

The role of vancomycin as the reference standard for the treatment of MRSA infection has also recently been challenged (16). The emerging resistance to vancomycin among Gram positive cocci, and the poor tissue penetration and weak antibacterial activity of this glycopeptides has led researchers to develop novel antistaphylococcal agents. Linezolid, daptomycin, tigecycline and quinupristine-dalfopristine have been introduced into clinical practice, each with their own pros and cons (1). In a study, comparison of activity of ceftobiprole, vancomycin, daptomycin and linezolid has revealed that ceftobiprole is highly active against MRSA, and was bactericidal at all concentrations tested. Comparison of kill rates in this study revealed daptomycin (1.6h) had a kill rate greater than ceftobiprole (8h) and vancomycin (8h), which was greater than that of linezolid (did not reach 99.9% time kill) ($p<0.001$) for community-acquired MRSA, and had similar results for hospital-acquired MRSA (43). Ceftobiprole (Basilea, Johnson and Johnson) is the first of a new generation of extended-spectrum cephalosporins with activity against clinically important Gram positive bacteria, including MRSA, penicillin-resistant *S. pneumoniae* and *E. faecalis* (2,17,18). The drug has also shown activity against clinically important Gram negative bacteria including *Citrobacter spp., Enterobacter* spp*., Klebsiella* spp*., S. marcescens* and *P. aeruginosa* (2). Ceftobiprole is a broad-spectrum cephalosporin with additional properties that circumvent many of the mechanisms of resistance to β-lactams. Ceftobiprole has been evaluated in phase 3 trials for treating complicated SSSIs (cSSSIs) caused by Gram positive and Gram negative bacteria (23). Preliminary surveys have indicated that ceftobiprole has excellent *in vitro* activity against MRSA, VRSA, VISA and coagulase-negative staphylococci (CONS) (20-22).

2. Mechanism of action

Methicillin resistance in *Staphylococcus aureus* is conferred by a penicillin binding protein (PBP) that is encoded by the *mec*A gene found in the staphylococcal cassette chromosome *mec* (SCC*mec*) (12,13). These mobile genetic elements may also carry additional genetic material that encode resistance to other classes of antimicrobials. Penicillin resistance in *Strep. pneumoniae* is mediated through a similar adaptive mechanism by the bacteria. Alterations of PBP2 to PBP2x by *Strep. pneumoniae* lead to a decrease in penicillin activity, necessitating higher doses to achieve activity, or may prevent binding altogether (2). MRSA produce the alternative PBP2a in addition to the 'normal' PBP. The protein is encoded by the *mec*A gene, and because PBP2a is not inhibited by antibiotics such as flucloxacillin, the cell wall and peptidoglycan synthesis continues (46).

Like all β-lactam antibiotics, ceftobiprole exerts its antibacterial effect by binding to PBP, inhibiting transpeptidation and formation of the bacterial cell wall, leading to cell lysis and death. The drug can bind to several different PBPs found in both Gram positive and Gram negative bacteria. Ceftobiprole rapidly binds and forms a stable inhibitory acyl complex with PBP 2' (PBP 2a) and PBP 2x, which provide activity against β-lactam resistant *staphylococci* and *streptococci* respectively. The stability of the enzyme complex, in combination with the long side chain that sits deep in the PBP 2'-binding pocket, enhances the stability of the bond and inhibition of the enzyme (1,2,19).

3. Spectrum of activity

Ceftobiprole is active against a wide range of Gram-positive and Gram-negative pathogens (Table 1) (1).

Perhaps ceftobiprole's most important characteristic is its activity against *Staphylococcus aureus* strains including MRSA. Ceftobiprole has also demonstrated activity against MSSA, MS- and MR-CONS, VISA and VRSA (23). Ceftobiprole is also effective against *Strep. pneumoniae*, an important feature, as penicillin-resistant, cephalosporin-resistant and macrolide-resistant strains have emerged worldwide (2). Unlike all other available cephalosporins, ceftobiprole retains activity against *E.faecalis.* The antibiotic was found to be highly active *in vitro* against a large collection of *E.faecalis* isolates, irrespective of their resistance to vancomycin or the production of β-lactamases (19,34).

Table 1. MIC values of Ceftobiprole against various Gram positive and Gram negative bacteria

Microorganism	MIC_{50} (mcg / ml)	MIC_{90} (mcg / ml)	References
MS-*Staphylococcus aureus*	0.25 - 0.5	<0.125 - 2	14, 16, 32, 34
MR-*Staphylococcus aureus*	0.5 - 2	0.12 - 4	14, 16, 32, 34
MS-CONS	<0.12 – 1	≤0.015 - 1	16, 32
MR-CONS	1	1 - 2	16, 32
Enterococcus faecalis	0.5	2-4	14, 34
Enterococcus faecium	4	8	34
Penicillin-susceptible *Strep. pneumoniae*	0.008-0.016	0.008-0.25	1, 32, 34
Penicillin-resistant *S.pneumoniae*	0.25-0.5	0.25-2	1, 32, 34
Moraxella catarrhalis	≤0.06-0.12	0.12-1	14, 34
Neisseria meningitidis	≤0.002	0.004	14
ESBL-negative *Escherichia coli*	0.03-0.06	0.06	1, 32 34
ESBL-positive *Escherichia coli*	4->32	>8->32	1, 32, 34
ESBL-negative *K. pneumoniae*	0.03-≤0.125	0.06-0.25	14, 32, 34
ESBL-positive *K. pneumoniae*	4-64	>32-128	14, 32, 34
Proteus mirabilis	≤0.06	≤0.06-0.12	14, 34
ESBL-negative *Proteus vulgaris*	0.03	0.06	1, 32
ESBL-positive *Proteus vulgaris*	>32	>32	1, 32
Pseudomonas aeruginosa	2-8	8-32	1, 14
Burkholderia cepacia	8	64	1, 14
Imipenem-sensitive *Acinetobacter spp.*	0.5	>32	1, 32
Imipenem-resistant *Acinetobacter spp.*	>32	>32	1, 32

MIC: Minimum inhibitory concentration; MR: Methicillin-resistant; MS; Methicillin-susceptible; CONS: Coagulase-negative staphylococci

Ceftobiprole is also active against clinically important Gram negative pathogens, including *Citrobacter* spp., *E.coli*, *Enterobacter* spp., *Klebsiella* spp., *S.marcescens* and *P.aeruginosa* (21, 23, 39). All Enterobacteriaceae (except some ESBL-producing strains and *Proteus vulgaris*) are intrinsically susceptible to ceftobiprole (1). The lack of activity against *Proteus vulgaris* results from efficient enzymatic hydrolysis (mediated by K1 beta-lactamase) of ceftobiprole by this organism (19). Synergistic anti-bacterial effect of ceftobiprole with amikacin and levofloxacin has also been reported (42). Although ceftobiprole has demonstrated activity against isolates expressing AmpC β-lactamases, it has not consistently shown activity against isolates expressing ESBLs. Ceftobiprole also inhibits *H.influenzae* and *M.catarrhalis*, including β-lactamase producers (19,37,39). The agent also inhibits *P.mirabilis*, *Providencia* spp., *M.morganii*, *Vibrionaceae* spp. and *N.gonorrhoeae* (39).

The susceptibility of anaerobes to ceftobiprole has also been studied. The agent is active against Gram positive anaerobes including *Propionibacterium acnes*, *Peptostreptococcus anaerobius*, *Clostridium inocuum*, *Finegoldia magna* etc (39). Like most cephalosporins, ceftobiprole is not active against species of *Bacteroides fragilis* group, *Prevotella bivia*, or strains of *Prevotella melaninogenica* (19).

4. Pharmacokinetic profile

Ceftobiprole is a pyrrolidinone-3-ylidenemethyl cephem (fig.1.). Ceftobiprole (formerly known as BAL 9141) is the active component of the prodrug ceftobiprole medocaril (formerly known

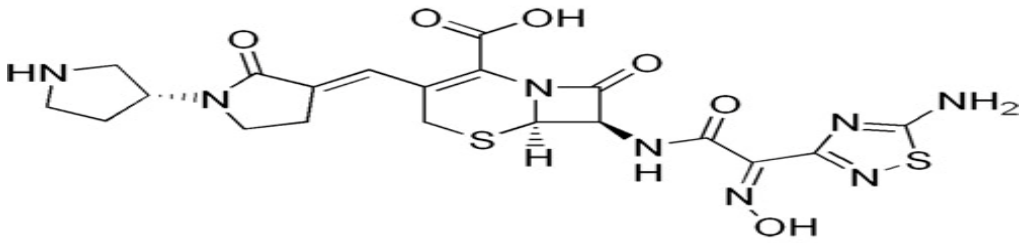

Fig.1. Chemical structure of Ceftobiprole

as BAL 5788). Ceftobiprole medocaril is a water-soluble prodrug developed to facilitate the i.v. administration of the active parent drug ceftobiprole (13,23). After i.v. administration, ceftobiprole medocaril is converted to the active drug ceftobiprole plus diacetyl and carbondioxide, by type A plasma esterases. This process is rapid (<1 minute) and complete, with minimal influence from other medications and disease states (1,2).

Single and multiple dose administration studies of ceftobiprole 125 to 1000 mg have been performed (24,25). In one study, the prodrug BAL 5788 was rapidly metabolized to ceftobiprole, and no prodrug could be measured in the plasma after the end of infusion (25).

The pharmacodynamic parameter most correlated with the clinical efficacy of ceftobiprole is the percentage of dosing interval in which free drug concentrations remain above the MIC (*f*T>MIC). The optimal %*f*T above the MIC required for ceftobiprole to achieve a bacteriostatic effect is 30% of the dosing interval for staphylococci, and for maximum bactericidal activity, the %*f*T above the MIC should be at least 50% (1,2). Studies in healthy volunteers demonstrated that after administration of ceftobiprole 500 mg and 750 mg, the time that the total drug concentration remained above 4 µg/ml (the MIC at which 100% of MRSA strains are inhibited) was 5 to 7 hours, and 7 to 9 hours respectively, which satisfies the bactericidal exposure requirement when dosing is administered every 8 hours (1,24).

The effect of sub-MIC concentrations on growh during the post-antibiotic effect (PAE) was longer than the PAE in a study, suggesting that continued exposure to sub-MIC levels of ceftobiprole following a supra-inhibitory level may allow for continued suppression in vivo. Staphylococcal PAEs were slightly lower for methicillin-susceptible isolates (mean: 0.4 hours; range: 0-0.8 hours) than for methicillin-resistant isolates (mean: 1.0 hours; range 0-1.8 hours) (19).

The pharmacokinetic properties of ceftobiprole have also been evaluated in healthy volunteers, in patients with varying degrees of renal dysfunction, and in patients enrolled in clinical trials for the treatment of cSSSI's (23-25). The volume of distribution at steady state (Vss) is ~18-20 litres. Like other β-lactams, this drug is comparable to the ECF compartment in adults. The pharmacokinetic parameters of ceftobiprole in patients of normal renal function, and in those with mild, moderate and severe renal impairment have been determined (23,27). Roos *et al* determined that systemic exposure, as measured by the AUC (area under the curve) concentration was increased in patients with impaired renal function. As a result, dosage adjustment is necessary in patients with renal insufficiency (27). Results of a multiple dose study indicate that ceftobiprole has stable pharmacokinetic properties over an 8-day course of dosing, with low inter-subject variability (25). In another study, accumulation of ceftobiprole was not apparent after 5 days of administration of 500 mg every 8 hours, infused over 2 hours (23).

Ceftobibrole demonstrates a low percentage of protein binding (16%) (28). It is neither an inhibitor nor a substrate for the cyt P450 system. Studies with cycloserine have also demonstrated that ceftobiprole is neither an inhibitor nor a

substrate for the p-glycoprotein (PGP) transporter system. Based on combination studies with probenecid, ceftobiprole is eliminated by the kidneys as unchanged drug via glomerular filtration, and not through active tubular secretion (2,23).The half-life of ceftobiprole is ~3 hours, with >80% of the active drug recovered in the urine within 12 hours after administration (2). The highest urine drug concentrations are observed within 2 hours after the start of the infusion, and the urine concentrations correlate with dose (19). Slight variations in the drug's pharmacokinetic profile are based on the patient's sex. However these do not warrant any dose adjustment (26). Pharmacokinetic properties in terms of race and optimal drug dosing for paediatric patients have not been published (23, 26).

The penetration of ceftobiprole into respiratory tissues is of great importance, as the antibiotic is being studied as a therapeutic option for pneumonia (1). The percentage of drug penetration into epithelial lining fluid (ELF) has also been studied in a murine model, with results showing an overall target attainment of 85.6% for 1-$\log_{10}$ CFU/g kill in *Streptococcus pneumoniae* (44).

The efficacy of ceftobiprole for the treatment of infections other than cSSSIs is also being explored. The superiority of ceftobiprole as compared to cefipime for the treatment of experimental meningitis has been reported (45).

5. Dosage and administration

Based on pharmacokinetic, pharmacodynamic and clinical data published, ceftobiprole dosing is likely to be based on the indication and the intended bacterial coverage. For cSSSI's caused by culture-proven or presumed Gram positive infection, the dose of ceftobiprole is expected to be 500 mg every 12 hours infused over 1 hour (29,30). For cSSSIs (including diabetic foot infections) caused by culture-proven or presumed Gram negative or mixed infections, the predicted dosing for ceftobiprole is expected to be 500 mg every 8 hours, infused over 2 hours (31-33).

Dose adjustment is required in patients with renal insufficiency. Preliminary data suggest that for patients with mild renal impairment (creatinine clearance (CrCl) of 50-80 ml/min), no dosage adjustment is necessary (23,27). In patients with moderate renal impairment (CrCl 30-50 ml/min), the predicted dosing of ceftobiprole would be 500 mg every 12 hours. For severe renal impairment (CrCl <30ml/min), the predicted dose of ceftobiprole would be 250 mg every 12 hours.

Pharmacokinetic data for ceftobiprole in patients receiving haemodialysis, peritoneal dialysis or continuous renal replacement therapy have not been published. However, it is unlikely that dosage adjustment would be necessary for patients of hepatic dysfunction (2).

6. Drug interactions

The potential for clinically significant drug interactions with ceftobiprole is considered low because of its favourable pharmacokinetic profile (1,2). Like all antimicrobials, ceftobiprole has the potential to decrease the effectiveness of oral contraceptive pills. Some of the clinically important medications found to be incompatible with ceftobiprole include aminoglycosides, amiodarone, calcium gluconate, diltiazem, dopamine, dobutamine, fluoroquinolones, hydromorphone, labetalol, magnesium sulphate, human regular insulin, midazolam, morphine sulphate and potassium phosphate. The timing and availability of i.v. lines are expected to be a concern for patients receiving ceftobiprole with incompatible medications (2).

7. Adverse events

Clinical studies have demonstrated that ceftobiprole is generally well-tolerated with few adverse events. The most frequent drug-related adverse event was a transient caramel-like taste disturbance during infusion, probably caused by the conversion of the prodrug to the active antibiotic, and the subsequent release of diacetyl, a substance known to have a caramel-buttery taste (24,25).

The reported adverse events in various studies were predominantly gastrointestinal events including nausea, taste disturbance and vomiting. Most of these events were mild to moderate, and did not require treatment discontinuation (24-30). [Table adapted from (1) and (2)]

8. Clinical trials

The clinical effectiveness of ceftobiprole in its primary indication has been demonstrated in the pivotal STRAUSS 1 and 2 international trials. These trials involved >1500 patients with skin and soft tissue infections, and have shown cure rates similar to those of the comparators (vancomycin or vancomycin plus ceftazidime). The STRAUSS 1 trial was a randomized, double-blind clinical trial involving patients with cSSSIs

Table 2. Overall incidence of adverse events related to Ceftobiprole

Adverse Event	Ceftobiprole (n= 932)	Comparator Drug* (n= 661)
	No. (%)	No. (%)
Nausea	113 (12)	49 (7)
Vomiting	61 (7)	27 (4)
Diarrhea	62 (7)	32 (5)
Constipation	33 (4)	25 (4)
Dysgeusia	30 (3)	2 (1)
Headache	68 (7)	39 (6)
Dizziness	14 (4)	8 (2)
Insomnia	26 (5)	13 (5)
Local reaction	48 (9)	26 (9)
Rash and pruritus	49 (5)	62 (9)
Discontinued therapy because of adverse drug events	39 (4)	32 (5)

*Comparator regimen: vancomycin (STRAUSS 1); vancomycin plus ceftazidime (STRAUSS 2).

in whom Gram positive organisms were documented and/or suspected based on microscopic examination (2, 30). Patients were classified according to the type of infection and were randomly assigned in a 1:1 ratio to receive either IV ceftobiprole 500mg every 12 hours as a 60 minute infusion (n=282) or IV vancomycin 100mg every 12 hours as a 60 minute infusion (n=277) for 7 to 14 days. The predominant pathogen was *S.aureus* (37% of which were MRSA). Cure rates in the ceftobiprole-treated (n=61) and vancomycin-treated (n=60) subjects were 91.8% and 90.0% respectively. The outcome was assessed in the clinically evaluable and intent to treat (ITT) populations. Clinical cure rates in the ceftobiprole and vancomycin groups were similar in the ITT group (77.8% vs. 77.5%) and in the clinically evaluable group (93.3% vs. 93.5%). Serious treatment-related adverse events were 1% in the ceftobiprole-treated group and 3% in the vancomycin-treated group (19).

A second ceftobiprole phase III cSSSI double-blind study (STRAUSS 2) enrolled 828 patients who were either treated with ceftobiprole medocaril or the combination of ceftazidime and vancomycin (31). This study group also included patients with diabetic foot infections. Patients were randomized 2:1 to receive either IV ceftobiprole (500 mg infused over 120 minutes every 8 hours) plus placebo (n=547), or IV vancomycin (1000 mg infused over 60 minutes every 12 hours) plus IV ceftazidime (1000 mg infused over 120 minutes every 8 hours) (n=281). A total of 91% of the patients were treated with ceftobiprole medocaril, as compared to 90% of patients treated with combination therapy. The clinical response in those with diabetic foot infections was 86% and 82% for ceftobiprole medocaril and combination therapy respectively (19). The clinical cure rates in the clinically evaluable and ITT populations were comparable in both groups, but patients receiving ceftobiprole required a shorter duration of therapy compared with those receiving vancomycin plus ceftazidime (8.7 days vs 9.5 days; $p<0.05$) (1).

In a trial for hospital-acquired pneumonia, investigators noted that non-inferiority could not be established in the subgroup of patients with ventilator-associated pneumonia, because clinical cure rates were significantly lower in the ceftobiprole group of patients than in the comparator group (2).

A phase III clinical trial for nosocomial pneumonia (CHOPIN) has also been completed but results have not been published (1,19). A trial for community-acquired pneumonia is ongoing (19).

9. Conclusions

With antimicrobial resistance on the rise, and the pipeline of agents active against Gram negative pathogens relatively non-existent, hospitals and clinics are constantly being challenged to develop new strategies to treat complicated infections while preserving antimicrobials for the future. MRSA has assumed increasing importance in both community- and

hospital-acquired infections. A broad-spectrum agent with bactericidal activity against MRSA is an attractive treatment option.

Ceftobiprole medocaril is a broad-spectrum cephalosporin with in vitro activity against MRSA, that has demonstrated favourable results in clinical trials. It exhibits *in vitro* activity against a number of bacteria that cause community- and hospital-acquired infection. The activity is comparable to that of available third and fourth generation cephalosporins. Ceftobiprole also appears to be relatively refractory to the development of endogenous resistance.

Although ceftobiprole provides us with another option in our antimicrobial armamentarium, judicious use of this agent will be imperative. The unique spectrum of this agent may allow it to be categorised as a new class of cephalosporins; it may be considered to be a member of the fifth-generation cephalosporins.

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