Ceftobiprole: in-vivo profile of a bactericidal cephalosporin

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ABSTRACT

Resistance to antimicrobials is a significant and growing problem, limiting treatment options, especially for serious Gram-positive infections. Ceftobiprole is a novel broad-spectrum cephalosporin that is active *in vitro* against streptococci and staphylococci, including penicillin-resistant strains of pneumococci and methicillin-resistant *Staphylococcus aureus* (MRSA). It maintains the activity of extended-spectrum cephalosporins against Gram-negative bacteria, including Enterobacteriaceae. The in-vivo activity of ceftobiprole has been demonstrated in mouse sepsis and subcutaneous abscess models of infection. Its activity also has been examined in several discriminative models of infection that mimic specific diseases in humans and permit testing of antimicrobial activity under a variety of defined pharmacokinetic conditions. These include experimental pneumonia in mice, a tissue cage model of foreign body infection in rats, and endocarditis models in rats and rabbits. In these models, ceftobiprole exhibits activity equivalent or superior to that of comparators against MRSA, including vancomycin-intermediate strains. These models also confirm the in-vivo activity of ceftobiprole against Gram-negative bacteria that are susceptible *in vitro*. The results from animal models support the evaluation of the clinical efficacy of ceftobiprole in humans and also predict clinical efficacy in the empirical treatment of severe infections. The broad spectrum of activity may allow ceftobiprole to be used as monotherapy for serious hospital-acquired infections where combination therapy would otherwise be required.

Keywords Antimicrobial resistance, ceftobiprole, *in vivo*, MRSA

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INTRODUCTION

Since the mid-1970s, resistance to antimicrobials has become a significant and escalating problem, limiting treatment options for serious Gram-positive infections in particular. The emphasis placed on controlling Gram-negative infections over recent decades may have unintentionally contributed to the emergence of Gram-positive bacteria as clinically significant nosocomial pathogens. Thus, hospitals increasingly have to deal with infections caused by multidrug-resistant organisms, particularly methicillin-resistant staphylococci, penicillin- and erythromycin-resistant pneumococci, and vancomycin-resistant enterococci [1,2]. Data from the US National Nosocomial Infections Surveillance System indicate that the percentage of *Staphylococcus aureus* isolates in hospitals that are resistant to methicillin, oxacillin or nafcillin (collectively referred to as MRSA) increased from 2% in 1975 to 29% in 1991 and further to 46% by 2004 [3,4]. In 2004, 60% of *Staph. aureus* isolates from intensive care unit patients were resistant to these agents, an increase of 11% compared with the period from 1998 to 2002 [3]. If this trend continues, nosocomial MRSA rates in the USA could exceed 70% by the end of the decade. Although MRSA rates vary between countries, similar increases are evident worldwide and, furthermore, most strains are also resistant to other classes of antibiotic [5–7]. The use of vancomycin, previously an effective antibiotic against MRSA, has led to the development of isolates with reduced susceptibility [8,9]. Cases of vancomycin-resistant *Staph. aureus* infections have been reported in the medical literature and are of particular concern [8,9]. Against such a background, there is a need for new antimicrobial agents that are

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effective against not only MRSA but also other antibiotic-resistant organisms.

Several new agents with Gram-positive activity, such as dalbavancin, daptomycin, linezolid, quinupristin–dalfopristin, and tigecycline, have or soon will reach the clinic [2]. Some, such as tigecycline and linezolid, however, are bacteriostatic rather than bactericidal [2,10,11]. Bactericidal activity is important for therapeutic efficacy in certain infections, such as endocarditis, meningitis, and infections in neutropenic patients [12], and bactericidal agents are often preferred in the treatment of serious infections in hospitalised patients [2]. Furthermore, none of the new agents listed above, apart from tigecycline, has a broad spectrum of activity including both Gram-positive and Gram-negative pathogens, frequently restricting their use to combination therapy [13,14].

Ceftobiprole is a novel broad-spectrum, β-lactamase-stable parenteral cephalosporin with a strong affinity for the penicillin-binding proteins PBP2a and PBP2x responsible for resistance in staphylococci and pneumococci, respectively. Ceftobiprole also can bind to relevant penicillin-binding proteins of resistant Gram-positive and Gram-negative bacteria and has a low ability to select for resistance [15,16]. On the basis of antimicrobial activity shown in animal models of infection, ceftobiprole is undergoing further clinical development.

ANIMAL MODELS OF INFECTION IN THE EVALUATION OF CEFTOBIPROLE

Several animal models have been used in the evaluation of ceftobiprole, including mouse sepsis, abscess and pneumonia models, rat endocarditis and tissue cage models, and a rabbit endocarditis model (Table 1).

Table 1. Animal models of infection in the evaluation of ceftobiprole

Animal	Model	Infective agent
Mouse	Sepsis	Gram-positive and Gram-negative
Mouse	Abscess	MRSA, VISA
Mouse	Pneumonia	*Haemophilus influenzae*, *Enterobacter cloacae*, *Klebsiella pneumoniae*
Rat	Endocarditis	MRSA
Rat	Tissue cage	MRSA
Rabbit	Endocarditis	MRSA, VISA

MRSA, methicillin-resistant *Staphylococcus aureus*; VISA, vancomycin-intermediate *Staph. aureus*.

Screening models

The activity of ceftobiprole against a range of Gram-positive and Gram-negative organisms has been investigated in a mouse experimental septicaemia model, using comparators such as ceftriaxone, vancomycin, and benzylpenicillin [15]. In this model, MIC values measured *in vitro* correlated well with in-vivo efficacy, as assessed by the 50% effective dose (ED_{50}) (the dose required for survival of 50% of the animals on the fourth day after infection). Ceftobiprole showed high in-vivo activity in infections caused by strains with MIC values ≤2 mg/L (Table 2). These included methicillin-susceptible *Staph. aureus*, MRSA, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii*, *Serratia marcescens*, and *Proteus mirabilis*. Ceftobiprole was superior to ceftriaxone and vancomycin against methicillin-susceptible *Staph. aureus*, with an ED_{50} below 0.2 mg/kg. The MIC_{90} obtained for ceftobiprole against 77 isolates of MRSA was ≤4 mg/L, as compared to >64, >32, >32, >8 and >2 mg/L, respectively, for cefotaxime, cefepime, meropenem, ciprofloxacin, and vancomycin.

Ceftobiprole exhibited good in-vivo activity against group A streptococci and penicillin-

Table 2. Activity of ceftobiprole and comparators in experimental mouse sepsis

Organism	Agent	MIC (mg/L)	ED_{50} (mg/kg)
Gram-positives			
MSSA	Ceftobiprole	0.25	< 0.2
	Ceftriaxone	4	0.89
	Vancomycin	1	0.73
MRSA	Ceftobiprole	2	2.4
	Vancomycin	2	6.7
GAS	Ceftobiprole	≤ 0.06	< 0.2
	Ceftriaxone	≤ 0.06	< 0.2
PSSP	Ceftobiprole	≤ 0.06	< 0.2
	Benzylpenicillin	≤ 0.06	< 0.4
PRSP[a]	Ceftobiprole	1	1.0
	Ceftriaxone	4	8.8
Gram-negatives			
Escherichia coli	Ceftobiprole	≤ 0.06	< 0.2
	Ceftriaxone	≤ 0.06	< 0.2
Enterobacter cloacae	Ceftobiprole	4	3.8
	Cefepime	2	1.1
	Meropenem	≤ 0.06	0.22
Serratia marcescens	Ceftobiprole	0.25	0.68
	Meropenem	≤ 0.06	0.45
Proteus vulgaris	Ceftobiprole	> 32	> 12
	Meropenem	≤ 0.06	< 0.4
Pseudomonas aeruginosa	Ceftobiprole	8	4.0
	Cefepime	4	1.0
	Meropenem	2	< 0.4

Adapted from Hebeisen *et al.* [15] with permission.
[a]Strain 23 F-CTR.
ED_{50}, dose at which 50% of animals survived, assessed on the fourth day after infection; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staph. aureus*; GAS, group A streptococci (*Streptococcus pyogenes*); PSSP, penicillin-susceptible *Streptococcus pneumoniae*; PRSP, penicillin-resistant *Strep. pneumoniae*.