POSTER E-0115
ICAAC 2006

In-vitro Activity of Ceftobiprole Tested Against a Recent Collection of North American *Pseudomonas aeruginosa*

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Updated Abstract

Background: Ceftobiprole (BAL9141; BPR) is an investigational cephalosporin with a broad spectrum of activity including methicillin-resistant *S. aureus.* PK/PD characteristics of the parenteral prodrug formulation are consistent with usable potencies against streptococci, *E. faecalis, H. influenzae,* and Enterobacteriaceae, in addition to staphylococci. We present global surveillance program results assessing the potency of BPR against *P. aeruginosa* (PSA).

Methods: Nonduplicate clinically-significant isolates of PSA (221 and 742) were collected from 24 medical centers in North America (NA) and worldwide (WW; 54 sites), respectively, participating in a BPR surveillance program. Identifications were confirmed by the central monitoring laboratory and all isolates were susceptibility (S) tested using CLSI methods against BPR and comparators including cefepime (FEP) and ceftazidime (CAZ).

Results[a]: BPR, FEP, and CAZ results are in the Table:

		MIC (µg/ml)		Cum. % inhibited at MIC (µg/ml)			
P. aeruginosa (741 strains)		50%	90%	≤1	2	4	8
Ceftobiprole	NA	2	>8	46	60	72	86
	WW	2	>8	40	56	68	81
Cefepime	NA	2	16	21	52	68	80
	WW	4	>16	20	48	66	78
Ceftazidime	NA	2	>16	13	59	74	79
	WW	2	>16	14	56	70	76

BPR was as active as CAZ and FEP (MIC_{50}, 2 µg/ml) against PSA. At established CLSI breakpoints for FEP and CAZ, 78-80% and 76-79% of isolates were S; at the same concentration of BPR, 81-86% of isolates were inhibited. Among other comparators, polymyxin B provided the greatest coverage (99.9% S), followed by amikacin (87.9%), piperacillin-tazobactam (84.1%), and meropenem (82.1%) for all (WW) isolates.

Conclusions: Ceftobiprole has been characterized as an anti-MRSA cephalosporin. In this study, ceftobiprole demonstrated anti-pseudomonal activity with a potency comparable to that of cefepime and ceftazidime. These characteristics warrant further evaluation of ceftobiprole as empiric therapy for hospital-acquired pneumonia, including locations where PSA may be prevalent.

[a]Updated to include additional strains.

Introduction

Ceftobiprole (previously known as BAL9141), is an investigational broad-spectrum cephalosporin with potent activity against both Gram-negative and Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) (3, 7-9). The agent is stable to many β-lactamases and has a strong affinity for penicillin binding proteins (PBPs), including PBP2a, which mediates resistance to β-lactams in methicillin (oxacillin)-resistant *S. aureus* and coagulase-negative staphylococci (9); PBP2x, which mediates penicillin resistance in pneumococci (6); and PBPs 2 and 3 in *Escherichia coli* and *Pseudomonas aeruginosa* (Davies, ICAAC 2006). Ceftobiprole is known to be active against most Enterobacteriaceae, similar to that of advanced generation cephalosporins (7, 9, 10).

Because of this unique spectrum, its safety profile characteristic of most β-lactams, and the predominantly bactericidal activities (2, 7, 8), ceftobiprole is an attractive therapeutic candidate with phase 3 clinical trials currently ongoing for the treatment of complicated skin and skin structure infections and pneumonia.

Despite the positive characteristics of this agent, few details have been published on its activity against *P. aeruginosa*, a critical opportunistic pathogen frequently found in the hospital environment. The objective of the current study was to examine susceptibility profiles of ceftobiprole and comparator agents tested against contemporary (2005) clinical isolates of *P. aeruginosa* collected as part of a longitudinal international surveillance protocol. A total of 742 strains were tested by reference methods of the Clinical and Laboratory Standards Institute (CLSI) with susceptibilities interpreted by current CLSI criteria.

Materials and Methods

Organism Collection

- A total of 742 nonduplicate *P. aeruginosa* strains were collected from significant infections in patients hospitalized in North America (24 sites, 221 strains), and other sites worldwide (Europe, 24 sites, 365 strains; South America, 10 sites, 156 strains).
- Organisms were identified locally and forwarded to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) where the identification was confirmed and susceptibility testing performed.

Susceptibility Test Methods

- Ceftobiprole and comparator agents were tested in validated microdilution trays in cation-adjusted Mueller-Hinton broth using the CLSI methods (M7-A7, 2006) (4).
- Quality control strains utilized included *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853; all MIC results were within CLSI-specified ranges (1, 5).
- Categorical interpretations were by CLSI M100-S16 breakpoint criteria (5).
- The results were analyzed by geographic region due to well-recognized differences known to occur in *P. aeruginosa* resistance rates.

Table 1. *In-vitro* activity of ceftobiprole in comparison to selected antimicrobial agents tested against 221 isolates of *P. aeruginosa* (North America)

Antimicrobial agent	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	Range (µg/ml)	% Susceptible/resistant[a]
Ceftobiprole	2	>8	≤0.06 – >8	- / -
Ceftazidime	2	>16	≤1 – >16	78.7 / 15.8
Cefepime	2	16	≤0.12 – >16	80.1 / 9.0
Meropenem	0.5	8	≤0.06 – >8	86.9 / 5.9
Imipenem	1	8	≤0.12 – >8	83.3 / 5.9
Ertapenem	4	>8	≤0.06 – >8	- / -
Piperacillin-tazobactam	4	>64	≤0.5 – >64	84.2 / 15.8
Ticarcillin-clavulanic acid	32	>128	≤16 – >128	75.1 / 24.9
Aztreonam	4	>16	≤0.12 – >16	67.9 / 17.2
Levofloxacin	≤0.5	>4	≤0.5 – >4	68.8 / 24.9
Tobramycin	0.5	16	≤0.25 – >16	88.7 / 10.4
Amikacin	2	8	≤0.25 – >32	95.5 / 3.6
Polymyxin B	≤0.5	1	≤0.5 – 2	100.0 / 0.0

[a]Criteria as published by the CLSI [2006], where available. No breakpoints have been assigned to ceftobiprole or ertapenem.

Table 2. *In-vitro* activity of ceftobiprole in comparison to selected antimicrobial agents tested against 742 isolates of *P. aeruginosa* (all regions)

Antimicrobial agent	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	Range (µg/ml)	% Susceptible/resistant[a]
Ceftobiprole	2	>8	≤0.06 – >8	- / -
Ceftazidime	2	>16	≤1 – >16	75.9 / 19.0
Cefepime	4	>16	≤0.12 – >16	78.2 / 11.5
Meropenem	0.5	>8	≤0.06 – >8	82.1 / 11.2
Imipenem	1	>8	≤0.12 – >8	77.2 / 11.6
Ertapenem	8	>8	≤0.06 – >8	- / -
Piperacillin-tazobactam	8	>64	≤0.5 – >64	84.1 / 15.9
Ticarcillin-clavulanic acid	32	>128	≤16 – >128	72.6 / 27.4
Aztreonam	4	>16	≤0.12 – >16	69.3 / 16.8
Levofloxacin	≤0.5	>4	≤0.5 – >4	68.5 / 27.6
Tobramycin	0.5	>16	≤0.25 – >16	78.2 / 20.8
Amikacin	≤4	32	≤4 – >32	87.9 / 9.4
Polymyxin B	≤0.5	1	≤0.5 – >4	99.9 / 0.1

[a]Criteria as published by the CLSI [2006], where available. No breakpoints have been assigned to ceftobiprole or ertapenem.

Table 3. Comparisons of 3 cephalosporins tested against *P. aeruginosa* comparing isolates recovered from patients in North America (221 isolates) with those from all geographic regions (North America, Europe, Latin America; 742 isolates)

	MIC (µg/ml)			Cumulative % Inhibited at MIC (µg/ml)			
P. aeruginosa	50%	90%	Range	≤1	2	4	8
Ceftobiprole							
North America	2	>8	≤0.06 – >8	46	60	72	86
All Regions	2	>8	≤0.06 – >8	40	56	68	81
Cefepime							
North America	2	16	≤0.12 – >16	21	52	68	80
All Regions	4	>16	≤0.12 – >16	20	48	66	78
Ceftazidime							
North America	2	>16	≤1 – >16	13	59	74	79
All Regions	2	>16	≤1 – >16	14	56	70	76

[a]CLSI breakpoints for susceptibility of the comparison cephalosporins are ≤8 µg/ml.

Results

- *P. aeruginosa* isolates recovered from patients in North America generally displayed less antibiotic resistance than did isolates from the all-isolate worldwide collection (examples: tobramycin, 3.6 and 20.8% resistance, respectively; imipenem, 5.9 and 11.6%; **Tables 1** and **2**).
- Ceftobiprole was as active as ceftazidime and cefepime (MIC_{50}, 2 µg/ml) against *P. aeruginosa* from North American patients; in the worldwide collection, cefepime was generally 2-fold less active than the other 2 agents (**Table 3**).
- At established CLSI breakpoints for cefepime and ceftazidime (8 µg/ml), 78 to 80% and 76 to 78% of isolates were susceptible; at the same concentration of ceftobiprole, 81 to 86% of isolates were inhibited (**Table 3**).
- Among other comparators, polymyxin B provided the highest rate of susceptibility (99.9%), followed by amikacin (87.9%), piperacillin-tazobactam (84.1%), and meropenem (82.1%) for the worldwide collection (**Table 2**).

Conclusions

- **Ceftobiprole has been characterized as a broad-spectrum anti-MRSA cephalosporin. In this study, the anti-pseudomonal activity of ceftobiprole was confirmed, with potency comparable to that of the extended-spectrum cephalosporins ceftazidime and cefepime.**
- **Among all tested agents, polymyxin B and amikacin provided the best overall anti-pseudomonal activity.**
- **These characteristics warrant further evaluation of ceftobiprole as empiric therapy for hospital-acquired pneumonia, including locations where *P. aeruginosa* may be prevalent.**

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Acknowledgment

This study was supported by Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, New Jersey, USA.