POSTER 216
IDSA 2010

Worldwide Summary of Ceftobiprole Activity Against 108,577 Gram-positive Pathogens

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Abstract

Background: The broad-spectrum cephalosporin ceftobiprole (BPR) was tested against prevalent Gram-positive pathogens isolated worldwide during 2005-2009. BPR is an investigational drug under development for the treatment of complicated skin and skin structure infections (cSSSI) including infections by methicillin-resistant (MR) staphylococci.

Methods: During 2005-2009, a total of 108,577 consecutive, non-duplicate isolates from a variety of infections were collected from the following regions (n countries; n isolates): Asia Pacific (12; 18,964), Europe (14; 30,792), Latin America (4; 11,797), and North America (2; 47,024). Susceptibility (S) testing was performed by CLSI methods (M07-A8 and M100-S20-U).

Results: BPR had high activity against methicillin-susceptible (MS) *S.aureus* (SA), MS-coagulase-negative staphylococci (CoNS), beta-haemolytic streptococci, viridans streptococci, and *S. pneumoniae* with MIC_{90} values of 0.5, 0.25, ≤0.06, 0.25, and 0.5 µg/ml, respectively. BPR was active against MRSA and MR-CoNS both with a MIC_{90} of 2 µg/ml and >98% of isolates inhibited by ≤2 and ≤4 µg/ml, respectively. MRSA $MIC_{50/90}$ of 1/2 µg/ml was identical for each year of the 5 year study. BPR was not active against the vast majority of *E. faecium*, but was potent against *E. faecalis* ($MIC_{50/90}$, 0.5/2 µg/ml).

Conclusions: BPR exhibited excellent potency against most Gram-positive pathogens including MRSA and MR-CoNS in this very large selection of geographically and temporally diverse collection of isolates. Importantly, the BPR SA MIC distribution remained geographically and temporally stable over this half-decade.

Introduction

Ceftobiprole is a broad-spectrum cephalosporin with potent activity against commonly occurring Gram-positive and –negative bacterial pathogens including some resistant strains. The compound is stable to many commonly occurring β-lactamases, and has a strong affinity for penicillin-binding proteins (PBPs), including PBP2' (PBP2a), which mediates resistance to β-lactams in methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci (MR-CoNS). Ceftobiprole is also known to display *in vitro* activity against most Enterobacteriaceae and *Pseudomonas aeruginosa*, similar to that of other advanced generation cephems and β-lactam/β-lactamase inhibitor combinations.

Following encouraging results from preclinical and early phase clinical studies, ceftobiprole is in Phase III clinical development for the treatment of complicated skin and skin structure infections (cSSSI) and hospital-acquired bacterial pneumonia (HABP).

In this study, we report *in vitro* testing results from a very large collection of Gram-positive pathogens isolated worldwide during 2005-2009 comparing ceftobiprole activity with that of other β-lactam agents and members of several antimicrobial classes used in the empiric or directed therapy of cSSSI and HABP.

Methods

Bacterial Strain Collection. During 2005-2009, a total of 108,577 consecutive, non-duplicate Gram-negative pathogens from a variety of infections (including cSSSI and HABP) were collected from 216 medical centers (32 countries) in four geographic regions representing five continents (Table 1). Species identifications were performed by the submitting laboratories with confirmation performed by the central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA).

Susceptibility Test Methods. All isolates were tested for susceptibility by reference broth microdilution methods using the Clinical Laboratory Standards Institute recommendations (CLSI; M07-A8, 2009). Susceptibility testing was performed by using validated broth microdilution panels manufactured by TREK Diagnostics Systems/Sensititre (Cleveland, Ohio, USA). Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S20-U, 2010) quality control (QC) strains, including *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619. Categorical interpretation of comparator MIC values was performed according to CLSI (M100-S20-U, 2010) criteria, when available.

Results

- Against 53,375 *S. aureus* isolates, ceftobiprole was very active against 29,872 oxacillin-susceptible isolates (MSSA; $MIC_{50/90}$, 0.25/0.5 µg/ml) and was only four-fold less active against 23,502 oxacillin-resistant isolates (MRSA; $MIC_{50/90}$, 1/2 µg/ml; Tables 2 and 3). All *S. aureus* isolates were inihibited at a MIC of ≤4 µg/ml (Table 2). Similar results were observed for coagulase-negative staphylococci (CoNS; Table 2 and 3).
- Against MSSA, ceftobiprole (MIC_{50}, 0.25 µg/ml) was eight- and sixteen-fold more active than cefepime (MIC_{50}, 2 µg/ml) and ceftriaxone (MIC_{50}, 4 µg/ml), respectively.
- Against MRSA, the $MIC_{50/90}$ of 1/2 µg/ml was identical for each year of the 5 year study. Against MSSA, the MIC_{50} was 0.25 µg/ml in 2005 to 2007 and 0.5 µg/ml in 2008 to 2009; the MIC_{90} of 0.5 µg/ml was identical for each year of the study.
- Ceftobiprole demonstrated very good activity against *E. faecalis* ($MIC_{50/90}$, 0.5/2 µg/ml; Tables 2 and 3) but was not active against most *E. faecium* (MIC_{50}, >8 µg/ml; Tables 2 and 3).
- Ceftobiprole exhibited excellent activity against 7,163 β-haemolytic streptococci ($MIC_{50/90}$, both ≤0.06 µg/ml; Tables 2 and 3) and very good potency against 2,966 viridans group streptococci (VGS; $MIC_{50/90}$, ≤0.06/0.25 µg/ml; Tables 2 and 3). Using the MIC_{90}, ceftobiprole was eight-fold more potent than penicillin and two-fold more potent than cefepime and ceftriaxone against VGS.
- Ceftobiprole exhibited high activity against 13,412 *S. pneumoniae* ($MIC_{50/90}$, ≤0.06/0.5 µg/ml; Tables 2 and 3). Overall, 62.9 and 89.3% of isolates were susceptible to penicillin at the CLSI oral (≤0.06 µg/ml) and parenteral (≤2 µg/ml) breakpoints, respectively.

Table 1. Distribution of 108,577 Gram-positive isolates and medical centers by geographic region

Region and country	Number of medical centers	Number of isolates	Region and country	Number of medical centers	Number of isolates
Asia Western Pacific (12 countries)	89	18964	Europe (14 countries)	30	30792
Latin America (4 countries)	10	11797	North America (2 countries)	87	47024

Table 2. Cumulative percent inhibited distribution of ceftobiprole MIC values for 108,577 Gram-positive pathogens (2005-2009)

	Cumulative % inhibited at ceftobiprole MIC (µg/ml):							
Organism (no. of strains)	≤0.06	0.12	0.25	0.5	1	2	4	8
S. aureus (53,375)	1	1	31	62	87	99.3	100	-
MRSA (23,502)	1	1	1	15	70	98	100	-
MSSA (29,872)	1	2	55	99.6	>99.9	100	-	-
CoNS (13,486)	4	15	28	52	82	94	99.9	100.0
MR-CoNS (10,276)	1	2	6	37	78	92	99.9	100.0
MS-CoNS (3,210)	16	60	97	99.7	>99.9	100	-	-
Enterococci (18,175)	1	8	21	47	55	62	67	68
E. faecalis (11,426)	1	12	33	71	83	92	97	98
E. faecium (6,035)	-	1	1	1	2	5	8	8
β-haemolytic strep. (7,163)	99	99.9	100	-	-	-	-	-
Viridans strep. (2,966)	75	87	93	95	97	99	99.1	99.3
S. pneumoniae (13,412)	72	75	85	98	99.7	99.9	>99.9	100.0

Table 3. Antimicrobial activity of ceftobiprole and comparator agents when tested against 108,577 Gram-positive pathogens

Organism (no. tested)/ Antimicrobial agent	MIC in µg/ml			CLSI[b] %S / %R	EUCAST[b] %S / %R
	MIC_{50}	MIC_{90}	Range		
S. aureus (53,375)					
Ceftobiprole	0.5	2	≤0.06 – 4	-[b] / -	- / -
Oxacillin	0.5	>2	≤0.25 – >2	56.0 / 44.0	56.0 / 44.0
Cefepime	4	>16	≤0.12 – >16	56.0 / 44.0	56.0 / 44.0
Ceftriaxone	4	>32	≤0.25 – >32	56.0 / 44.0	56.0 / 44.0
Daptomycin	0.25	0.5	≤0.06 – 4	99.9 / -	99.9 / 0.1
Imipenem	≤0.12	>8	≤0.12 – >8	56.0 / 44.0	56.0 / 44.0
Levofloxacin	≤0.5	>4	≤0.5 – >4	61.1 / 38.2	61.1 / 38.2
Linezolid	2	2	≤0.06 – >8	>99.9 / <0.1	>99.9 / <0.1
Tetracycline	≤2	>8	≤2 – >8	87.6 / 11.9	87.1 / 12.9
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	95.4 / 4.6	95.4 / 4.6
Vancomycin	1	1	≤0.12 – 4	>99.9 / 0.0	>99.9 / <0.1
Oxacillin-susceptible (29,872)					
Ceftobiprole	0.25	0.5	≤0.06 – 2	- / -	- / -
Cefepime	2	4	≤0.12 – 16	>99.9 / 0.0	100.0 / 0.0
Ceftriaxone	4	4	≤0.25 – 32	99.8 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 4	>99.9 / -	>99.9 / <0.1
Imipenem	≤0.12	≤0.12	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	92.4 / 7.1	92.4 / 7.1
Linezolid	2	2	≤0.06 – 4	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	≤2	≤2 – >8	93.5 / 5.9	93.2 / 6.8
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.5 / 1.5	98.5 / 1.5
Vancomycin	1	1	≤0.12 – 4	>99.9 / 0.0	>99.9 / <0.1
Oxacillin-resistant (23,502)					
Ceftobiprole	1	2	≤0.06 – 4	- / -	- / -
Daptomycin	0.25	0.5	≤0.06 – 4	99.9 / -	99.9 / 0.1
Levofloxacin	>4	>4	≤0.5 – >4	21.3 / 77.7	21.3 / 77.7
Linezolid	1	2	0.12 – >8	99.9 / 0.1	99.9 / 0.1
Tetracycline	≤2	>8	≤2 – >8	80.1 / 19.4	79.4 / 20.6
Trimethoprim/sulfamethoxazole	≤0.5	1	≤0.5 – >2	91.5 / 8.5	91.5 / 8.5
Vancomycin	1	1	≤0.12 – 4	>99.9 / 0.0	>99.9 / <0.1
Coagulase-negative staphylococci (13,486)					
Ceftobiprole	0.5	2	≤0.06 – 8	- / -	- / -
Oxacillin	>2	>2	≤0.25 – >2	23.8 / 76.2	23.8 / 76.2
Cefepime	4	>16	≤0.12 – >16	23.8 / 76.2	23.8 / 76.2
Ceftriaxone	16	>32	≤0.25 – >32	23.8 / 76.2	23.8 / 76.2
Daptomycin	0.25	0.5	≤0.06 – 4	99.8 / -	99.8 / 0.2
Imipenem	0.25	>8	≤0.12 – >8	23.8 / 76.2	23.8 / 76.2
Levofloxacin	4	>4	≤0.5 – >4	43.3 / 53.0	43.3 / 53.0
Linezolid	1	1	≤0.06 – >8	99.4 / 0.6	99.4 / 0.6
Tetracycline	≤2	>8	≤2 – >8	85.0 / 14.1	82.6 / 17.4
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	61.2 / 38.8	61.2 / 38.8
Vancomycin	1	2	≤0.12 – 8	>99.9 / 0.0	99.4 / 0.6
Oxacillin-susceptible (3,210)					
Ceftobiprole	0.12	0.25	≤0.06 – 2	- / -	- / -
Cefepime	0.5	2	≤0.12 – 16	>99.9 / 0.0	100.0 / 0.0
Ceftriaxone	2	4	≤0.25 – 32	99.1 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 4	99.7 / -	99.7 / 0.3
Imipenem	≤0.12	≤0.12	≤0.12 – 1	100.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.5	4	≤0.5 – >4	86.4 / 12.5	86.4 / 12.5
Linezolid	1	1	≤0.06 – >8	99.8 / 0.2	99.8 / 0.2
Tetracycline	≤2	>8	≤2 – >8	89.1 / 10.1	87.9 / 12.1
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	88.2 / 11.8	88.2 / 11.8
Vancomycin	1	2	≤0.12 – 4	100.0 / 0.0	99.7 / 0.3
Oxacillin-resistant (10,276)					
Ceftobiprole	1	2	≤0.06 – 8	- / -	- / -
Daptomycin	0.25	0.5	≤0.06 – 4	99.8 / -	99.8 / 0.2
Levofloxacin	4	>4	≤0.5 – >4	29.9 / 65.6	29.9 / 65.6
Linezolid	1	1	≤0.06 – >8	99.2 / 0.8	99.2 / 0.8
Tetracycline	≤2	>8	≤2 – >8	83.7 / 15.4	81.0 / 19.0
Trimethoprim/sulfamethoxazole	2	>2	≤0.5 – >2	52.7 / 47.3	52.7 / 47.3
Vancomycin	1	2	≤0.12 – 8	>99.9 / 0.0	99.3 / 0.7
Enterococci (18,175)					
Ceftobiprole	1	>8	≤0.06 – >8	- / -	- / -
Ampicillin	≤1	>16	≤1 – >16	68.6 / 31.4	67.6 / 31.4
Daptomycin	1	2	≤0.06 – >8	99.9 / -	- / -
Levofloxacin	>4	>4	≤0.5 – >4	47.9 / 50.2	- / -
Linezolid	1	2	≤0.06 – >8	99.4 / 0.4	99.6 / 0.4
Quinupristin/dalfopristin	>2	>2	≤0.25 – >2	27.5 / 65.2	27.5 / 65.2
Teicoplanin	≤2	>16	≤2 – >16	84.7 / 14.2	84.2 / 15.8
Vancomycin	1	>16	≤0.12 – >16	82.7 / 16.6	82.7 / 17.3
Enterococcus faecalis (11,426)					
Ceftobiprole	0.5	2	≤0.06 – >8	- / -	- / -
Ampicillin	≤1	2	≤1 – >16	99.7 / 0.3	98.7 / 0.3
Daptomycin	1	2	≤0.06 – 8	>99.9 / -	- / -
Levofloxacin	1	>4	≤0.5 – >4	66.1 / 33.3	- / -
Linezolid	1	2	≤0.06 – >8	99.8 / 0.1	99.9 / 0.1
Quinupristin/dalfopristin	>2	>2	≤0.25 – >2	0.8 / 95.6	0.8 / 95.6
Teicoplanin	≤2	≤2	≤2 – >16	97.8 / 2.2	97.6 / 2.4
Vancomycin	1	2	≤0.12 – >16	97.1 / 2.7	97.1 / 2.9
Enterococcus faecium (6,035)					
Ceftobiprole	>8	>8	0.12 – >8	- / -	- / -
Ampicillin	>16	>16	≤1 – >16	8.0 / 92.0	7.3 / 92.0
Daptomycin	2	4	≤0.06 – >8	99.8 / -	- / -
Levofloxacin	>4	>4	≤0.5 – >4	9.9 / 86.2	- / -
Linezolid	1	2	0.25 – >8	98.6 / 1.0	99.0 / 1.0
Quinupristin/dalfopristin	1	>2	≤0.25 – >2	79.2 / 10.8	79.2 / 10.8
Teicoplanin	≤2	>16	≤2 – >16	58.7 / 38.1	57.8 / 42.2
Vancomycin	1	>16	≤0.12 – >16	55.0 / 44.0	55.0 / 45.0
β-haemolytic streptococci (7,163)[c]					
Ceftobiprole	≤0.06	≤0.06	≤0.06 – 0.25	- / -	- / -
Penicillin	≤0.015	0.06	≤0.015 – 1	99.9 / -	>99.9 / <0.1
Cefepime	≤0.12	≤0.12	≤0.12 – 2	99.9 / -	>99.9 / <0.1
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 4	99.9 / -	>99.9 / <0.1
Clindamycin	≤0.25	1	≤0.25 – >2	89.4 / 10.1	89.9 / 10.1
Daptomycin	≤0.06	0.25	≤0.06 – 1	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	>2	≤0.25 – >2	78.1 / 21.2	78.1 / 21.2
Levofloxacin	≤0.5	1	≤0.5 – >4	98.5 / 1.5	95.0 / 1.5
Linezolid	1	1	≤0.06 – 2	100.0 / -	100.0 / 0.0
Vancomycin	0.5	0.5	≤0.12 – 1	100.0 / -	100.0 / 0.0
Viridans streptococci (2,966)					
Ceftobiprole	≤0.06	0.25	≤0.06 – >8	- / -	- / -
Penicillin	0.06	1	≤0.015 – >32	75.2 / 5.1	82.4 / 5.1
Cefepime	≤0.12	1	≤0.12 – >16	92.6 / 3.6	87.1 / 12.9
Ceftriaxone	≤0.25	1	≤0.25 – >32	92.5 / 4.1	88.6 / 11.4
Clindamycin	≤0.25	>2	≤0.25 – >2	88.5 / 10.8	89.2 / 10.8
Daptomycin	0.25	0.5	≤0.06 – 2	99.6 / -	- / -
Erythromycin	≤0.25	>2	≤0.25 – >2	55.4 / 42.7	- / -
Levofloxacin	1	2	≤0.5 – >4	93.9 / 4.9	- / -
Linezolid	1	1	≤0.06 – 8	>99.9 / -	- / -
Vancomycin	0.5	1	≤0.12 – 2	99.9 / -	100.0 / 0.0
S. pneumoniae (13,412)					
Ceftobiprole	≤0.06	0.5	≤0.06 – 8	- / -	- / -
Penicillin[d]	≤0.03	4	≤0.03 – >4	89.3 / 1.2	- / -
Penicillin[e]	≤0.03	4	≤0.03 – >4	62.9 / 20.8	62.9 / 10.7
Cefepime	≤0.12	1	≤0.12 – >16	91.5 / 1.1	91.5 / 1.1
Ceftriaxone	≤0.25	1	≤0.25 – >32	91.2 / 2.3	79.1 / 2.3
Clindamycin	≤0.25	>1	≤0.25 – >1	76.0 / 23.6	76.4 / 23.6
Erythromycin	≤0.25	>2	≤0.25 – >2	61.2 / 38.4	61.2 / 38.4
Levofloxacin	1	1	≤0.5 – >4	98.8 / 1.1	98.8 / 1.2
Linezolid	1	1	≤0.12 – 2	100.0 / -	100.0 / 0.0
Tetracycline	≤2	>8	≤2 – >8	69.2 / 29.9	69.2 / 30.8
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	65.2 / 24.4	72.3 / 24.4
Vancomycin	≤1	≤1	≤1 – >1	>99.9 / -	100.0 / 0.0

a. Criteria as published by the CLSI [2010] and EUCAST [2010].
b. - = No breakpoint has been established.
c. Includes: *Streptococcus dysgalactiae* (197 isolates), *Streptococcus equi* (4 isolates), *Streptococcus equisimilis* (17 isolates), Group A *Streptococcus* (2802 isolates), Group B *Streptococcus* (3151 isolates), Group C *Streptococcus* (261 isolates), Group F *Streptococcus* (45 isolates), Group G *Streptococcus* (651 isolates), and unspeciated beta-haemolytic streptococci (35 isolates).
d. Criteria as published by the CLSI [2010] for 'Penicillin parenteral (non-meningitis)'.
e. Criteria as published by the CLSI [2010] for 'Penicillin (oral penicillin V)'.

Conclusions

- Ceftobiprole exhibited excellent potency against a very large (n=53,375) sample of contemporary (2005-2009) and geographically diverse *S. aureus* isolates including 23,502 methicillin-resistant (MRSA) isolates. Importantly, the *S. aureus* MIC distribution remained geographically and temporally stable over this half-decade. Similar results were observed against coagulase-negative staphylococci.
- Ceftobiprole was potent against *E. faecalis*, but not against most *E. faecium,* and demonstrated excellent potency against β-haemolytic streptococci, viridans group streptococci, and *S. pneumoniae*.
- This data expands the definition of ceftobiprole activity against the majority of contemporary Gram-positive pathogens on a global scale. This anti-MRSA parenteral cephalosporin may be potentially useful as empiric or targeted therapy to treat patients with cSSSI and HABP.

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Acknowledgments

This study was supported by Janssen Pharmaceuticals.