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Antimicrobial Activity of LB11058 Tested Against *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*

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ABSTRACT

Background: LB11058 (LB) is a novel cephalosporin with a C-3 pyrimidinyl-substituted vinyl sulfide group and a C-7 2 amino-5-chloro-1, 3-thiazole radical. Previous studies have shown that this compound has excellent activity against Gram-positive and -negative bacteria, especially those species implicated in community-acquired respiratory tract infections (CARTI). We evaluated the activity of LB against recent clinical isolates in comparison to other antimicrobial agents used to treat these infections.

Methods: A total of 510 organisms were tested, including 205 *S. pneumoniae* (SPN; 103 penicillin [PEN]-non-susceptible), 203 *H. influenzae* (HI; 101 ß-lactamase [BL] producers) and 102 *M. catarrhalis* (MCAT). LB MICs were determined by methods recommended by NCCLS (M7-A6).

Results: LB was the most potent compound tested against SPN. LB was more active against PEN-S (MIC_{90}, ≤0.008 μg/ml) than against PEN-intermediate (I; MIC_{90}, 0.06 μg/ml) or PEN-resistant (R) strains (MIC_{90}, 0.12 μg/ml; range 0.06 - 0.25 μg/ml). LB was 8- to 16-fold more active than ceftriaxone (CRO), cefepime (CPM) or amoxicillin/clavulanate (A/C) against PEN-I and -R strains. LB activity against HI (MIC_{90}, 0.25-0.5 μg/ml) was not influenced by BL production, and it was similar to that of CPM (MIC_{90}, 0.12-0.25 μg/ml), but inferior to CRO (MIC_{90}, ≤0.008-0.015 μg/ml). Against MCAT, LB activity (MIC_{90}, 0.25 μg/ml) was most similar to A/C and superior to CRO (MIC_{90}, 0.5 μg/ml) and CPM (MIC_{90}, 1 μg/ml).

Conclusions: LB showed excellent activity against the most significant pathogens causing CARTI, SPN and HI also represent important causes of meningitis. Thus, LB may become an acceptable therapeutic option for empiric therapy of these infections, especially in areas with high rates of ß-lactam resistance and MRSA. Continued studies to analyze the potential clinical role of this compound against these pathogens appears warranted.

INTRODUCTION

Community-acquired respiratory tract infections (CARTI) are the leading causes of primary care physician office visits and the majority of prescribed antimicrobials are for these indications. *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* are the three most significant bacterial pathogens for these infections. The emergence of clinical isolates with resistance to one or more commonly prescribed oral agents drives the development of new compounds to overcome these resistant phenotypes.

S. pneumoniae is the most commonly identified bacterial cause of community-acquired pneumonia, otitis media and meningitis, and it is a frequent pathogen in associated bacteremia. Morbidity and mortality may be high among patients with bacteremia and meningitis, especially when appropriate antimicrobial therapy is delayed. Resistance to penicillin and other antimicrobial agents has increased significantly in the last decade, making the treatment of serious pneumococcal infections very difficult, especially among children.

LB11058 is a novel parenteral cephalosporin with a C-3 pyrimidinyl-substituted vinyl sulfide group and a C-7 2-amino-5-chloro-1, 3-thiazole group (Figure 1). This compound has demonstrated excellent in vitro activity against Gram-positive bacteria, including oxacillin-resistant *S. aureus* and penicillin-resistant *S. pneumoniae*, and against Gram-negative bacteria implicated in respiratory tract infections such as *H.influenzae* and *M. catarrhalis*. In the present study, we evaluated the in vitro activity of LB11058 tested against recent clinical isolates collected from patients with CARTI worldwide.

MATERIALS & METHODS

The LB11058 reagent grade compound was provided by LG Life Science, Ltd. (Taejon, South Korea). Comparator agents were purchased from Sigma Chemical Co. (St Louis, MO) or obtained from their respective manufacturers in the USA. Fifteen comparators were evaluated depending upon the species tested.

A total of 510 well characterized strains derived from numerous laboratories worldwide, were processed in the study. The collection of organisms included: 205 *S. pneumoniae* (103 penicillin non-susceptible), 203 *Haemophilus influenzae* (101 ß-lactamase-positive) and 102 *Moraxella catarrhalis* (nearly all ß-lactamase-producers).

LB11058 minimum inhibitory concentrations (MICs) were determined by the reference methods according to procedures recommended by the National Committee for Clinical Laboratory Standards (NCCLS). On each day of testing, a fresh stock solution (1,280 μg/ml) of LB11058 (LG Life Science, Ltd., Taejon, South Korea) was prepared and then serial diluted for a testing concentration range of 0.008 to 64 μg/ml. Supplemented 5% lysed horse blood was added for testing *Streptococcus* spp. and Haemophilus Test Medium (HTM) with NAD supplement was utilized for testing *H. influenzae*. The MIC values were interpreted according to NCCLS criteria.

COMMENTS

- LB11058 was the most potent compound tested against *S. pneumoniae*, but activity varied according to the organism's susceptibility to penicillin. Penicillin-susceptible *S. pneumoniae* were highly susceptible to LB11058 (MIC_{90}, ≤0.008 μg/ml), while penicillin-intermediate (LB11058 MIC_{90}, 0.06 μg/ml) strains and penicillin-resistant strains (LB11058 MIC_{90}, 0.12 μg/ml) showed slightly higher LB11058 MIC results (0.06 - 0.25 μg/ml).
- The novel cephalosporin was eight to 16-fold more potent than ceftriaxone, cefepime or amoxicillin-clavulanate against both penicillin-intermediate and –resistant pneumococcal strains.
- LB11058 activity against *H. influenzae* (MIC_{90}, 0.25 – 0.5 μg/ml) was not significantly affected by the production of ß-lactamase, and it was similar to that of cefepime (MIC_{90}, 0.12 - 0.25 μg/ml) and cefuroxime (MIC_{90}, 0.12 – 0.25 μg/ml), but inferior to that of ceftriaxone (MIC_{90}, ≤0.008 – 0.015 μg/ml).
- LB11058 (MIC_{50}, 0.03 μg/ml) was the most potent ß-lactam tested against *M. catarrhalis*, followed by ceftriaxone (MIC_{50}, 0.12 μg/ml), amoxicillin/clavulanate (MIC_{50}, 0.12 μg/ml) and cefepime (MIC_{50}, 0.5 μg/ml; see Table 2).

RESULTS

Table 1. Antimicrobial activity of LB11058 and selected comparison drugs tested against Gram-positive species.

Organism/antimicrobial agent (no. tested)	MIC (μg/ml) 50%	90%	Range	% Susceptible
Streptococcus pneumoniae Penicillin-susceptible (102)				
LB11058	≤0.008	≤0.008	≤0.008-0.06	-[a]
Ceftriaxone	0.015	0.03	≤0.008-0.12	100.0
Cefepime	≤0.06	≤0.06	≤0.06-0.5	100.0
Amoxicillin/Clavulanate	≤0.06	≤0.06	≤0.06	100.0
Erythromycin	≤0.25	≤0.25	≤0.25-16	93.1
Azithromycin	≤0.12	0.25	≤0.12-16	92.2
Clindamycin	≤0.06	≤0.06	≤0.06-0.5	100.0
Chloramphenicol	≤2	4	≤2-16	99.0
Levofloxacin	1	1	≤0.03->4	99.0
Trim/Sulfa[b]	≤0.5	1	≤0.5->4	86.3
Vancomycin	0.25	0.5	≤0.06-1	100.0
Quinupristin/Dalfopristin	0.5	0.5	≤0.06-0.5	100.0
Linezolid	0.5	1	≤0.25-2	100.0
Streptococcus pneumoniae Penicillin-intermediate (52)				
LB11058	0.03	0.06	≤0.008-0.12	-
Ceftriaxone	0.25	0.5	0.015-2	98.1
Cefepime	0.25	1	≤0.06-4	98.1
Amoxicillin/Clavulanate	0.25	1	≤0.06-2	100.0
Erythromycin	2	>32	≤0.25->32	44.2
Azithromycin	2	>16	≤0.12->16	46.2
Clindamycin	≤0.06	>8	≤0.06->8	79.6
Chloramphenicol	4	4	≤2->16	92.3
Levofloxacin	1	1	0.25->4	98.1
Trim/Sulfa[b]	≤0.5	4	≤0.5->4	50.0
Vancomycin	0.25	0.5	≤0.06-1	100.0
Quinupristin/Dalfopristin	0.5	0.5	0.12-1	100.0
Linezolid	0.5	1	0.25-1	100.0
Streptococcus pneumoniae Penicillin-resistant (51)				
LB11058	0.12	0.12	0.06-0.25	-
Ceftriaxone	1	1	0.03-8	92.2
Cefepime	1	2	0.5-2	84.3
Amoxicillin/Clavulanate	2	8	<1-8	64.7
Erythromycin	4	>32	≤0.25->32	26.9
Azithromycin	4	>16	2->16	25.5
Clindamycin	≤0.06	>8	≤0.06->8	74.0
Chloramphenicol	4	16	≤2-16	82.7
Levofloxacin	1	1	0.5->4	94.2
Trim/Sulfa[b]	4	>4	≤0.5->4	17.3
Vancomycin	0.25	0.5	0.25-0.5	100.0
Quinupristin/Dalfopristin	0.5	0.5	0.12-1	100.0
Linezolid	0.5	1	0.25-2	100.0

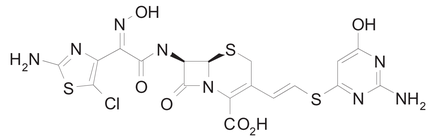
Organism/antimicrobial agent (no. tested)	MIC (μg/ml) 50%	90%	Range	% Susceptible
Haemophilus influenzae ß-lactamase-negative (102)				
LB11058	0.12	0.5	0.015-0.5	-
Ceftriaxone	≤0.008	0.015	≤0.008-0.03	100.0
Cefepime	≤0.06	0.12	≤0.06-0.5	100.0
Amoxicillin/Clavulanate	0.5	1	≤0.06-2	100.0
Azithromycin	1	2	≤0.12-4	100.0
Chloramphenicol	≤2	≤2	≤2	100.0
Ciprofloxacin	≤0.03	≤0.03	≤0.03	100.0
Levofloxacin	≤0.03	≤0.03	≤0.03	100.0
Trim/Sulfa[b]	≤0.5	>4	≤0.5->4	80.2
Haemophilus influenzae ß-lactamase-positive (101)				
LB11058	0.12	0.25	0.03-0.5	-
Ceftriaxone	≤0.008	≤0.008	≤0.008-0.015	100.0
Cefepime	≤0.06	0.25	≤0.06-0.25	100.0
Amoxicillin/Clavulanate	1	2	0.25-4	100.0
Azithromycin	1	2	≤0.12-4	100.0
Chloramphenicol	≤2	≤2	≤2->16	96.0
Ciprofloxacin	≤0.03	≤0.03	≤0.03	100.0
Levofloxacin	≤0.03	≤0.03	≤0.03	100.0
Trim/Sulfa[b]	≤0.5	>4	≤0.5->4	96.0
Moraxella catarrhalis (102)[c]				
LB11058	0.03	0.25	≤0.008-0.5	-
Ceftriaxone	0.12	0.5	≤0.008-1	100.0
Cefepime	0.5	1	≤0.06-4	99.0
Amoxicillin/Clavulanate	0.12	0.25	≤0.06-0.5	100.0
Azithromycin	≤0.12	≤0.12	≤0.12	100.0
Chloramphenicol	≤2	≤2	≤2	100.0
Ciprofloxacin	≤0.03	0.06	≤0.03-0.06	100.0
Levofloxacin	≤0.03	0.06	≤0.03-0.06	100.0
Trim/Sulfa[b]	≤0.5	≤0.5	≤0.5-1	99.0

a. - = No interpretive criteria has been established by the NCCLS.
b. Trimethoprim/Sulfamethoxazole
c. Susceptibility as defined by the NCCLS for *H. influenzae* was used for all drugs except erythromycin where guidelines for staphylococci were applied (≤ 0.5 mg/ml).

CONCLUSIONS

- LB11058 was highly active against the three most common pathogens isolated from CARTI worldwide.
- Since LB11058 showed higher potency than the currently prescribed third-generation cephalosporin (ceftriaxone) against *S. pneumoniae*, and retained potent activity against *H. influenzae* and *M. catarrhalis*, this compound may represent an excellent therapeutic candidate for empiric therapy of CARTI and bacterial meningitis, especially in areas with high rates of antimicrobial resistance.

Figure 1: Chemical structure of LB11058.



LB11058

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