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DC-159a, a Novel Oral Quinolone, Activity Tested Against Community-Acquired Respiratory Tract (CA-RTI) Pathogens

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ABSTRACT

Background: DC-159a, a new potent orally administered fluoroquinolone (FQ), was developed to possess an enhanced and balanced spectrum against commonly encountered Gram-positive and -negative organisms associated with CA-RTI.

Methods: Organisms (316) causing pharyngitis and other CA-RTI (sinusitis, bronchitis, pneumonia) were isolated from patients on 3 continents and susceptibility (S) tested against DC-159a and 19 comparators by CLSI (M7-A7) methods, including: *S. pyogenes* (30), gr. B streptococci (30), *S. pneumoniae* (SPN; 92 wide type [WT], 32 penicillin [PEN] resistant [R]), *H. influenzae* (HI; 80), *H. parainfluenzae* (HPAR; 30), *M. catarrhalis* (29) and *B. pertussis* (12). CLSI interpretive criteria were applied with ≤2 µg/ml used for DC-159a comparisons only.

Results: The Table exhibits a DC-159a potency up to 8-fold greater than levofloxacin (LEVO). ß-haemolytic streptococci and SPN were uniformly very S to DC-159a (MIC_{90}, 0.12 µg/ml) with LEVO-R strains showing an 8 -fold MIC elevation (100% S at ≤2 µg/ml). Gram-negative CA-RTI pathogens were very S to DC-159a (MIC_{90} range, 0.008-0.03 µg/ml). HPAR (MIC_{90}, 0.12 µg/ml) had slightly higher MIC values compared to HI, and ß-lactamase or altered PBP targets (BLNAR) did not affect DC-159a activity.

	DC-159a		LEVO	
Organism (no. tested)	$MIC_{50/90}$	% S	$MIC_{50/90}$	% S
ß-haemolytic streptococci (60)	0.12 / 0.12	100	0.5 / 1	100
S. pneumoniae, all (92, WT)	0.12 / 0.12	100	1 / 1	100
S. pneumoniae, PEN-R (32)	0.12 / 0.12	100	1 / 1	100
S. pneumoniae, LEVO-R (13)	1 / 2	100	>8 / >8	0
H. influenzae (80)	0.015 / 0.015	100	0.015 / 0.015	100
M. catarrhalis (29)	0.03 / 0.03	100	0.03 / 0.03	100
B. pertussis (12)	0.008 / 0.015	100	0.06 / 0.06	100

Conclusions: DC-159a demonstrated greater activity compared to marketed FQs against a recent sampling of CA-RTI pathogens, including residual potency (MIC_{90}, 2 µg/ml) against PEN- and LEVO-R pneumococci; almost 8-fold more potent than LEVO. Further development of DC-159a in vitro and in vivo appears warranted.

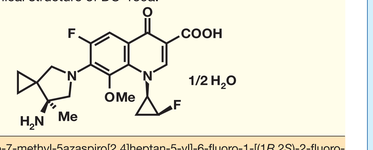
INTRODUCTION

As further development of fluoroquinolone resistance evolves, newer agents in the class must be focused on achieving high potency against mutant strains having DNA gyrase and topoisomerase target alterations. This activity should be associated with high oral/parenteral bioavailability to assure the greatest likelihood of pharmacodynamic target attainment especially for key respiratory tract pathogens such as *Streptococcus pneumoniae*, other streptococci, *Haemophilus* spp. and *Moraxella catarrhalis*. Although the rate of fluoroquinolone-resistant pneumococci (≤2% worldwide) remains low, escalation appears possible driven by popular use of gatifloxacin, gemifloxacin, levofloxacin and moxifloxacin.

DC-159a, a novel orally administered fluoroquinolones from Daiichi Pharmaceutical Co., Ltd. (Japan), is said to have residual affinity for mutated target sites (Figure 1). To assess this possibility, a challenge collection of contemporary respiratory tract pathogen isolates was selected to contain organisms with well characterized resistance mechanisms or phenotypic expression of resistant level MIC values. All tests were performed by reference Clinical and Laboratory Standards Institute (CLSI; formerly the NCCLS) methods with appropriate medium supplements for fastidious staphylococci (2-5% lysed horse blood) and *Haemophilus* spp. (HTM formulation) strains.

INTRODUCTION (Continued)

Figure 1. Chemical structure of DC-159a.



(+)-7-[(7S)-7-amino-7-methyl-5azaspiro[2.4]heptan-5-yl]-6-fluoro-1-[(1*R*,2*S*)-2-fluoro-1-cyclopropyl]-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid hemihydrate

MATERIALS AND METHODS

Bacterial Strains. Respiratory tract pathogens were collected from patients with documented infections. A total of 316 strains were selected to produce representative examples of prevailing resistance mechanisms or resistance phenotypes. A list follows:

- *S. pneumoniae* (92 strains; 62 non-susceptible to penicillin)
- *S. pneumoniae* (13 resistant to levofloxacin)
- *S. pyogenes* (Group A ; 30 strains)
- *S. agalactiae* (Group B; 30 strains)
- *H. influenzae* (70 strains; 30 ß-lactamase-positive)
- *H. influenzae* (10 strains; 10 ß-lactamase negative and ampicillin-resistant [BLNAR])
- *H. parainfluenzae* (30 strains; 4 ß-lactamase-positive)
- *M. catarrhalis* (29 strains; 19 ß-lactamase-positive)
- *B. pertussis* (12 strains, all macrolide-susceptible)

Specific antimicrobial-resistant subsets are listed in Tables 1 and 2.

Susceptibility Testing. All tests were performed using the CLSI M7-A7 (2006) broth microdilution method. Appropriate supplements to the cation-adjusted Mueller-Hinton medium were used for streptococci and for *Haemophilus* spp. Category interpretations of MIC results used current M100-S16 (2006) criteria. Quality control (QC) was assured by use of several CLSI-recommended ATCC strains; all QC results were within defined ranges (M100-S16, 2006). DC-159a was provided by Daiichi and all other comparison agents were obtained from their manufacturers or from Sigma Chemical Co. (St. Louis, MO). Frozen-form broth microdilution panels were produced by JMI Laboratories (North Liberty, IA).

RESULTS

- DC-159a potency against *S. pneumoniae* was eight-fold greater than levofloxacin and equal to moxifloxacin. Resistance to penicillin did not adversely influence DC-159a activity (Table 1).
- Levofloxacin-resistant pneumococci were generally eight- to 16-fold less susceptible to DC-159a (MIC_{90} and highest MIC, 2 µg/ml). DC-159a was two-fold more potent than moxifloxacin versus QRDR mutants (Table 1).
- ß-haemolytic streptococci (*S. pyogenes* and *S. agalactiae*) were very susceptible to DC-159a (MIC_{90}, 0.12 µg/ml), see Table 1.

RESULTS (Continued)

Table 1. Activity of DC-159a tested by reference CLSI methods against streptococci (165 strains).

	MIC (µg/ml):			% by category:[a]
Organism (no. tested)/antimicrobial agent	50%	90%	Range	Susceptible/Resistant
S. pneumoniae				
Penicillin-susceptible (30)				
DC-159a	0.12	0.12	0.06-0.25	- / -
Levofloxacin	1	1	0.5-1	100.0 / 0.0
Gatifloxacin	0.25	0.25	0.06-0.5	00.0 / 0.0
Gemifloxacin	≤0.015	≤0.015	≤0.015-0.03	100.0 / 0.0
Moxifloxacin	0.12	0.12	≤0.03-0.25	100.0 / 0.0
Ciprofloxacin	1	2	0.25-2	- / -
Erythromycin	≤0.25	≤0.25	≤0.25->32	96.7 / 3.3
Clindamycin	≤0.25	≤0.25	≤0.25->2	96.7 / 3.3
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0 / 0.0
Cefuroxime	≤0.06	0.25	≤0.06->16	96.7 / 3.3
Tetracycline	≤2	≤2	≤2->8	96.7 / 3.3
Trimethoprim/sulfamethoxazole	≤0.5	2	≤0.5->4	80.0 / 6.7
Vancomycin	0.25	0.5	≤0.06-0.5	100.0 / -
Linezolid	1	1	0.12-2	100.0 / -
Penicillin-intermediate (30)				
DC-159a	0.06	0.12	0.06-0.12	- / -
Levofloxacin	1	1	0.5-1	100.0 / 0.0
Gatifloxacin	0.25	0.25	0.12-1	100.0 / 0.0
Gemifloxacin	≤0.015	0.03	≤0.015-0.06	100.0 / 0.0
Moxifloxacin	0.12	0.12	0.06-0.5	100.0 / 0.0
Ciprofloxacin	1	2	0.5-2	- / -
Erythromycin	2	>32	≤0.25->32	43.3 / 53.3
Clindamycin	≤0.25	>2	≤0.25->2	73.3 / 26.7
Ceftriaxone	0.25	0.5	0.015-1	100.0 / 0.0
Cefuroxime	0.5	4	≤0.06-4	66.7 / 13.3
Tetracycline	≤2	>8	≤2->8	66.7 / 33.3
Trimethoprim/sulfamethoxazole	1	4	≤0.5->4	36.7 / 36.7
Vancomycin	0.25	0.5	0.12-1	100.0 / -
Linezolid	1	1	0.25-2	100.0 / -
Penicillin-resistant (32)				
DC-159a	0.12	0.12	0.06-0.12	- / -
Levofloxacin	1	1	0.5-2	100.0 / 0.0
Gatifloxacin	0.25	0.5	0.25-1	100.0 / 0.0
Gemifloxacin	≤0.015	0.03	≤0.015-0.03	100.0 / 0.0
Moxifloxacin	0.12	0.25	0.06-1	100.0 / 0.0
Ciprofloxacin	1	2	0.5-4	- / -
Erythromycin	4	>32	≤0.25->32	37.5 / 62.5
Clindamycin	≤0.25	>2	≤0.25->2	56.3 / 43.8
Ceftriaxone	1	2	≤0.008-8	84.4 / 3.1
Cefuroxime	4	>8	≤0.06->8	3.1 / 93.8
Tetracycline	>8	>8	≤2->8	43.8 / 56.3
Trimethoprim/sulfamethoxazole	4	>4	≤0.5->4	12.5 / 81.3
Vancomycin	0.25	0.5	0.25-0.5	100.0 / -
Linezolid	1	1	0.5-2	100.0 / -
Levofloxacin-resistant (13)				
DC-159a	1	2	0.5-2	- / -
Levofloxacin	>8	>8	8->8	0.0 / 100.0
Gatifloxacin	4	>4	2->4	0.0 / 92.3
Gemifloxacin	0.25	0.5	0.06-1	46.2 / 15.4
Moxifloxacin	2	4	1-4	7.7 / 30.8
Ciprofloxacin	>4	>4	>4	- / -
Erythromycin	≤0.25	>32	≤0.25->32	53.8 / 46.2
Clindamycin	≤0.25	>2	≤0.25->2	69.2 / 23.1
Ceftriaxone	0.015	1	≤0.008-2	92.3 / 0.0
Cefuroxime	≤0.06	8	≤0.06-8	69.2 / 30.8
Tetracycline	≤2	>8	≤2->8	76.9 / 23.1
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5->4	61.5 / 38.5
Vancomycin	0.25	0.5	0.12-0.5	100.0 / -
Linezolid	1	1	0.25-1	100.0 / -
ß-haemolytic streptococci				
Group A (30)				
DC-159a	0.12	0.12	0.06-0.12	- / -
Levofloxacin	0.5	1	0.25-2	100.0 / 0.0
Gatifloxacin	0.25	0.25	0.12-0.5	100.0 / 0.0
Gemifloxacin	0.015	0.03	0.008-0.06	- / -
Moxifloxacin	0.12	0.25	0.06-0.25	- / -
Ciprofloxacin	0.5	0.5	0.25-2	- / -
Penicillin	≤0.015	≤0.015	≤0.015	100.0 / -
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0 / -
Erythromycin	≤0.06	4	≤0.06->8	86.7 / 13.3
Clindamycin	≤0.06	≤0.06	≤0.06->8	96.7 / 3.3
Tetracycline	≤2	>8	≤2->8	73.3 / 26.7
Vancomycin	0.25	0.5	0.25-1	100.0 / -
Linezolid	1	1	0.5-1	100.0 / -
Group B (30)				
DC-159a	0.12	0.12	0.06-0.25	- / -
Levofloxacin	1	1	0.5-1	100.0 / 0.0
Gatifloxacin	0.25	0.25	0.12-0.5	100.0 / 0.0
Gemifloxacin	0.015	0.03	0.008-0.06	- / -
Moxifloxacin	0.12	0.25	0.06-0.25	- / -
Ciprofloxacin	0.5	1	0.25-1	- / -
Penicillin	0.06	0.12	≤0.015-0.12	100.0 / -
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0 / -
Erythromycin	≤0.06	2	≤0.06->8	76.7 / 23.3
Clindamycin	≤0.06	≤0.06	≤0.06->8	90.0 / 10.0
Tetracycline	>8	>8	≤2->8	10.0 / 86.7
Vancomycin	0.5	0.5	0.25-1	100.0 / -
Linezolid	1	1	0.5-1	100.0 / -

a. Criteria as published by the CLSI (2006).

RESULTS (Continued)

Table 2. In vitro activity of DC-159a tested against Gram-negative pathogens associated with respiratory tract infections (151 strains).

	MIC (µg/ml):			% by category:[a]
Organism (no. tested)/antimicrobial agent	50%	90%	Range	Susceptible/Resistant
H. influenzae				
ß-lactamase-negative (40)				
DC-159a	0.008	0.015	0.008-0.015	- / -
Levofloxacin	0.015	0.015	≤0.008-0.03	100.0 / -
Gatifloxacin	≤0.03	≤0.03	≤0.03	100.0 / -
Gemifloxacin	≤0.015	≤0.015	≤0.015	100.0 / -
Moxifloxacin	≤0.03	≤0.03	≤0.03	100.0 / -
Ciprofloxacin	≤0.12	≤0.12	≤0.12	100.0 / -
Ampicillin	≤0.5	1	≤0.5-1	100.0 / 0.0
Amoxicillin/clavulanic acid	0.5	1	0.25-2	100.0 / 0.0
Ceftriaxone	≤0.008	≤0.008	≤0.008-0.015	100.0 / -
Cefuroxime	1	2	0.5-8	97.5 / 0.0
Azithromycin	1	2	≤0.5->16	97.5 / -
Tetracycline	≤2	≤2	≤2	100.0 / 0.0
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5->4	77.5 / 22.5
ß-lactamase-positive (30)				
DC-159a	0.015	0.03	≤0.004-0.03	- / -
Levofloxacin	0.015	0.015	≤0.008-0.03	100.0 / -
Gatifloxacin	≤0.03	≤0.03	≤0.03	100.0 / -
Gemifloxacin	≤0.015	≤0.015	≤0.015	100.0 / -
Moxifloxacin	≤0.03	≤0.03	≤0.03-0.06	100.0 / -
Ciprofloxacin	≤0.12	≤0.12	≤0.12	100.0 / -
Ampicillin	>4	>4	2->4	0.0 / 96.7
Amoxicillin/clavulanic acid	≤1	≤1	≤1	100.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0 / -
Cefuroxime	0.5	1	≤0.06-2	100.0 / 0.0
Azithromycin	1	2	≤0.5->4	96.7 / -
Tetracycline	≤2	≤2	≤2-16	93.3 / 6.7
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	80.0 / 16.7
ß-lactamase-negative, ampicillin-resistant (10)[c]				
DC-159a	0.015	0.015	0.008-0.015	- / -
Levofloxacin	0.015	0.015	0.015	100.0 / -
Gatifloxacin	≤0.03	≤0.03	≤0.03	100.0 / -
Gemifloxacin	≤0.12	≤0.12	≤0.12	100.0 / -
Moxifloxacin	≤0.03	≤0.03	≤0.03	100.0 / -
Ciprofloxacin	≤0.12	≤0.12	≤0.12	100.0 / -
Ampicillin	2	2	2-4	0.0 / 10.0
Amoxicillin/clavulanic acid	4	4	2-8	90.0 / 10.0
Ceftriaxone	0.015	0.03	0.015-2	100.0 / -
Cefuroxime	4	>8	2->8	60.0 / 20.0
Azithromycin	1	1	0.5-1	100.0 / -
Tetracycline	≤2	≤2	≤2	100.0 / 0.0
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5->4	70.0 / 30.0
H. parainfluenzae (30)				
DC-159a	0.06	0.12	0.008-0.25	- / -
Levofloxacin	0.03	0.06	0.015-0.12	100.0 / -
Gatifloxacin	≤0.03	≤0.03	≤0.03-0.12	100.0 / -
Gemifloxacin	≤0.12	≤0.12	≤0.12	100.0 / -
Moxifloxacin	≤0.03	0.12	≤0.03-0.5	100.0 / -
Ciprofloxacin	≤0.25	≤0.25	≤0.25	100.0 / -
Ampicillin	≤1	2	≤1->4	86.7 / 10.0
Amoxicillin/clavulanic acid	≤2	≤2	≤2-4	100.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25-0.5	100.0 / -
Cefuroxime	0.5	1	≤0.12-4	100.0 / 0.0
Azithromycin	0.5	2	0.12-2	100.0 / -
Tetracycline	≤2	≤2	≤2->8	90.0 / 10.0
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	93.3 / 3.3
M. catarrhalis				
ß-lactamase-negative (10)				
DC-159a	0.03	0.03	0.015-0.03	- / -
Levofloxacin	0.03	0.03	0.015-0.03	- / -
Gatifloxacin	≤0.03	≤0.03	≤0.03	- / -
Gemifloxacin	≤0.12	≤0.12	≤0.12	- / -
Moxifloxacin	0.06	0.06	≤0.03-0.06	- / -
Ciprofloxacin	≤0.12	≤0.12	≤0.12	- / -
Penicillin	≤0.03	≤0.03	≤0.03-0.06	- / -
Amoxicillin/clavulanic acid	≤0.06	≤0.06	≤0.06	- / -
Ceftriaxone	≤0.008	0.015	≤0.008-0.015	- / -
Cefuroxime	0.5	0.5	0.25-0.5	- / -
Erythromycin	≤0.25	≤0.25	≤0.25	- / -
Tetracycline	≤2	≤2	≤2	- / -
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5	- / -
ß-lactamase-positive (19)				
DC-159a	0.03	0.03	0.015-0.03	- / -
Levofloxacin	0.03	0.03	0.015-0.03	- / -
Gatifloxacin	≤0.03	≤0.03	≤0.03-0.06	- / -
Gemifloxacin	≤0.12	≤0.12	≤0.12	- / -
Moxifloxacin	0.06	0.06	≤0.03-0.06	- / -
Ciprofloxacin	≤0.12	≤0.12	≤0.12	- / -
Penicillin	2	>4	0.25->4	- / -
Amoxicillin/clavulanic acid	≤0.25	≤0.25	≤0.25	- / -
Ceftriaxone	0.06	0.5	≤0.008-0.5	- / -
Cefuroxime	1	2	0.5-2	- / -
Erythromycin	≤0.25	≤0.25	≤0.25	- / -
Tetracycline	≤2	≤2	≤2	- / -
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5-2	- / -
B. pertussis (12)				
DC-159a	0.008	0.015	0.008-0.015	- / -
Levofloxacin	0.06	0.06	0.03-0.06	100.0 / 0.0
Ciprofloxacin	0.03	0.03	0.015-0.03	100.0 / 0.0
Azithromycin	0.06	0.12	0.03-0.12	- / -
Clarithromycin	0.06	0.12	0.03-0.25	- / -
Clindamycin	0.25	0.25	0.06-0.5	- / -
Erythromycin	0.12	0.12	0.06-0.25	- / -
Trimethoprim/sulfamethoxazole	0.008	0.008	≤0.002-0.015	100.0 / 0.0

a. Criteria as published by the CLSI (2006).
b. - = no breakpoint criteria have been established for this category.
c. Ampicillin at ≥8 µg/ml.

RESULTS (Continued)

- DC-159a and comparator fluoroquinolones were very active against all *Haemophilus* species regardless of ß-lactamase production (MIC_{90} range, 0.015-0.12 µg/ml).
- DC-159a was equal to levofloxacin (MIC_{90}, 0.03 µg/ml) and two-fold more potent than moxifloxacin against *M. catarrhalis*. *B. pertussis* strains were also very susceptible to DC-159a (MIC range, 0.008-0.015 µg/ml).

CONCLUSIONS

- DC-159a effectively inhibits all important respiratory tract pathogens at MIC values equal or lower than many currently marketed fluoroquinolones.
- All wildtype strains tested (seven species) were inhibited by DC-159a at ≤0.25 µg/ml and fluoroquinolone-resistant *S. pneumoniae* strains at ≤2 µg/ml.
- The balance of DC-159a activity versus respiratory tract pathogens warrants further development for sinusitis, bronchitis and community-acquired pneumonia indications.

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