



Characterization and In Vitro Activity of Delafloxacin (DLX) Against Isolates from a Phase 2 Study of Acute Bacterial Skin and Skin Structure Infections (ABSSI)

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Abstract

Background

DLX, an investigational fluoroquinolone (FQ), has potent activity against clinically relevant Gram-positive and -negative bacteria, including methicillin-resistant (MR) and FQ resistant *Staphylococcus aureus* (SA) strains.

Methods

Isolates from a US study of ABSSI (256 patients) were identified and tested for antimicrobial susceptibility utilizing CLSI broth microdilution methods. Antibacterials tested included DLX, levofloxacin (LVX), ciprofloxacin (CIP), oxacillin (OXA), tigecycline (TIG), linezolid (LNZ), vancomycin (VAN), gentamicin (GEN), and erythromycin (ERY). Strains were evaluated by PCR and PFGE for PVL, mecA genes, and phenotypic analysis.

Results

Sixty-two percent of SA strains were mecA positive and 73% contained PVL. Strain differences between baseline and post baseline SA in treatment failure patients were not detected. ABSSI SA isolates were comprised of 61% MRSA, 53% CIP non-susceptible (NS), and 49% LVX NS strains. MIC values are presented below for aerobic isolates with >10 isolates per organism group. The MIC₉₀ values against all SA for VAN, LNZ, TIG, GEN, ERY, OXA were 0.5, 2, 0.12, 0.5, >8, and >4 µg/mL, respectively.

Organism	Number of Strains	DLX MIC _{50/90}	LVX MIC _{50/90}	CIP MIC _{50/90}
SA – All	188	0.015/0.12	1/4	4/16
MRSA	115	0.06/0.12	4/4	8/16
MSSA	73	0.004/0.06	0.12/4	0.25/8
CIP NS	100	0.06/0.12	4/4	8/16
LVX NS	93	0.06/0.12	4/8	8/16
β-hemolytic streptococci	17	0.008/0.015	0.5/2	0.5/2
Gram-negative bacilli	17	0.06/0.06	ND	0.03/0.03

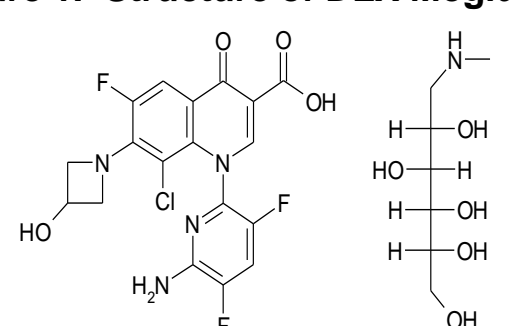
Conclusion

DLX was >32 fold more potent than LVX and CIP, more potent than VAN and LNZ, and equally potent to TIG against strains of SA isolated from this clinical study of ABSSI. DLX was equally potent to CIP against 17 strains of Gram-negative bacilli. These *in vitro* findings support development of DLX for the treatment of gram-positive and –negative infections, including those caused by strains resistant to currently available FQs.

Introduction

Delafloxacin (DLX, RX-3341) is an investigational fluoroquinolone active against Gram-positive and –negative bacteria, including methicillin- and quinolone-resistant strains of *Staphylococcus aureus* (MRSA, QRSA). In general, the *in vitro* antibacterial activity of DLX is more potent than that of levofloxacin (LVX) against most quinolone-susceptible pathogens. DLX is more active than LVX against most gram-positive pathogens, and notably is 64-fold more active than LVX against MRSA isolates, including LVX-nonsusceptible isolates. In addition, DLX has good activity against gram-negative organisms that are susceptible to LVX (1-3). A US Phase 2 clinical study was executed in order to investigate the efficacy and safety of delafloxacin for the treatment of ABSSI. Microbial isolates from skin and blood specimens were evaluated for *in vitro* susceptibility, and phenotypic and genetic typing.

Figure 1. Structure of DLX Meglumine



Methods / Results

Specimens from the ABSSI site (256 patients) were collected at Screening and sent to a local laboratory for microbiological Gram stain, culture, and susceptibility testing. Subcultures of identified bacterial isolates were sent to the central microbiology laboratory for confirmatory identification and susceptibility testing. If material was available for culture, samples were collected from the ABSSI site at the Follow-up and Late Follow-up visits. The specimens were obtained by one of the following means:

- A punch biopsy or aspirate of the leading edge of redness for subjects with cellulitis/erysipelas.
- Biopsy, needle aspiration, or surgically obtained specimens of purulent material from an infected wound or burn.
- Using sterile techniques that minimize potential isolation of normal skin flora, aspiration of purulent material from a cutaneous abscess.
- Swabs **were not** an accepted means for specimen collection.

Isolates were identified and tested for antimicrobial susceptibility utilizing CLSI broth microdilution methods (4-6). Antibacterials tested included DLX, levofloxacin (LVX), ciprofloxacin (CIP), moxifloxacin (MXF), oxacillin (OXA), tigecycline (TIG), ceftioxone (CTX), ceftazidime (CFZ), linezolid (LNZ), metronidazole (MET), imipenem (IMP), clindamycin (CLI), aztreonam (AZT), ampicillin (AMP), piperacillin/tazobactam (PIP/TAZ), tobramycin (TOB), linezolid (LNZ), vancomycin (VAN), gentamicin (GEN), and erythromycin (ERY) as appropriate. Strains were evaluated by PCR and PFGE for PVL, mecA genes, and phenotypic analysis.

Table 1. Activity Profile (µg/mL) of DLX and Quinolones Against *S. aureus* Overall and by Relevant Phenotypes

Organism	Drug	Phenotype ¹	Total N	Range	Mode	MIC ₅₀	MIC ₉₀
<i>S. aureus</i>	DLX	All	188	≤0.0005-2	0.002	0.015	0.12
		MRSA	115	0.001-2	0.06	0.06	0.12
		MSSA	73	≤0.0005-0.25	0.002	0.004	0.06
	CIP	All	100	0.002-2	0.06	0.06	0.12
		CIP S	88	≤0.0005-0.06	0.002	0.002	0.004
		LVX NS	93	0.015-2	0.06	0.06	0.12
	LVX S	All	95	≤0.001-0.06	0.002	0.002	0.008
		CIP NS	100	0.06-32	8	4	16
		MRSA	115	0.12-32	8	8	16
	MSSA	All	73	0.06-32	0.25	0.25	8
		CIP NS	100	2-32	8	8	16
		CIP S	88	0.06-1	0.25	0.25	0.5
LVX NS	All	93	4-32	8	8	16	
	LVX S	95	0.06-8	0.25	0.25	1	
	All	188	0.06-32	4	1	4	
MRSA	All	115	0.12-32	4	4	4	
	MSSA	73	0.06-16	0.12	0.12	4	
	CIP NS	100	0.25-32	4	4	4	
CIP S	All	88	0.06-1	0.12	0.12	0.25	
	LVX NS	93	2-32	4	4	8	
	LVX S	95	0.06-1	0.12	0.12	0.25	

¹MRSA: Methicillin-resistant, MSSA: Methicillin-susceptible, CIP NS: Ciprofloxacin non-susceptible, CIP S: Ciprofloxacin-susceptible, LVX NS: Levofloxacin non-susceptible, LVX S: Levofloxacin-susceptible

Table 2. Activity Profile (µg/mL) of DLX and Comparators Against *S. aureus* Overall and by Relevant Phenotypes

Organism	Drug	Phenotype ¹	Total N	Range	Mode	MIC ₅₀	MIC ₉₀
<i>S. aureus</i>	DLX	All	188	≤0.0005-2	0.002	0.015	0.12
		MRSA	115	0.001-2	0.06	0.06	0.12
		MSSA	73	≤0.0005-0.25	0.002	0.004	0.06
	CLI	All	188	≤0.03->16	0.12	0.12	0.12
		MRSA	115	≤0.03->16	0.12	0.12	0.12
		MSSA	73	≤0.03-0.5	0.12	0.12	0.12
	DAP	All	188	≤0.5-1	≤0.5	≤0.5	1
		MRSA	115	≤0.5-1	≤0.5	≤0.5	1
		MSSA	73	≤0.5-1	≤0.5	≤0.5	≤0.5
	ERY	All	188	0.25->8	>8	>8	>8
		MRSA	115	0.25->8	>8	>8	>8
		MSSA	73	0.25->8	0.25	0.5	>8
GEN	All	188	0.12-1	0.25	0.25	0.5	
	MRSA	115	0.12-1	0.25	0.25	0.5	
	MSSA	73	0.12-0.5	0.25	0.25	0.5	
LNZ	All	188	1-4	2	2	2	
	MRSA	115	1-2	2	2	2	
	MSSA	73	1-4	2	2	2	
OXA	All	188	≤0.06->4	>4	>4	>4	
	MRSA	115	4->4	>4	>4	>4	
	MSSA	73	≤0.06-2	0.5	0.25	0.5	
TIG	All	188	0.06-0.5	0.06	0.06	0.12	
	MRSA	115	0.06-0.5	0.06	0.06	0.12	
	MSSA	73	0.06-0.5	0.12	0.12	0.25	
VAN	All	188	≤0.25-2	0.5	0.5	0.5	
	MRSA	115	≤0.25-1	0.5	0.5	0.5	
	MSSA	73	0.5-2	0.5	0.5	0.5	

¹MRSA: Methicillin-resistant, MSSA: Methicillin-susceptible.

Table 3. Activity Profile (µg/mL) of Delafloxacin and Quinolones Against Coagulase-Negative Staphylococci Overall and by Relevant Phenotypes

Organism ¹	Drug	Phenotype ²	Total N	Range	Mode	MIC ₅₀	MIC ₉₀
Coagulase-negative staphylococci ¹	DLX	All	19	0.001-2	0.002	0.004	1
		MR	7	0.001-2	0.015	NA ³	NA
		MS	12	0.002-1	0.002	0.004	0.5
	CIP	All	19	0.06-32	0.12	0.12	>32
		MR	7	0.06-32	0.12	NA	NA
		MS	12	0.12-32	0.12	0.12	>32
	LVX	All	19	0.06-32	0.12	0.12	>32
		MR	7	0.06-32	0.12	NA	NA
		MS	12	0.12-32	0.12	0.12	>32

¹Coagulase-negative staphylococci includes: *S. epidermidis* (n=14), *S. capitis* (n=1), and *S. lugdunensis* (n=4)

²MR: Methicillin-resistant, MS: Methicillin-susceptible; ³NA: Number of isolates not sufficient for this calculation.

Table 4. Activity Profile (µg/mL) of Delafloxacin and Comparator Drugs Against Coagulase-Negative Staphylococci Overall and by Relevant Phenotypes

Organism ¹	Drug	Phenotype ²	Total N	Range	Mode	MIC ₅₀	MIC ₉₀
<i>S. aureus</i>	DLX	All	19	0.001-2	0.002	0.004	1
		MR	7	0.001-2	0.015	NA ³	NA
		MS	12	0.002-1	0.002	0.004	0.5
	CLI	All	19	0.06->16	0.06	0.06	1
		MR	7	0.06->16	0.06	0.12	>16
		MS	12	0.06-1	0.06	0.06	1
	DAP	All	19	≤0.5-1	≤0.5	≤0.5	1
		MR	7	≤0.5-1	≤0.5	≤0.5	1
		MS	12	≤0.5-1	≤0.5	≤0.5	≤0.5
	ERY	All	19	≤0.12->8	>8	1	>8
		MR	7	≤0.12->8	>8	>8	>8
		MS	12	≤0.12->8	≤0.12	0.25	>8
GEN	All	19	≤0.06-0.12	≤0.06	≤0.06	0.12	
	MR	7	≤0.06-0.12	≤0.06	≤0.06	0.12	
	MS	12	≤0.06-0.12	≤0.06	≤0.06	0.12	
LNZ	All	19	≤0.5-2	1	1	1	
	MR	7	≤0.5-1	1	1	1	
	MS	12	≤0.5-2	1	1	1	
OXA	All	19	≤0.06->4	0.5	0.5	>4	
	MR	7	0.5->4	>4	>4	>4	
	MS	12	≤0.06-0.5	0.12	0.12	0.5	
TIG	All	19	0.03-0.5	0.12	0.12	0.5	
	MR	7	0.06-0.5	0.25	0.25	0.5	
	MS	12	0.03-0.5	0.12	0.12	0.25	
VAN	All	19	≤0.25-2	1	1	1	
	MR	7	0.5-1	1	1	1	
	MS	12	≤0.25-2	1	1	1	

¹Coagulase-negative staphylococci includes: *S. epidermidis* (n=14), *S. capitis* (n=1), and *S. lugdunensis* (n=4)

²MR: Methicillin-resistant, MS: Methicillin-susceptible; ³NA: Number of isolates not sufficient for this calculation.

Results

Table 5. Activity Profile (µg/mL) of Delafloxacin and Comparator Drugs Against Beta-Hemolytic Streptococci

Organism ¹	Drug	Total N	Range	Mode	MIC ₅₀	MIC ₉₀
Beta-haemolytic streptococci	DLX	17	≤0.002-0.015	0.008	0.008	0.015
	CIP	17	0.12-2	0.5	0.5	2
	LVX	17	0.03-2	0.5	0.5	2
	MXF	17	0.03-0.25	0.12	0.12	0.25
	CTX	17	≤0.015-0.25	≤0.015	0.03	0.06
	CLI	17	≤0.015->0.5	0.06	0.06	0.06
	DAP	17	≤0.03-0.5	0.06	0.06	0.5
	ERY	17	≤0.015->0.5	0.03	0.03	>0.5
	LNZ	17	≤0.25-1	1	1	1
	PEN	17	≤0.03-0.12	≤0.03	≤0.03	0.06
	TIG	17	≤0.008-0.06	0.03	0.03	0.03
	VAN	17	0.12-0.5	0.25	0.25	0.5

¹Beta-haemolytic streptococci includes: *S. agalactiae* (n=5), *S. pyogenes* (n=8), *Streptococcus* Group F (n=2), and *Streptococcus* Group G (n=2)

Table 6. Antimicrobial MICs (µg/mL) for Other Aerobic Gram-Positive Organisms

Organism	DLX	LVX	MXF	CTX	CIP	CLI	DAP	ERY	GEN	LNZ	PEN	TIG	VAN
<i>Corynebacterium</i> spp.	0.008	0.06	0.03	1	0.06	>0.5	≤0.03	>0.5	-	0.5	0.12	0.03	0.25
<i>Dermabacter hominis</i>	0.015	1	0.25	0.03	1	0.06	>0.5	>0.5	-	0.5	0.25	0.03	0.25
<i>Enterococcus faecalis</i>	0.06	1	-	-	1	16	2	2	16	1	-	0.06	2
<i>Enterococcus faecalis</i>	>8	>32	-	-	>32	>16	4	>8	>16	2	-	0.12	>16
<i>Enterococcus faecalis</i>	0.03	0.5	-	-	0.5	>16	2	>8	8	1	-	0.06	0.5
<i>Enterococcus faecalis</i>	0.03	0.5	-	-	0.25	>16	1	>8	8	1	-	0.06	0.5
<i>Enterococcus faecalis</i>	0.004	0.25	-	-	0.5	>16	4	>8	>16	1	-	0.06	0.5
<i>Lactobacillus</i> species	0.015	4	0.12	0.12	4	≤0.015	>0.5	≤0.015	-	0.5	≤0.03	≤0.008	0.5
<i>Streptococcus anginosus</i>	0.004	0.25	0.12	0.12	0.25	≤0.015	0.25	0.03	-	1	≤0.03	≤0.008	0.5