CHARACTERIZATION AND IN VITRO ACTIVITY OF DELAFLOXACIN (DLX) AGAINST ISOLATES FROM A PHASE 3 STUDY OF ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS (ABSSSI)

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Revised Abstract

BACKGROUND: Delafloxacin (DLX) is an investigational anionic fluoroquinolone (FQ) antibiotic with broad spectrum activity against an array of bacteria, including Gram-positive organisms (MSSA, MRSA, *Streptococcus pyogenes*, enterococci), Gram-negative organisms (*Escherichia coli, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*), atypical organisms, and anaerobes such as *Bacteroides fragilis* and *Clostridium* spp.

METHODS: Isolates from a global study of ABSSSI (660 patients) were identified and tested for antimicrobial susceptibility utilizing CLSI M07-A10 and M02-A12 broth microdilution and agar method and reference standards M100-S25, 2015. Antibacterials tested included DLX, levofloxacin (LVX), ciprofloxacin (CIP), oxacillin (OXA), tigecycline (TIG), linezolid (LNZ), vancomycin (VAN), clindamycin (CLI), and erythromycin (ERY). Strains were evaluated by PCR for PVL and for QRDR analysis.

RESULTS: 50.9% of SA strains were MRSA and 94.8% contained PVL. Strain differences between baseline and post baseline SA in treatment failure patients were not detected for DLX. ABSSSI SA isolates were comprised of 44.4% CIP non-susceptible (NS), and 43.6% LVX NS strains, while 72% of MRSA strains were CIP resistant. MIC values are presented below for aerobic isolates with >10 isolates per organism group:

Baseline Organism	Number of Patients	DLX $MIC_{50/90}$	LVX $MIC_{50/90}$	CIP $MIC_{50/90}$
SA – All	324	0.008/0.25	0.25/4	0.5/>8
MRSA	169	0.12/0.25	4/8	8/>8
MSSA	156	0.008/0.12	0.25/4	0.25/8
CIP NS	150	0.25/0.25	4/8	>8/>8
LVX NS	147	0.25/0.25	4/8	>8/>8
S. epidermidis	38	0.008/0.25	0.25/4	0.25/8
S. pyogenes	13	0.015/0.03	0.5/0.5	0.25/0.5
K. pneumoniae	23	0.12/0.25	≤0.06/0.12	≤0.06/0.12
All gram negative bacilli	81	0.12/0.5	≤0.06/0.5	≤0.06/0.12

The MIC_{90} values against all SA for VAN, LNZ, TIG, CLI, ERY, OXA were 1, 1, 0.12, ≤0.06, >8, and 2 µg/mL, respectively.

CONCLUSIONS: DLX was 32 fold more potent than LVX and CIP and more potent than VAN and LNZ, against strains of MRSA isolated from this clinical study of ABSSSI. DLX was equally potent to LVX against strains from 81 patients with baseline 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) is an anionic investigational antibiotic of the fluoroquinolone class distinguished by excellent antibacterial activity against gram-positive organisms including both methicillin susceptible *S. aureus* and MRSA, while retaining good activity against gram negative organisms. The chemical name of delafloxacin is 1 deoxy-1-(methylamino)-D-glucitol, 1-(6-amino-3,5-difluoro-2-pyrdinyl)-8-chloro-6-fluoro-7-(3-hydroxy-1-azetidinyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate (salt).

Delafloxacin is active against an array of bacteria, including Gram-positive organisms (methicillin-susceptible *Staphylococcus aureus* [MSSA], MRSA, *Streptococcus pyogenes*, enterococci), Gram-negative organisms (*Escherichia coli, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*), atypical organisms, and anaerobes (*Bacteroides fragilis* and *Clostridium* spp.). Delafloxacin is more active than levofloxacin against most Gram-positive pathogens, and notably has been found to have an MIC_{90} at least 32-fold more active than levofloxacin against MRSA isolates. Delafloxacin has good activity against Gram-negative organisms that are susceptible to levofloxacin, including species responsible for surgical site infections, community and nosocomial respiratory tract infections, urinary tract infections, blood stream infections, skin and skin structure infections, and anaerobic infections. Delafloxacin is being developed as a sterile 300-mg lyophilized formulation for intravenous (IV) administration as well as an oral 450-mg tablet formulation that provides similar exposure to the IV dose.

Methods

A Phase 3 ABSSSI study was performed at sites in North America and Europe comparing 300 mg intravenous delafloxacin to 15 mg/kg vancomycin + aztreonam BID for 5 - 14 days.[1]

Deep cultures of the primary infection site were obtained from patients at Screening by either punch biopsy, aspirate of leading edge, surgically obtained specimens of purulent material, or deep sterile swab inside cavity of post-incision and drainage wound, abscess or wound. Specimens were sent to a local laboratory for initial identification and frozen in duplicate for later transport to the central microbiological laboratory.

Reference MIC testing methodologies were Clinical and Laboratory Standards Institute using validated frozen-form reference broth microdilution panels and disk diffusion reagents. Cation-adjusted Mueller-Hinton broth (± supplemental 2 - 5% lysed horse blood for testing of streptococci and additional drug-specific supplementations specified by CLSI, as required) was used and QC organisms and ranges utilized for antimicrobial susceptibility tests were performed as specified in CLSI documents M07-A10, M2-A12 and M100-S25.[2, 3]

Identification confirmation of pathogens to genus and species level was performed by colonial morphology, Gram staining characteristics and rapid tests such as catalase, coagulase, bile solubility, PYR test, latex agglutination methods, oxidase reaction, indole reaction and other biochemical or serotype tests, as appropriate or specified by recognized authoritative references.[4] Automated identification systems[5] were also utilized as needed.

Results

Table 1

ACTIVITY PROFILE (µg/mL) OF DELAFLOXACIN AND COMPARATORS AGAINST *S. AUREUS* OVERALL AND BY RELEVANT PHENOTYPES

Drug	Phenotype[1]	Total N	Range	Mode	MIC50	MIC90
DLX	ALL	344	≤0.004 - 4	0.008	0.008	0.25
	MRSA	175	≤0.004 - 4	0.25	0.12	0.25
	MSSA	171	≤0.004 - 0.5	0.008	0.008	0.12
	CIP NS	153	0.015 - 4	0.25	0.25	0.25
	LVX NS	150	0.03 - 4	0.25	0.25	0.25
CIP	ALL	344	0.12 - >8	0.25	0.25	>8
	MRSA	175	0.25 - >8	8	>8	>8
	MSSA	171	0.12 - >8	0.25	0.25	8
	CIP NS	153	2 - >8	>8	>8	>8
	LVX NS	150	4 - >8	>8	>8	>8
LVX	ALL	344	0.12 - >8	0.25	0.25	4
	MRSA	175	0.12 - >8	4	4	8
	MSSA	171	0.12 - >8	0.25	0.25	4
	CIP NS	153	0.12 - >8	4	4	8
	LVX NS	150	2 - >8	4	4	8
VAN	ALL	344	0.5 - 2	0.5	0.5	1
	MRSA	175	0.5 - 2	0.5	0.5	1
	MSSA	171	0.5 - 1	0.5	0.5	1
	CIP NS	153	0.5 - 2	0.5	0.5	1
	LVX NS	150	0.5 - 2	0.5	0.5	1
LNZ	ALL	344	0.5 - 2	1	1	1
	MRSA	175	0.5 - 1	1	1	1
	MSSA	171	0.5 - 2	1	1	1
	CIP NS	153	0.5 - 1	1	1	1
	LVX NS	150	0.5 - 1	1	1	1
TIG	ALL	344	0.03 - 0.25	0.06	0.06	0.12
	MRSA	175	0.03 - 0.25	0.06	0.06	0.12
	MSSA	171	0.03 - 0.25	0.06	0.06	0.12
	CIP NS	153	0.03 - 0.25	0.06	0.06	0.12
	LVX NS	150	0.03 - 0.25	0.06	0.06	0.12
CLI	ALL	344	≤0.06 - >8	≤0.06	≤0.06	≤0.06
	MRSA	175	≤0.06 - >8	≤0.06	≤0.06	≤0.06
	MSSA	171	≤0.06 - >8	≤0.06	≤0.06	≤0.06
	CIP NS	153	≤0.06 - >8	≤0.06	≤0.06	≤0.06
	LVX NS	150	≤0.06 - >8	≤0.06	≤0.06	≤0.06
ERY	ALL	344	0.25 - >8	>8	>8	>8
	MRSA	175	0.25 - >8	>8	>8	>8
	MSSA	171	0.25 - >8	0.25	0.5	>8
	CIP NS	153	0.25 - >8	>8	>8	>8
	LVX NS	150	0.25 - >8	>8	>8	>8
OXA	ALL	344	≤0.25 - >2	>2	>2	>2
	MRSA	175	≤0.25 - >2	>2	>2	>2
	MSSA	171	≤0.25 - >2	0.5	0.5	1
	CIP NS	153	≤0.25 - >2	>2	>2	>2
	LVX NS	150	≤0.25 - >2	>2	>2	>2

(1) MRSA = methicillin resistant; MSSA = Methicillin-susceptible; CIP NS = ciprofloxacin non-susceptible; LVX NS = levofloxacin nonsusceptible. N = number of strains at baseline; CIP = ciprofloxacin; LVX = levofloxacin; VAN = vancomycin; LNZ = linezolid; TIG = tigecycline; CLI = clindamycin; ERY = erythromycin; OXA = oxacillin; NS = nonsusceptible

Table 2

ACTIVITY PROFILE (µg/mL) OF DELAFLOXACIN AND COMPARATORS AGAINST COAGULASE-NEGATIVE STAPHYLOCOCCI (CoNS) OVERALL AND BY RELEVANT PHENOTYPES

Drug	Phenotype	Total N	Range	Mode	MIC50	MIC90
DLX	ALL	88	≤0.004 - 1	0.008	0.008	0.25
	MR	26	≤0.004 -1	0.008	0.015	0.5
	MS	62	≤0.004 - 0.25	0.008	0.008	0.015
	CIP NS	13	0.008 - 1	0.25	0.25	1
	LVX NS	11	0.12 - 1	0.25	0.25	1
CIP	ALL	88	≤0.06 - >8	0.25	0.25	8
	MRSA	26	0.12 - >8	0.25	0.25	>8
	MSSA	62	≤0.06 - >8	0.25	0.25	0.5
	CIP NS	13	2 - >8	>8	>8	>8
	LVX NS	11	4 - >8	>8	>8	>8
LVX	ALL	88	≤0.06 - >8	0.25	0.25	4
	MRSA	26	0.12 - >8	0.25	0.25	>8
	MSSA	62	≤0.06 - >8	0.25	0.25	0.25
	CIP NS	13	1 - >8	>8	8	>8
	LVX NS	11	4 - >8	>8	8	>8
VAN	ALL	88	0.25 - 2	1	1	2
	MRSA	26	0.25 - 2	1	1	2
	MSSA	62	0.25 - 2	1	1	1
	CIP NS	13	0.5 - 2	1	1	2
	LVX NS	11	0.5 – 2	1	1	2
LNZ	ALL	88	≤0.06 – 2	0.5	0.5	1
	MRSA	26	0.5 - 1	0.5	0.5	1
	MSSA	62	≤0.06 – 2	0.5	0.5	1
	CIP NS	13	0.5 - 1	0.5	0.5	1
	LVX NS	11	0.5 - 1	0.5	0.5	1
TIG	ALL	88	≤0.015 – 0.5	0.12	0.06	0.25
	MRSA	26	0.03 - 0.5	0.12	0.12	0.25
	MSSA	62	≤0.015 – 0.5	0.06	0.06	0.25
	CIP NS	13	0.03 - 0.5	0.12	0.12	0.25
	LVX NS	11	0.03 - 0.5	0.12	0.12	0.5
CLI	ALL	88	≤0.06 - >8	≤0.06	≤0.06	>8
	MRSA	26	≤0.06 - >8	≤0.06	≤0.06	>8
	MSSA	62	≤0.06 - >8	≤0.06	≤0.06	0.12
	CIP NS	13	≤0.06 - >8	≤0.06	0.12	>8
	LVX NS	11	≤0.06 - >8	≤0.06	0.12	>8
ERY	ALL	88	≤0.06 - >8	>8	0.25	>8
	MRSA	26	0.12 - >8	>8	>8	>8
	MSSA	62	≤0.06 - >8	0.12	0.25	>8
	CIP NS	13	≤0.06 - >8	>8	>8	>8
	LVX NS	11	≤0.06 - >8	>8	>8	>8
OXA	ALL	88	≤0.25 - >2	≤0.25	≤0.25	>2
	MRSA	26	0.5 - >2	>2	>2	>2
	MSSA	62	≤0.25 - >1	≤0.25	≤0.25	≤0.25
	CIP NS	13	≤0.25 - >2	>2	>2	>2
	LVX NS	11	≤0.25 - >2	>2	>2	>2

N = number of strains at baseline
CoNS includes *S. capitis* (3), *S. caprae* (2), *S. epidermidis* (44), *S. haemolyticus* (9), *S. hominis* (10), *S. lugdunensis* (10), *S. saprophyticus* (1), *S. simulans* (6), and *S. warneri* (3).

Table 3

ACTIVITY PROFILE (µg/mL) OF DELAFLOXACIN AND COMPARATORS AGAINST BETA-HEMOLYTIC STREPTOCOCCI OVERALL AND BY RELEVANT PHENOTYPES

Drug	Phenotype	Total N	Range	Mode	MIC50	MIC90
DLX	ALL	58	≤0.004 – 0.06	0.015	0.015	0.03
	CIP NS	58	≤0.004 – 0.06	0.015	0.015	0.03
CIP	ALL	58	≤0.06 – 1	0.5	0.5	1
	CIP NS	58	≤0.06 – 1	0.5	0.5	1
LVX	ALL	58	≤0.06 – 1	0.5	0.5	1
	CIP NS	58	≤0.06 – 1	0.5	0.5	1
VAN	ALL	58	≤0.12 – 1	0.5	0.5	0.5
	CIP NS	58	≤0.12 – 1	0.5	0.5	0.5
LNZ	ALL	58	≤0.06 – 2	1	1	1
	CIP NS	58	≤0.06 – 2	1	1	1
TIG	ALL	58	≤0.015 – 0.25	0.03	0.03	0.12
	CIP NS	58	≤0.015 – 0.25	0.03	0.03	0.12
CLI	ALL	58	≤0.06 – >8	≤0.06	≤0.06	0.25
	CIP NS	58	≤0.06 – >8	≤0.06	≤0.06	0.25
ERY	ALL	58	≤0.06 – >8	≤0.06	≤0.06	>8
	CIP NS	58	≤0.06 – >8	≤0.06	≤0.06	>8
OXA	ALL	58	≤0.25 – 1	≤0.25	≤0.25	≤0.25
	CIP NS	58	≤0.25 – 1	≤0.25	≤0.25	≤0.25

N = number of strains at baseline
Beta-hemolytic streptococci includes *S. agalactiae* (8), *S. anginosus* (20), *S. constellatus* (8), *S. dysgalactiae* (6), *S. pyogenes* (16).

Figure 1

DELAFLOXACIN MIC DISTRIBUTIONS AGAINST *S. AUREUS* BY PHENOTYPE

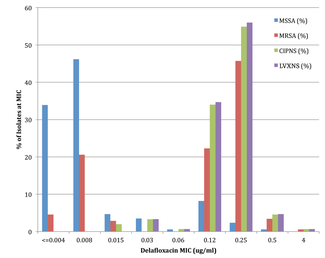

Table 4

ACTIVITY PROFILE FOR GRAM NEGATIVE STRAINS (µg/mL)

Organism	Total N	MIC, MIC Range or MIC50/90 (µg/mL)											
		DLX	AMI	AZT	CEF	CTX	CIP	COL	DOX	LVX	MER	PIP-TAZ	TMP-SMX
Acinetobacter johnsonii	1	0.03	≤0.5	4	4	2	0.12	1	≤0.12	0.12	0.25	≤0.5	≤0.5
Citrobacter amalonaticus	1	0.12	1	1	≤0.25	≤0.25	≤0.06	1	2	≤0.06	≤0.12	2	≤0.5
Citrobacter freundii	1	0.12	2	≤0.5	0.25	≤0.25	≤0.06	1	2	≤0.06	≤0.12	2	≤0.5
Citrobacter koseri	1	0.06	≤0.5	≤0.5	≤0.12	≤0.25	≤0.06	1	0.5	≤0.06	≤0.12	2	≤0.5
Eikenella corrodens	5	0.008-0.03	4-16	1- 32	≤0.12-8	≤0.25-0.5	≤0.06	0.25-4	0.25-1	≤0.06	≤0.12	≤0.5-4	≤0.5-1
Enterobacter cloacae	8	0.06-2	1-2	≤0.5-16	0.25-4	≤0.25-16	≤0.06-0.12	1->8	1-4	≤0.06-0.25	≤0.12	2-4	≤0.5-0.5
Enterobacter cloacae species complex	1	0.12	2	≤0.5	≤0.12	≤0.25	≤0.06	2	2	≤0.06	≤0.12	≤0.5	≤0.5
Escherichia coli	14	0.06/2	2/8	≤0.5/≤0.5	≤0.12/25	≤0.25/≤0.25	≤0.06/0.5	1/2	1/2	≤0.06/1	≤0.12/≤0.12	2/4	≤0.5/>4
Haemophilus parainfluenzae	7	≤0.004-0.015	≤.5-4	≤0.5	≤0.12	≤0.25	≤0.06	2	0.5-2	≤0.06	≤0.12	≤0.5	≤0.5-2
Klebsiella oxytoca	4	0.06-0.25	1-2	≤0.5-2	≤0.12-1	≤0.25-8	≤0.06-0. 25	1-2	0.5-2	≤0.06-1	≤0.12-0.5	1-2	≤0.5->4
Klebsiella pneumoniae	23	0.12/0.25	1/1	≤0.5/≤0.5	0.25/0.5	≤0.25/≤0.25	≤0.06/0.12	1/2	1/4	≤0.06/0.12	≤0.12/≤0.12	4/8	≤0.5/≤0.5
Leclercia adecarboxylata	1	0.06	≤0.5	≤0.5	≤0.12	≤0.25	≤0.06	1	0.5	≤0.06	≤0.12	≤0.5	≤0.5
Morganella morganii	1	0.5	4	≤0.5	0.25	≤0.25	≤0.06	>8	16	0.12	≤0.12	≤0.5	≤0.5
Proteus mirabilis	2	0.06	4	≤0.5	≤0.12	≤0.25	≤0.06	>8	16->16	≤0.06	≤0.12	≤0.5	≤0.5
Pseudomonas aeruginosa	7	0.12-4	1-16	≤0.5-32	0.5-8	0.5->32	≤0.06-1	1-2	4->16	0.25-4	≤0.12-2	≤0.5-32	≤0.5->4
Raoultella ornithinolytica	1	0.06	1	≤0.5	≤0.12	≤0.25	≤0.06	1	1	≤0.06	≤0.12	2	≤0.5
Serratia marcescens	2	0.5-4	2	≤0.5	≤0.12-0.25	≤0.25	≤0.06-0.5	>8	2-8	0.12-1	≤0.12	2	≤0.5-2
Stenotrophomonas maltophilia	1	1	-	>32	8	>32	2	2	0.5	1	>16	16	≤0.5

N = number of strains at baseline; AMI = amikacin; AZT = aztreonam, CEF = ceftazidime; CTX= ceftriaxone; CIP = ciprofloxacin; COL = colistin; DOX = doxycycline; MER = meropenem; Pip-Taz = piperacillin/tazobactam; TMP-SMX = trimethoprim/sulfamethoxazole

Table 5

PHENOTYPIC CHARACTERIZATION OF *S. AUREUS* STRAINS (n=179)

Organism	MRSA / PVL n(%)				PVL n(%)
	+ / +	+ / -	- / +	- / -	+ / -
S. aureus	165 (92.2)	9 (5.0)	5 (2.8)	0	170 (95) / 9 (5)

Conclusions

- Delafloxacin was >32 fold more potent than levofloxacin and ciprofloxacin, more potent than vancomycin and linezolid against 344 strains of SA isolated from this clinical study of ABSSSI.
- Delafloxacin was equally potent to ciprofloxacin against strains of Gram-negative bacilli from 81 patients.
- 94.8% percent of MRSA strains were positive for PVL.
- Against *S. aureus* (n = 344) the delafloxacin MICs ranged from ≤0.004 - 4µg/mL, with an MIC_{90} of 0.25 µg/mL.
- For MRSA (n = 175) the delafloxacin MICs ranged from ≤0.004 - 4 µg/mL, with an MIC_{90} of 0.25 µg/mL.
- For MSSA (n = 171) the delafloxacin MICs ranged from ≤0.004 - 0.5 µg/mL, with an MIC_{90} of 0.12 µg/mL.
- In comparison, the MIC90's for ciprofloxacin against MRSA and MSSA were >8 and 8 µg/mL, respectively. Levofloxacin's MIC_{90}'s for MRSA and MSSA were 8 and 4 µg/ml, respectively.
- Against ciprofloxacin and levofloxacin-non-susceptible(NS)populations delafloxacin MIC_{90}'s were 0.25.
- For all *S. aureus* considered together there was a bimodal distribution in the delafloxacin MIC distribution.

References

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