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Evaluation of Delafloxacin Activity and Treatment Outcome for Phase 3 Acute Bacterial Skin and Skin Structure Infection Clinical Trial Anaerobic Isolates

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Abstract

- **Background**: Delafloxacin (DLX) is a broad-spectrum fluoroquinolone (FQ) antibacterial approved in 2017 by the Food and Drug Administration for treatment of acute bacterial skin and skin structure infections (ABSSSIs). DLX is in clinical development for community-acquired bacterial pneumonia (CABP). In this study, *in vitro* susceptibility (S) for DLX and comparator agents for gram-negative (GN) and gram-positive (GP) anaerobic isolates from Phase 3 ABSSSI clinical trials were determined and compared with the microbiologic response for evaluable isolates.
- **Methods**: A total of 84 anaerobic isolates were collected during Phase 3 ABSSSI clinical trials and 9 additional *Bacteroides fragilis* (BF) were collected as part of the 2017 SENTRY surveillance program. The isolates tested included 11 BF, 13 *Clostridium perfringens* (CP), and other species with <10 isolates (Table 1). Isolate identifications were confirmed by molecular methods. Susceptibility testing was performed according to CLSI agar dilution methodology (M11, 2012). Other antimicrobials tested included clindamycin (CD), metronidazole (MTZ), and moxifloxacin (MXF). In addition, the activity of DLX and MXF were compared at standard pH 7.0 and at pH 6.0.
- **Results**: DLX had the lowest $MIC_{50/90}$ values against both GP and GN species and was 32-fold more active than MXF for all organisms. For BF, DLX was 4- to 16-fold more active than the other comparators. For CP, DLX was 32- to 64-fold more active than the 3 comparators. When comparing the activity of DLX and MXF at pH 6.0 vs. pH 7.0, DLX had the same $MIC_{50/90}$ values while MXF $MIC_{50/90}$ values were 2-fold less active at the lower pH (Table 1). Of the 84 clinical trial isolates, 21 were recovered from subjects in the microbiologically evaluable-at-follow-up (MEFU) population. All of the subjects had a favorable microbiological response (presumed eradication) at follow-up.
- **Conclusions**: DLX demonstrated potent *in vitro* antibacterial activity against anaerobic isolates tested, including BF and CP, and was more active than MXF. For all isolates combined, DLX activity was unchanged at lower pH while MXF MIC values increased 2-fold. These data suggest that DLX activity remains potent at a lower pH, common at sites of infection.

Introduction

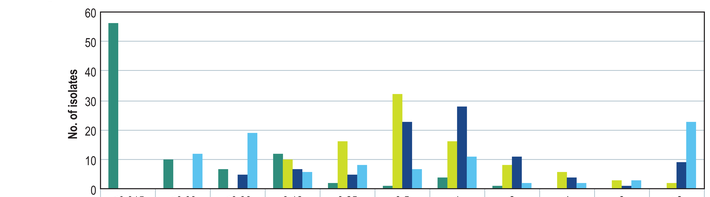
- Delafloxacin (DLX) is a broad-spectrum fluoroquinolone (FQ) antibacterial approved in 2017 by the Food and Drug Administration for treatment of acute bacterial skin and skin structure infections (ABSSSIs)
  - DLX is also in clinical development for community-acquired bacterial pneumonia (CABP)
- In ABSSSI, anaerobic isolates may also be recovered and may be significant pathogens, depending on site and type of infection
  - Anaerobic infection sites generally have a low pH

Table 1 Susceptibilities of delafloxacin and comparators tested against 93 anaerobic organisms and organism groups

Organism/ organism group Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	CLSI[a] %S	%I	%R
All [b] (n=93)						
Delafloxacin pH 7	≤0.015	0.12	≤0.015 to 2			
Moxifloxacin pH 7	0.5	4	0.12 to >8	88.2	6.5	5.4
Delafloxacin pH 6	≤0.015	0.12	≤0.015 to 1			
Moxifloxacin pH 6	1	8	≤0.06 to >8			
Clindamycin	0.5	>8	≤0.03 to >8	69.9	2.2	28.0
Metronidazole	1	8	≤0.06 to >32	90.3	0	9.7
Bacteroides fragilis (n=11)						
Delafloxacin pH 7	0.12	1	0.06 to 2			
Moxifloxacin pH 7	0.5	8	0.5 to >8	72.7	0	27.3
Clindamycin	0.5	1	0.25 to >8	90.9	0	9.1
Metronidazole	1	1	0.5 to 1	100	0	0
Clostridium perfringens (n=13)						
Delafloxacin pH 7	≤0.015	0.03	≤0.015 to 0.12			
Moxifloxacin pH 7	0.5	0.5	0.25 to 4	92.3	7.7	0
Clindamycin	1	2	0.06 to >8	92.3	0	7.7
Metronidazole	1	2	1 to 4	100	0	0

[a] CLSI M100 (2018)
[b] Organisms include: *Anaerococcus octavius* (1), *Bacteroides fragilis* (11), *B. thetaiotaomicron* (6), *B. uniformis* (1), *Bifidobacterium dentium* (1), *Clostridium innocuum* (1), *C. perfringens* (13), *C. sordellii* (2), *C. sporogenes* (1), *C. subterminale* (1), *C. tertium* (1), *Finegoldia magna* (7), *Fusobacterium nucleatum* (7), *Prevotella bivia* (2), *P. buccae* (2), *P. denticola* (6), *P. melaninogenica* (1), *P. nigrescens* (2), *P. oralis* (7), *P. timonensis* (1), unspeciated *Anaerococcus* (1), unspeciated *Clostridium* (1), unspeciated *Fusobacterium* (3), unspeciated *Prevotella* (2), unspeciated *Propionibacterium* (9), unspeciated *Veillonella* (1), *Veillonella atypica* (1), *V. parvula* (1)

Figure 1 MIC distributions of 93 anaerobes tested against delafloxacin and comparators moxifloxacin, metronidazole, and clindamycin



	≤0.015	≤0.03	≤0.06	0.12	0.25	0.5	1	2	4	8	>8
Delafloxacin	56	10	7	12	2	1	4	1			
Moxifloxacin	0	0	0	10	16	32	16	8	6	3	2
Metronidazole	0	0	5	7	5	23	28	11	4	1	9
Clindamycin	0	12	19	6	8	7	11	2	2	3	23

Table 3 Susceptibilities, monomicrobial or polymicrobial infection, and microbiologic outcomes of isolates from the delafloxacin treatment arm

Organism	Gram	MIC (mg/L) Delafloxacin	Moxifloxacin	Clindamycin	Metronidazole	Monomicrobial or polymicrobial infections at baseline	Treatment outcome
Clostridium perfringens	positive	≤0.015	0.5	0.5	1	Polymicrobial gram-positive	Presumed eradication
Clostridium perfringens	positive	≤0.015	0.5	1	2	Polymicrobial gram-positive	Presumed eradication
Prevotella oralis	negative	≤0.015	1	>8	0.5	Monomicrobial gram-negative	Presumed eradication
Prevotella bivia	negative	≤0.015	2	>8	8	Polymicrobial gram mixed	Presumed eradication
Fusobacterium nucleatum	negative	≤0.015	0.12	0.06	0.25	Polymicrobial gram mixed	Presumed eradication
Clostridium subterminale	positive	≤0.015	0.25	1	≤0.06	Monomicrobial gram-positive	Presumed eradication
Clostridium perfringens	positive	≤0.015	0.5	1	1	Polymicrobial gram-positive	Presumed eradication
Clostridium perfringens	positive	≤0.015	0.5	0.25	2	Polymicrobial gram positive	Presumed eradication
Clostridium tertium	positive	≤0.015	0.5	8	0.5	Polymicrobial gram positive	Presumed eradication
Prevotella oralis	negative	≤0.015	1	>8	0.5	Polymicrobial gram mixed	Presumed eradication
Unspeciated *Fusobacterium*	negative	≤0.015	0.25	0.06	≤0.06	Polymicrobial gram mixed	Presumed eradication
Prevotella oralis	negative	≤0.015	1	>8	0.12	Polymicrobial gram mixed	Presumed eradication
Fusobacterium nucleatum	negative	≤0.015	0.12	≤0.03	0.12	Polymicrobial gram-negative	Presumed eradication
Finegoldia magna	positive	≤0.015	0.12	0.12	0.25	Monomicrobial gram-positive	Presumed eradication
Unspeciated *Anaerococcus*	positive	≤0.015	2	0.06	4	Monomicrobial gram-positive	Presumed eradication
Unspeciated *Propionibacterium*	positive	0.03	0.25	0.06	>32	Polymicrobial gram positive	Presumed eradication
Unspeciated *Veillonella*	negative	0.06	0.12	0.06	2	Polymicrobial gram mixed	Presumed eradication
Clostridium sordellii	positive	0.06	0.5	>8	1	Polymicrobial gram-positive	Presumed eradication
Bacteroides thetaiotaomicron	negative	0.12	1	>8	1	Polymicrobial gram mixed	Presumed eradication
Bacteroides fragilis	negative	0.12	0.5	0.5	0.5	Polymicrobial gram-negative	Presumed eradication
Veillonella atypica	negative	1	4	0.12	4	Polymicrobial gram mixed	Presumed eradication

Delafloxacin and moxifloxacin were tested at pH 7.0.

Figure 2 Comparison of delafloxacin activity in medium at pH 6.0 or 7.0 when tested against 93 anaerobic isolates

pH 6.0 \ pH 7.0	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2
≤0.015	56	6						
0.03		4	3					
0.06			4	8				
0.12				4				
0.25					2			
0.5						1	3	
1							1	1

Delafloxacin MIC (mg/L)[a]

[a] Each shaded cell lists the number of isolates with the same MIC value at pH 6.0 and pH 7.0.

Figure 3 Comparison of moxifloxacin activity in medium at pH 6.0 or 7.0 when tested against 93 anaerobic isolates

pH 6.0 \ pH 7.0	0.12	0.25	0.5	1	2	4	8	>8
≤0.06	1							
0.12	2							
0.25	7	10						
0.5		6	19					
1			13	5				
2				11	5			
4					3	1		
8						5	1	
>8							2	2

Moxifloxacin MIC (mg/L)[a]

[a] Each shaded cell lists the number of isolates with the same MIC value at pH 6.0 and pH 7.0.

Table 2 Delafloxacin MIC when tested against 11 moxifloxacin-nonsusceptible isolates

Organism	Delafloxacin MIC (mg/L) ≤0.015	0.06	0.12	0.5	1	2
Bacteroides fragilis					2	1
Bacteroides thetaiotaomicron			2			
Clostridium perfringens			1			
Finegoldia magna		1		1	1	
Prevotella bivia	1					
Veillonella atypica					1	

Delafloxacin was tested at pH 7.0.
Moxifloxacin-nonsusceptible defined as moxifloxacin MIC >2 mg/mL (CLSI, 2018)

Materials and Methods

- In this study, *in vitro* susceptibility (S) for DLX and comparator agents for gram-negative (GN) and gram-positive (GP) anaerobic isolates from the 2 Phase 3 ABSSSI clinical trials were determined and compared with the microbiologic response for evaluable isolates
  - Delafloxacin and moxifloxacin were also tested at pH 6.0 to compare activities at the site of anaerobic infections
- A total of 84 anaerobic isolates were collected from both trial arms during 2 Phase 3 ABSSSI clinical trials
  - 9 additional *Bacteroides fragilis* (BF) isolates were included, which were collected in the 2017 SENTRY Antimicrobial Surveillance Program
  - The isolates tested included 11 BF, 13 *Clostridium perfringens* (CP), and other species with <10 isolates (Table 1)
    - Isolate identifications were confirmed by matrix-assisted laser desorption ionization- time of flight mass spectrometry or DNA sequencing, as needed
- Susceptibility testing was performed according to CLSI agar dilution methodology (pH 7.0) (M11, 2012)
  - Other antimicrobials tested included clindamycin (CD), metronidazole (MTZ), and moxifloxacin (MXF)
  - Interpretive criteria from M100 (2018) were applied where applicable
  - Delafloxacin and moxifloxacin were also tested with agar dilution at pH 6.0
- The activity of DLX and MXF were compared at standard pH 7.0 and at pH 6.0
- Susceptibilities of 21 isolates from the DLX treatment arm were compared with microbiologic outcome
  - Microbiologic outcomes were based on the results of baseline and post-baseline cultures at the follow-up visit
    - Documented eradicated: The baseline pathogen was absent in cultures of the original site of infection at the post-baseline visit; investigator-assessed response is not considered a determining factor for this microbiologic response definition
    - Presumed eradicated: There was no material available for culture or no culture was done and the patient had an investigator-assessed response of success (cure or improved with total or near resolution of signs and symptoms and no further antibiotics were needed)
    - Documented persisted: The baseline pathogen was present in cultures of the original site of infection at the visit; investigator-assessed response was not considered a determining factor for this microbiologic response definition
    - Presumed persisted: There was no material available for culture or no culture was done and the patient has an investigator-assessed response of failure

Results

- In the 2 Phase 3 ABSSSI clinical trials, 1,042 subjects had positive cultures at enrollment of which 84 had anaerobic isolates (8.1%)
- Activities of all antimicrobials tested against 93 anaerobic isolates are shown in Table 1
  - DLX had the lowest $MIC_{50/90}$ values ($MIC_{50/90}$, ≤0.015/0.12 mg/L) and was 32-fold more active than MXF
  - 88.2% of isolates were susceptible to MXF ($MIC_{50/90}$, 0.5/4 mg/L)
  - 69.9% of isolates were susceptible to CD ($MIC_{50/90}$, 0.5/>8 mg/L)
  - 90.3% were susceptible to MTZ ($MIC_{50/90}$, 1/8 mg/L)
  - For BF, DLX ($MIC_{50/90}$, 0.12/1 mg/L) was 4- to 16-fold more active than the other comparators
  - For CP, DLX ($MIC_{50/90}$, ≤0.015/0.03 mg/L) was 16- to 64-fold more active than the 3 comparators
- MIC distributions for DLX and comparators are shown in Figure 1
- When comparing the activity of DLX and MXF at pH 6.0 vs. pH 7.0, DLX had the same $MIC_{50/90}$ values ($MIC_{50/90}$, ≤0.015/0.12mg/L) while MXF $MIC_{50/90}$ values (pH 6 $MIC_{50/90}$, 1/8 mg/L) were 2-fold less active at the lower pH (Table 1)
  - DLX MIC was 1 dilution more active at pH 6.0 for 21/93 isolates (Figure 2)
  - MXF MIC was 1 dilution less active at pH 6.0 for 47/93 isolates (Figure 3)
    - Only 1 isolate, *Fusobacterium nucleatum*, had a lower MXF MIC at pH 6.0
- Table 2 shows the DLX MIC values of 11 MXF-nonsusceptible isolates
  - 11 isolates were MXF-nonsusceptible with MIC values >2 mg/L
  - 5 of these had DLX MIC values ≤0.12 mg/L
- Of the 84 clinical trial isolates, 21 were recovered from subjects in the DLX treatment arm and were microbiologically evaluable (Table 3)
  - All of the subjects had a favorable microbiological response of presumed eradication at the follow-up visit
  - 17/21 isolates were from polymicrobic infections
  - 1 isolate was MXF-resistant (MIC, >2 mg/L)

Conclusions

- DLX demonstrated potent *in vitro* antibacterial activity against species of anaerobic isolates tested, including BF and CP, and was more active than MXF
  - DLX was active against 5/11 MXF-resistant isolates with DLX MIC values <0.5 mg/L
- For all isolates combined, DLX MIC values were the same or slighter lower at pH 6.0 while almost half of MXF MIC values increased 2-fold at pH 6.0
- All 21 isolates in the DLX treatment arm were eradicated, including 1 MXF-resistant isolate
- These data suggest that DLX has activity in ABSSSI where anaerobes may be isolated
- More studies are needed to demonstrate the efficacy of DLX against anaerobic infections

Acknowledgements

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References

Clinical and Laboratory Standards Institute (2018). *M100Ed28E. Performance standards for antimicrobial susceptibility testing: 28th informational supplement.* Wayne, PA: CLSI.

Clinical and Laboratory Standards Institute (2012). *M11-A8. Methods for antimicrobial susceptibility testing of anaerobic bacteria; approved standard—eighth edition.* Wayne, PA: CLSI.