52nd ECCMID
Barcelona 2014

P1669

Efficacy of the Investigational Fluoroquinolone Finafloxacin against Resistant Staphylococci as Compared to Ciprofloxacin, Levofloxacin, and Moxifloxacin

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Introduction

Finafloxacin (FIN) is an investigational broad spectrum fluoroquinolone belonging to a new 8-cyano subclass. Finafloxacin contains a novel base component which confers improved antibacterial activity at slightly acidic pH (pH 5.0 – 6.0) conditions ususally reducing the antibacterial activity of other marketed fluoroquinolones drastically. Finafloxacin exhibited superior activity to comparator FQs against slowly growing, adherent and intracellular bacteria *in vitro,* including multi-resistant bacteria like MRSA. Finafloxacin displayed an outstanding safety profile in a wide range of *in vitro* and *in vivo* animal models aand in in human phase I-III studies with oral, intraveneous and topical formulations.

Purpose

Finafloxacin contains a novel base component which confers improved antibacterial activity under acidic conditions. In contrast, the activity of commercially available FQs is impaired at low pH. Both, acute and complicated bacterial skin and skin-structure infections are frequently caused by *Staphylococcus aureus*. To show that finafloxacin may be advantageous for treatment of such skin infections associated with inflammation and a low pH the activity of finafloxacin and comparators was evaluated against recent clinical isolates of *S. aureus* and *Staphylococcus epidermidis*.

Methods

237 recent clinical isolates of *S. aureus* and *S. epidermidis* were obtained from patients worldwide and enhanced with antibiotic-resistant strains from the NARSA collection. The tested strains contained 100 methicillin-resistant *S. aureus* (MRSA) and 50 methicillin-resistant *S. epidermidis* (MRSE) as well as 135 ciprofloxacin-resistant staphylococci. MICs of finafloxacin, ciprofloxacin (CFX), levofloxacin (LFX), moxifloxacin (MFX) and other comparators were determined by broth microdilution and susceptibility was determined and classified (susceptible (S), intermediate (I) and resistant (R) according to CLSI for all agents except for finafloxacin (no CLSI breakpoints available yet but for this study set at S≤1; I=2 and R≥4 mg/L) and tigecycline (FDA MIC-breakpoints used). Susceptibilities were evaluated at pH 5.8 and pH 7.2.

Results

Summary MIC and susceptibility data for methicillin resistant *S. aureus* (MRSA) (100) at pH 7.2 and pH 5.8 are shown in Table 1 and Figure 1a.

Table 1. Summary MIC and susceptibility of 100 MRSA isolates to finafloxacin and comparator fluoroquinolones at pH 7.2 and pH 5.8

Pathogen (N)	Cpd	pH	MIC (µg/ml)					Breakpoints (µg/ml) S|I|R	Percentage:		
			50% (median)	90%	Mode	MIN	MAX		S	I	R
S. aureus methicillin resistant (100)	FIN	5.8	0.5	4	0.06	0.06	16	≤1|2|≥4	79	9	12
		7.2	1	8	0.06	0.06	32		63	14	23
	CFX	5.8	16	>128	1	0.25	>128	≤1|2|≥4	33	0	67
		7.2	8	>128	0.25	0.12	>128		33	1	66
	LFX	5.8	8	64	0.5	0.25	>128	≤1|2|≥4	33	2	65
		7.2	4	32	4	0.12	>128		35	1	64
	MFX	5.8	4	32	0.12	0.06	128	≤0.5|1|≥2	35	0	65
		7.2	1	4	0.06	0.06	16		35	20	45

Summary MIC and susceptibility data for methicillin resistant *S. epidermidis* (MRSE) (50) at pH 7.2 and pH 5.8 are shown in Table 2 and Figure 1b.

Table 2. Summary MIC and susceptibility of 100 MRSE isolates to finafloxacin and comparator fluoroquinolones at pH 7.2 and pH 5.8

Pathogen (N)	Cpd	pH	MIC (µg/ml)					Breakpoints (µg/ml) S|I|R	Percentage:		
			50% (median)	90%	Mode	MIN	MAX		S	I	R
S. epidermidis Methicillin-resistant (50)	FIN	5.8	0.5	2	0.06	0.06	16	≤1|2|≥4	66	26	8
		7.2	1	8	1 / 4	0.06	32		58	8	34
	CFX	5.8	16	128	128	0.12	128	≤1|2|≥4	28	0	72
		7.2	4	64	64	0.06	64		32	8	60
	LFX	5.8	16	64	0.5 / 32	0.25	>128	≤1|2|≥4	28	4	68
		7.2	4	16	16	0.12	>128		32	8	60
	MFX	5.8	4	32	8	0.12	128	≤0.5|1|≥2	30	2	68
		7.2	1	4	2	0.06	32		38	18	44

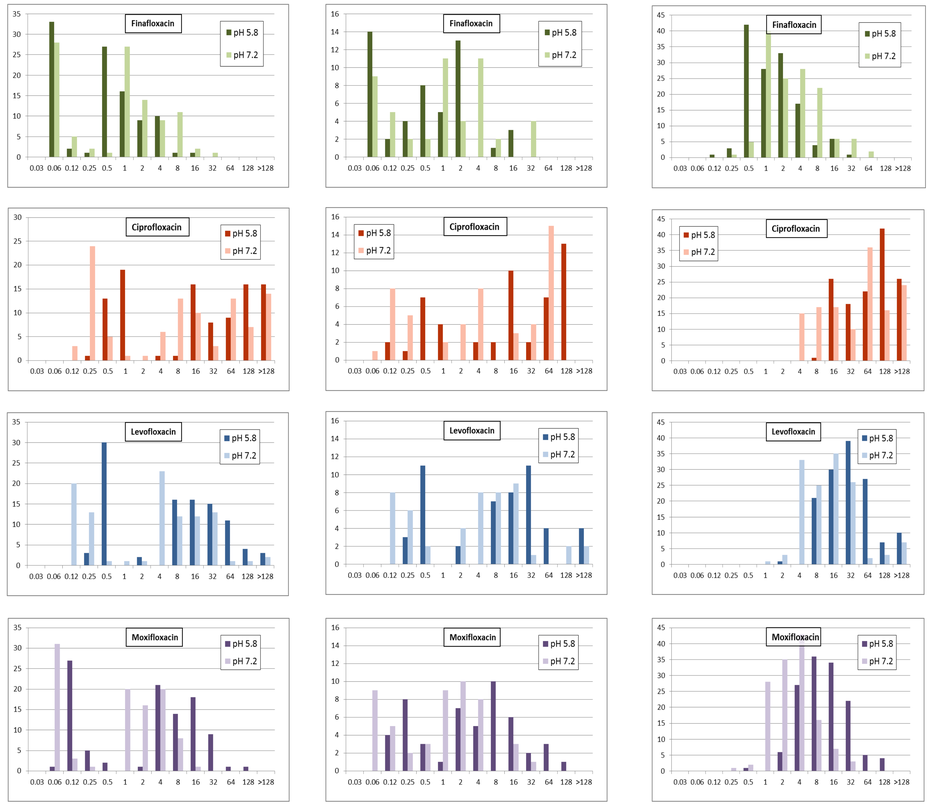
Summary MIC and susceptibility data for ciprofloxacin-resistant *S. epidermidis and S. aureus* (135) at pH 7.2 and pH 5.8 are shown in Table 3 and Figure 1c.

Table 3. Summary MIC and susceptibility of 135 ciprofloxacin-resistant Staphylococci isolates to finafloxacin and comparator fluoroquinolones at pH 7.2 and pH 5.8

Pathogen (N)	Cpd	pH	MIC (µg/ml)					Breakpoints (µg/ml) S|I|R	Percentage:		
			50% (median)	90%	Mode	MIN	MAX		S	I	R
Ciprofloxacin-resistant Staphylococci (135)	FIN	5.8	1	4	0.5	0.12	32	≤1|2|≥4	54.8	24.4	20.7
		7.2	2	16	1	0.25	64		34.1	18.5	47.4
	CFX	5.8	128	>128	16	8	>128	≤1|2|≥4	0	0	100
		7.2	64	>128	64	4	>128		0	0	100
	LFX	5.8	32	128	32	2	>128	≤1|2|≥4	0	0.7	99.3
		7.2	16	32	16	1	>128		0.7	2.2	97
	MFX	5.8	8	32	8	0.5	128	≤0.5|1|≥2	0.7	0	99.3
		7.2	4	8	4	0.25	32		2.2	20.7	77

Figure 1. MIC distribution of finafloxacin, ciprofloxacin, levofloxacin and moxifloxacin against **a**) 100 MRSA **b**) 50 MRSA **c**) 135 cipro-resistant Staphylococci isolates at pH 7.2 and pH 5.8. The number of strains (y-axis) are displayed for each MIC ([µg/ml]; x-axis).

a) MRSA **b) MRSE** **c) cipro-resistant Staphylococci**



Conclusions

- **Resistance rates of the strains for ciprofloxacin and levofloxacin where above 60% irrespective of the pH. However, only 12% of the tested MRSA were resistant to finafloxacin at pH 5.8 (23% at pH 7.2).**
- **Around 70% of the MRSE strains tested were resistant to ciprofloxacin and levofloxacin, but only 8% were resistant to finafloxacin at an acidic pH (34% at pH 7.2).**
- **Ciprofloxacin-resistance of the tested staphylococci could not be overcome by levofloxacin and was only slightly reduced by moxifloxacin at pH 7.2 (77% resistant) but not at pH 5.8 at which 99% of the ciprofloxacin-resistant isolates were moxifloxacin-resistant, too. However, only 21% of these strains were resistant to finafloxacin at an acidic pH and 47.4 % at a neutral pH. For comparison, tigecycline MIC90 for the MRSA, MRSE and MSSE strains studied increased from 0.25 to >0.5mg/L at neutral to acidic pH (data not shown).**
- **Of all tested drugs finafloxacin was the only one with an enhanced antibacterial activity at low pH. The activity of finafloxacin against MRSA, MRSE and ciprofloxacin-resistant staphylococci was much better than that of the other fluoroquinolones tested.**