Potency of Garenoxacin Tested Against an International Collection of *Staphylococcus aureus* Isolates, Including Oxacillin- and Ciprofloxacin-Resistant Subsets (2004-2005)

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Abstract

Objective: To characterize the antimicrobial activity of garenoxacin (GRN), a novel des-F(6)-quinolone in late stage clinical development, against a large international collection of *S. aureus* (SA), including oxacillin (OXA)- and ciprofloxacin (CIPRO)-susceptible (S) and resistant (R) subsets, collected in 2004-2005.

Methods: Consecutive, non-duplicate bacterial isolates (10,068 strains) acquired from patients with bloodstream, respiratory, and skin and skin structure infections both nosocomial and community acquired were submitted from >70 medical centers in Europe, the Americas and the Asia-Pacific region. All isolates were tested using CLSI/NCCLS broth microdilution methods against GRN, the currently marketed fluoroquinolones (FQ) including CIPRO, levofloxacin (LEVO), gatifloxacin (GATI) and representative comparator agents. OXA- and CIPRO-S and -R subsets were included. A GRN-S breakpoint of <= 0.12 mg/L was applied for comparative purposes only and was based upon the MIC population distributions of strains that included quinolone resistance determining region (QRDR) mutations.

Results: Potency for GRN and comparator FQs tested against SA:

	MIC_{50}(mg/L)/%S			
Organisms (no. total)	GRN	CIPRO	LEVO	GATI
	S<=0.12 mg/L	S<=1 mg/L	S<=1 mg/L	S<=0.5 mg/L
All SA (10,068)	<=0.03/64	0.5/63	0.12/64	0.06/64
OXA-S (6,009)	<=0.03/95	0.25/94	0.12/94	0.06/95
OXA-R (4,059)	1/18	>4/17	>4/18	4/18
CIPRO-S (6,312)	<=0.03/>99	0.25/100	0.25/>99	0.06/>99
CIPRO-R (3,667)	1/1	>4/0	>4/<1	4/1

Key resistance patterns (%) among this SA collection included OXA (40.3), CIPRO (36.4), erythromycin (47.5), clindamycin (13.4), tetracycline (9.7), and trimethoprim/sulfamethoxazole (4.8%); Gram-positive-targeted comparators including vancomycin, linezolid, daptomycin and quinupristin/dalfopristin all remained >99% S. Compared with currently marketed FQs when tested against all SA, GRN was 2- to 16-fold more active (MIC_{50}, <= 0.03 vs. 0.06 or 0.5 mg/L). Against both OXA-S and -R SA, GRN displayed markedly enhanced potency compared with CIPRO and LEVO (>= 4-fold), and GATI (2- to 4-fold). Among CIPRO-R isolates, GRN also maintained >= 4-fold greater potency (MIC_{50}, 1 vs. >= 4 mg/L) although overall S for all FQs was 0-1%.

Conclusions: Compared to the FQ agents tested against SA, GRN was the most potent agent and maintained the broadest coverage against OXA- and CIPRO-R strains even when applying a very conservative epidemiologic breakpoint. When a FQ is indicated for staphylococcal coverage, this des-F(6) quinolone may represent a superior alternative among FQ class agents, while minimizing selection of resistance.

Introduction

Infections of skin and soft tissues (SSTI) are among the most common of community-acquired infections, usually requiring therapeutic interventions consisting of local wound management, surgical incision and debridement, and treatment with an orally-active antimicrobic, usually a penicillin, cephalosporin, macrolide or fluoroquinolone. The rapid spread of methicillin-resistant *Staphylococcus aureus* (MRSA) SSTI in the community is especially worrisome, given the clonal nature of the responsible strains, unique genetic virulence markers (Panton-Valentine leucocidin and the staphylococcal chromosomal cassette *mec* Type IVa) and lack of established risk factors. In hospitalized patients, SSTI are also known to produce significant morbidity and mortality, resulting in increased costs due to required intensive management and extended hospital stays.

The role of fluoroquinolones in the setting of SSTI has primarily been as an alternative agent as recognized by various professional guidelines, and is usually reserved for those patients who cannot tolerate ß-lactam agents or clindamycin. As a class, the fluoroquinolones are generally very active against SSTI pathogens, and are well tolerated, although there are concerns over emergence of resistance through target mutations occurring in the quinolone-resistance determining region (QRDR). The novel des-F(6)quinolone garenoxacin has been shown to provide even greater activity against staphylococci and streptococci, including strains with reduced susceptibility to ciprofloxacin due to alterations in *parC* and *gyrA*. These features are complemented by the high probability of favorable target attainment (AUC/MIC) that would be expected to predict successful bacterial eradication and minimization of mutational events (low mutant prevention concentration [MPC]). The antimicrobial activity and pharmacodynamic profile of garenoxacin make it especially attractive for empirical therapy, especially in cases where the ability to culture is compromised. Furthermore, a number of recent clinical trials have validated the equivalency of garenoxacin against "standard of care" regimens when used to treat SSTIs, upper and lower respiratory tract infections and acute pelvic infections. These characteristics of garenoxacin are attractive, considering the inherent limitations of older fluoroquinolones in the treatment of staphylococcal infections, especially those resistant to oxacillin (methicillin).

In this study, *in vitro* testing results from the SENTRY Antimicrobial Surveillance Program were summarized from 2004 and 2005 assessing the activity of garenoxacin and comparator agents against a large (10,068 isolates) international collection of *S. aureus* isolates, including oxacillin- and ciprofloxacin-resistant subsets.

Materials and Methods

Bacterial strains. The organism collection (10,068 consecutively acquired *S. aureus* isolates) was processed in a central laboratory system (JMI Laboratories, North Liberty, Iowa, USA) using common reference test reagents for identification and susceptibility testing. The isolates were obtained from medical centers in North America (≥ 30 sites in the USA and Canada), Latin America (10 nations), Europe (≥ 30 sites) and the Asia-Pacific region (nine nations plus South Africa).

Susceptibility testing. All isolates were tested by the reference broth microdilution method of the CLSI in Mueller-Hinton broth against garenoxacin, comparator fluoroquinolones and other agents representing the most common classes and examples of drugs used in the treatment of the indicated pathogens. Dry-form microdilution panels and broth reagents were purchased from TREK Diagnostics (Cleveland, Ohio, USA). Interpretation of MIC results for comparator agents was in accordance with CLSI criteria. A garenoxacin susceptible breakpoint of ≤ 0.12 mg/L was applied for comparative purposes only and was based upon MIC population distributions of strains that included quinolone resistance determining region (QRDR) mutations; the percentage susceptible at ≤ 1 mg/L, equivalent to peer agents, is also provided in the Table.

Results

- Among this large surveillance collection of *S. aureus*, a relatively high rate of resistance was observed for a number of commonly used antimicrobial agents: oxacillin (40.3%), ciprofloxacin (36.4%), erythromycin (47.5%), clindamycin (24.4%), tetracycline (9.7%) and trimethoprim/ sulfamethoxazole (4.8%).
- Garenoxacin demonstrated potent activity against all *S. aureus* isolates (MIC_{50}, ≤ 0.03 and MIC_{90}, 4 mg/L), with 84% of strains being inhibited by 1 mg/L. When compared with currently marketed fluoroquinolones, garenoxacin was two- to 16-fold more active (MIC_{50} values, 0.06 to 0.5 mg/L and MIC_{90} values, > 4 mg/L; 63 to 64% susceptible).

Table 1. Antimicrobial activity of garenoxacin and selected comparison agents tested against 10,068 *S. aureus* isolates analyzed as part of the SENTRY Antimicrobial Surveillance Program (2004-2005).

	MIC (mg/L)		% by category:[a]	
Organism (no. tested)/ antimicrobial agent	50%	90%	Susceptible	Resistant
S. aureus (10,068)				
All Isolates				
Garenoxacin	≤0.03	4	63.7 (84.1)[b]	35.7 (10.2)[b]
Ciprofloxacin	0.5	>4	62.7	36.4
Gatifloxacin	0.06	>4	63.6	35.5
Levofloxacin	0.12	>4	63.6	35.4
Oxacillin	0.5	>2	59.7	40.3
Erythromycin	0.5	>8	51.7	47.5
Clindamycin	0.12	>8	75.3	24.4
Linezolid	2	2	100.0	-[c]
Daptomycin	0.25	0.5	99.9	-[c]
Quinupristin/Dalfopristin	≤0.25	0.5	99.8	0.1
Tetracycline	≤0.25	8	89.8	9.7
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	95.2	4.8
Vancomycin	1	1	100.0	0.0
Oxacillin-susceptible (6,009)				
Garenoxacin	≤0.03	0.03	94.5 (98.0)[b]	5.2 (0.9)[b]
Ciprofloxacin	0.25	0.5	93.5	5.4
Gatifloxacin	0.06	0.12	94.5	5.1
Levofloxacin	0.12	0.25	94.5	5.2
Erythromycin	0.25	>8	80.0	19.1
Clindamycin	0.12	0.12	96.4	3.3
Linezolid	2	2	100.0	-[c]
Daptomycin	0.25	0.5	100.0	-[c]
Quinupristin/Dalfopristin	≤0.25	0.5	99.8	0.1
Tetracycline	≤0.25	0.5	94.0	5.5
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	99.0	0.1
Vancomycin	1	1	100.0	0.0
Oxacillin-resistant (4,059)				
Garenoxacin	1	>4	18.0 (63.4)[b]	80.9 (24.0)
Ciprofloxacin	>4	>4	17.1	82.3
Gatifloxacin	4	>4	17.9	80.4
Levofloxacin	>4	>4	17.8	80.1
Erythromycin	>8	>8	9.9	89.5
Clindamycin	4	>8	44.1	55.7
Linezolid	2	2	100.0	-[c]
Daptomycin	0.5	0.5	99.9	-[c]
Quinupristin/Dalfopristin	≤0.25	0.5	99.7	0.2
Tetracycline	≤0.25	>8	83.6	15.8
Trimethoprim/Sulfamethoxazole	≤0.5	>2	89.5	10.5
Vancomycin	1	1	100.0	0.0
Ciprofloxacin-susceptible (6,312)				
Garenoxacin	≤0.03	0.03	99.7 (99.9)[b]	0.2 (0.0)[b]
Ciprofloxacin	0.25	0.5	100.0	0.0
Gatifloxacin	0.06	0.12	99.7	0.2
Levofloxacin	0.12	0.25	99.9	0.1
Erythromycin	0.25	>8	76.3	22.8
Clindamycin	0.12	0.12	98.2	1.5
Linezolid	2	2	100.0	-[c]
Daptomycin	0.25	0.5	100.0	-[c]
Quinupristin/Dalfopristin	≤0.25	0.5	99.9	0.0
Tetracycline	≤0.25	0.5	93.6	5.8
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	99.4	0.6
Vancomycin	1	1	100.0	0.0
Ciprofloxacin-resistant (3,667)				
Garenoxacin	1	>4	1.0 (56.3)[b]	97.7 (28.1)[b]
Ciprofloxacin	>4	>4	0.0	100.0
Gatifloxacin	4	>4	0.7	97.1
Levofloxacin	>4	>4	0.3	97.0
Erythromycin	>8	>8	9.2	90.1
Clindamycin	4	>8	35.5	64.3
Linezolid	2	2	100.0	-[c]
Daptomycin	0.5	0.5	99.9	-[c]
Quinupristin/Dalfopristin	≤0.25	0.5	99.6	0.3
Tetracycline	0.5	>8	83.1	16.5
Trimethoprim/Sulfamethoxazole	≤0.5	>2	87.8	12.2
Vancomycin	1	1	99.9	0.0

a. Susceptibility breakpoint criteria of the CLSI (2006).
b. Garenoxacin breakpoints (≤0.12/0.25/≥0.5 mg/L for S/I/R) based upon MIC population distributions; number in parentheses represents results using breakpoints equivalent to those of a peer agent such as ciprofloxacin or levofloxacin (≤1/2/≥4 mg/L for S/I/R).
c. - = no interpretive criteria.

- Against both oxacillin- susceptible and -resistant *S. aureus*, garenoxacin displayed markedly enhanced potency compared with ciprofloxacin and levofloxacin (≥ four-fold), and gatifloxacin (two- to eight-fold). All fluoroquinolones inhibited ≥ 94% of oxacillin-susceptible *S. aureus*. However, garenoxacin inhibited 63% of oxacillin-resistant isolates at ≤ 1 mg/L while other fluoroquinolones inhibited 17 to 18% of isolates.
- Garenoxacin was also active (≥ four-fold) against ciprofloxacin-resistant *S. aureus*, with 56% of isolates being inhibited by ≤ 1 mg/L compared with ≤ 1% of isolates being susceptible to the other fluoroquinolones.
- Gram-positive-targeted comparator agents displaying near-complete coverage (>99% susceptibility) of these isolates included vancomycin, linezolid, daptomycin and quinupristin/dalfopristin (Table 1).

Conclusions

- Resistance among contemporary *S. aureus* to currently marketed fluoroquinolones has increased dramatically in recent years and ranges from 35.4 to 36.4% (Table 1).
- In this study, garenoxacin was the most potent of the quinolone agents (two- to 16-fold more active) against all *S. aureus* isolates (MIC_{50}, ≤ 0.03 and MIC_{90}, 4 mg/L), with 84% being inhibited by ≤ 1 mg/L.
- When a fluoroquinolone is indicated for staphylococcal coverage, the des-F(6) quinolone garenoxacin may represent a good alternative to other fluoroquinolone class agents. Its enhanced potency may help minimize the selection of resistant organisms.
- The availability of garenoxacin in both an IV and bioequivalent oral formulation will make this agent a valuable addition to the antimicrobial armamentarium.

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