Potency and Spectrum of Garenoxacin Tested Against an International Collection of Skin and Soft Tissue Infection (SSTI) Pathogens: Report from the SENTRY Antimicrobial Surveillance Program (1999-2004)

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Abstract

Background: The spectrum and potency of garenoxacin (GRN), a novel des-F(6)-quinolone, and comparator fluoroquinolones (FQ) were evaluated against an international collection (11,723) of Gram-positive and -negative bacterial pathogens causing SSTI for years 1999-2004.
Methods: Consecutive, non-duplicate bacterial isolates were studied from patients with community-acquired or nosocomial SSTI in >70 medical centers participating in surveillance programs in North America (37.4%), Europe (26.7%), Latin America (16.7%) and the Asia-Pacific region (19.2%). All isolates were tested using CLSI broth microdilution methods against GRN, ciprofloxacin, levofloxacin (LEVO), gatifloxacin (GATI), moxifloxacin and other appropriate comparators.
Results: Ranking SSTI pathogens included *Staphylococcus aureus* (SA; 42.8%), *Pseudomonas aeruginosa* (PA; 11.1%), *Escherichia coli* (EC; 9.0%), *Enterococcus* spp. (7.3%), *Klebsiella* spp. (KSP; 4.8%), *Enterobacter* spp. (4.7%), ß-haemolytic streptococci (4.3%), coagulase-negative staphylococci (4.0%), *Proteus mirabilis* (2.5%), *Acinetobacter* spp. (ASP; 2.1%), and others (7.2%). GRN was the most potent agent tested against SA, and was at least two-fold more potent than GATI (MIC_{50}, 0.06 mg/L) and 8-fold more potent than LEVO (MIC_{50}, 0.25 mg/L). Furthermore, GRN was two- to eight-fold more potent than the FQs against ß-haemolytic and viridans group streptococci, and up to four-fold more potent against enterococci. GRN was largely comparable to the tested FQs against EC, KSP, and ASP, but less active than these agents against PA. Among confirmed ESBL-producing EC (6.1%) and KSP (17.2%), potencies of quinolone agents were markedly decreased (MIC_{90}, >4 mg/L); only carbapenems retained complete coverage of these strains.
Conclusion: These studies demonstrated that GRN was the most potent quinolone when tested against SA, ß-haemolytic streptococci, viridans group streptococci and enterococci, and was similar in activity to these agents against other species including commonly occurring Enterobacteriaceae (all quinolones had reduced susceptibilities to ESBL-producing strains) and ASP. GRN appears to offer advantages to the FQs for the treatment of SSTI infections, especially among Gram-positive pathogens.

Introduction

Options for successful antimicrobial treatment of skin and soft issue infections (SSTI) are complicated by patient-specific risk factors (age, severity of disease, underlying co-morbidities, allergies), spectrum of pathogens responsible, organism-specific resistances (innate or acquired), pharmacokinetic/ pharmacodynamic parameters of the drugs being utilized and the anatomic site being targeted. Of all characteristics that may result in clinical failure, selection for or acquisition of, resistance among the offending pathogen(s) to existing antimicrobial agents is known to occur rapidly and spread globally, resulting in rising health-care costs. With these changes there is a critical need to modify, and add to, our antimicrobial therapeutic armamentarium.

Among new agents, garenoxacin (formerly T-3811ME or BMS-284756) is a novel des-F(6)-quinolone that has a structure lacking the C6-position fluorine, but having a unique difluoromethoxy substitution at position C8. These alterations are known to favorably influence potency against both DNA gyrase and topoisomerase IV at achievable serum concentrations following garenoxacin 400 mg doses by oral or intravenous routes. Garenoxacin has been found to be highly active *in vitro* against important Gram-positive and -negative pathogens and phase 3 studies using either oral or iv dosing was found to be effective in treating complicated skin and soft tissue infections. These features are complimented 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]) among indicated species. A number of recent clinical trials have demonstrated equivalency of garenoxacin against standard of care regimens when used to treat SSTI, upper and lower respiratory tract infections and acute pelvic infections.

As garenoxacin moves through the clinical development pathway, surveillance to detect emerging antimicrobial resistance becomes necessary to further characterize the spectrum and potency of this agent against contemporary SSTI pathogens. In this study, *in vitro* testing results from the global SENTRY Antimicrobial Surveillance Program were summarized from 1999 to 2004, comparing activity of garenoxacin with that of other quinolone agents and members of other antimicrobial classes used in the empiric or directed therapy of SSTI.

Materials and Methods

Bacterial strains tested: Non-duplicate, consecutive clinical isolates (11,723 total) were submitted from > 70 medical centers annually, located in North America (≥30 sites in the USA and Canada; 37.4% of isolates), South America (10 nations; 16.7%) Asia-Pacific region (nine nations plus South Africa; 19.2%) and Europe (≥30 sites; 26.7%) as part of global surveillance programs for the years 1999 to 2004. Isolates originated from patients with documented SSTI and were of either nosocomial (42%) or community-acquired origin (58%). Isolates were predominantly from adults (≥18 years; 84.2%) and mostly from male patients (56.6%). Species identifications were performed by the submitting laboratories with confirmation performed by the central laboratory monitors (JMI Laboratories, North Liberty, Iowa; Women's and Children's Hospital, Adelaide, Australia) using established biochemical algorithms, and use of the Vitek Microbial Identification System (bioMerieux, Hazelwood, Missouri, USA).

Antimicrobial susceptibility testing: All isolates were tested by the CLSI reference broth microdilution method in Mueller-Hinton broth (with the addition of 2-5% lysed horse blood for testing of fastidious species) against a variety of antimicrobial agents used in the treatment of the indicated pathogen. Dry-form microdilution panels and broth reagents were purchased from TREK Diagnostics (Cleveland, Ohio, USA). Garenoxacin standard powder was provided by Bristol-Meyers Squibb, Inc. (New York, New York, USA). Interpretation of MIC results was in accordance with CLSI criteria; breakpoints used for garenoxacin (≤0.12/0.25/≥0.5 mg/L for S/I/R for Gram-positive isolates and ≤1/2/≥4 mg/L for Gram-negative isolates) are for comparison purposes only. Enterobacteriaceae with elevated MIC values (≥2 mg/L) for ceftazidime and/or ceftriaxone were considered as extended-spectrum ß-lactamase (ESBL)-producing phenotypes according to CLSI criteria. ESBL confirmation was performed using the disk approximation method. Quality control isolates utilized included *Escherichia coli* ATCC 25922 and 35218, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 29213, *S. pneumoniae* ATCC 49619 and *Enterococcus faecalis* ATCC 29212.

Results

- The top ten ranked pathogens (92.8%) producing SSTI during these years included *Staphylococcus aureus* (42.8%), *Pseudomonas aeruginosa* (11.1%), *Escherichia coli* (9.0%), *Enterococcus* spp. (7.3%), *Klebsiella* spp.(4.8%), *Enterobacter* spp. (4.7%), ß-haemolytic streptococci (4.3%), coagulase negative staphylococci (4.0%), *Proteus mirabilis* (2.5%), *Acinetobacter* spp. (2.1%) and others (7.2%; Tables 1 and 3).
- Among a large population of *S. aureus*, including 33.1% oxacillin-(methicillin-) resistant strains, garenoxacin was the most potent agent tested, and was at least two-fold more active than gatifloxacin (MIC_{50}, 0.06 mg/L) and eight-fold more active than levofloxacin (MIC_{50}, 0.25 mg/L). At a tentative breakpoint of ≤0.12 mg/L, garenoxacin displayed near-identical activity (71.3% susceptibility) to other fluoroquinolones.
- Oxacillin-resistant *S. aureus* were largely resistant to the quinolones (51.9 to 80.1%) although garenoxacin retained the most activity with MIC_{50} and MIC_{90} values each being two-fold lower than those of the other quinolones (Table 2).
- Garenoxacin was equally active, or superior to, the other quinolones against coagulase-negative staphylococci. Only moxifloxacin demonstrated enhanced potency (MIC_{90} two-fold lower; Table 1) against these strains, including oxacillin-resistant strains (MIC_{50}, two-fold lower; Table 2).
- ß-haemolytic streptococci were uniformly susceptible (>99%) to all agents tested, with the exceptions of erythromycin and clindamycin (Table 1). Garenoxacin exhibited two- to eight-fold greater potency than other quinolones (gatifloxacin/ moxifloxacin and ciprofloxacin/levofloxacin, respectively) against these species and against viridans group streptococci (data not shown; only 0.7% of all SSTI isolates).
- Garenoxacin was largely comparable to the comparator fluoroquinolones against *E. coli*, *Klebsiella* spp. and *Acinetobacter* spp., but less active than these agents against *P. aeruginosa*.

Table 1. Antimicrobial activity of garenoxacin and selected comparison agents tested against the top four ranked Gram-positive pathogens causing SSTI in the SENTRY Program (1999 - 2004).[a]

Organism (rank/no. tested/prevalence)/ Antimicrobial agent	MIC (mg/L) 50%	MIC (mg/L) 90%	% by category:[b] Susceptible	% by category:[b] Resistant
S. aureus (1/5,015/42.8%)				
Garenoxacin	≤0.03	2	71.3[c]	27.5
Ciprofloxacin	≤0.25	>2	70.3	28.8
Gatifloxacin	0.06	4	71.7	26.6
Levofloxacin	0.25	>4	71.4	27.5
Moxifloxacin	0.06	4	70.3	20.1
Oxacillin	0.5	>8	66.9	33.1
Erythromycin	0.5	>8	58.1	41.2
Clindamycin	0.12	>8	78.2	21.6
Gentamicin	≤2	>8	86.3	13.2
Linezolid	2	2	100.0	-[d]
Quinupristin/Dalfopristin	≤0.25	0.5	99.8	0.1
Tetracycline	≤4	>8	84.5	15.1
Trimethoprim/Sulfamethoxazole	≤0.5	1	95.1	4.9
Vancomycin	1	1	100.0	0.0
Enterococci (4/859/7.3%)				
Garenoxacin	0.25	>4	61.1[c]	30.5
Ciprofloxacin	1	>2	52.2	40.4
Gatifloxacin	0.5	>4	64.1	33.9
Levofloxacin	1	>4	61.1	37.0
Moxifloxacin	0.25	>4	-	-
Ampicillin	≤2	>16	85.9	14.1
Chloramphenicol	8	>16	83.6	14.2
Gentamicin (high-level)	≤500	>1000	69.8	30.2
Linezolid	2	2	99.5	0.2
Teicoplanin	≤2	≤2	93.1	5.8
Vancomycin	1	4	91.6	7.8
ß-haemolytic streptococci (7/510/4.3%)[e]				
Garenoxacin	0.06	0.12	100.0[c]	0.0
Ciprofloxacin	0.5	1	-	-
Gatifloxacin	0.25	0.25	100.0	0.0
Levofloxacin	0.5	1	100.0	0.0
Moxifloxacin	0.12	0.25	-	-
Cefepime	≤0.12	≤0.12	99.8	-
Ceftriaxone	≤0.25	≤0.25	100.0	-
Clindamycin	≤0.06	≤0.06	94.1	5.7
Erythromycin	≤0.06	2	85.1	14.7
Linezolid	1	1	100.0	-
Meropenem	≤0.06	≤0.06	100.0	-
Penicillin	≤0.016	0.06	100.0	-
Vancomycin	0.5	0.5	100.0	-
Coagulase-negative staphylococci (8/474/4.0%)				
Garenoxacin	0.12	4	53.6[c]	44.9
Ciprofloxacin	0.25	>2	54.2	43.2
Gatifloxacin	0.25	4	55.5	32.9
Levofloxacin	0.25	>4	54.1	38.5
Moxifloxacin	0.12	2	62.7	23.5
Oxacillin	2	>8	24.3	75.7
Erythromycin	>8	>8	42.2	57.6
Clindamycin	0.12	>8	70.3	29.1
Gentamicin	≤2	>8	65.4	27.8
Linezolid	1	2	100.0	-
Quinupristin/Dalfopristin	≤0.25	0.5	99.8	0.0
Tetracycline	≤4	>8	81.4	17.5
Trimethoprim/Sulfamethoxazole	≤0.5	>2	76.7	23.3
Vancomycin	1	2	100.0	0.0

a. Includes 6,858 isolates or 98.8% of tested Gram-positive SSTI pathogens.
b. Susceptibility breakpoint criteria of the CLSI.
c. Garenoxacin breakpoints utilized (≤0.12/0.25/0.5 mg/L for S/I/R) are for comparison purposes only.
d. - = no interpretive criteria.
e. Includes streptococci from groups A (242 strains), B (168), C (18), F (six), G (68); ß-haemolytic streptococci (not otherwise identified; seven); and *S. equisimilis* (one).

Table 2. Antimicrobial activity of garenoxacin and other quinolone agents tested against oxacillin-susceptible and -resistant subsets of staphylococci causing SSTI (SENTRY Program, 1999 - 2004).

Organism (no. tested)/antimicrobial agent	MIC (mg/L) 50%	MIC (mg/L) 90%	% by category:[a] Susceptible	% by category:[a] Resistant
S. aureus				
Oxacillin-susceptible (3,356)				
Garenoxacin	≤0.03	0.03	96.4	3.3
Ciprofloxacin	0.25	0.5	95.6	3.5
Gatifloxacin	0.06	0.12	96.7	3.0
Levofloxacin	0.12	0.25	96.2	3.4
Moxifloxacin	≤0.03	0.06	95.6	3.1
Oxacillin-resistant (1,659)				
Garenoxacin	1	4	20.6	76.6
Ciprofloxacin	>4	>4	19.1	80.1
Gatifloxacin	2	>4	21.1	79.9
Levofloxacin	4	>4	20.8	76.6
Moxifloxacin	2	>4	23.1	51.9
Coagulase-negative staphylococci				
Oxacillin-susceptible (115)				
Garenoxacin	0.03	0.12	92.2	7.8
Ciprofloxacin	≤0.25	0.5	92.2	7.0
Gatifloxacin	0.12	0.25	93.0	4.3
Levofloxacin	0.25	0.5	90.7	7.2
Moxifloxacin	0.06	0.25	90.7	1.9
Oxacillin-resistant (359)				
Garenoxacin	1	4	41.2	56.8
Ciprofloxacin	>2	>2	42.1	54.9
Gatifloxacin	1	4	43.5	42.1
Levofloxacin	2	>4	42.0	48.8
Moxifloxacin	0.5	4	52.7	31.3

a. Susceptibility breakpoint criteria of the CLSI; garenoxacin breakpoints utilized (≤0.12/0.25/0.5 mg/L for S/I/R) are for comparison purposes only.

- Among confirmed ESBL-producing *E. coli* (6.1%) and *Klebsiella* spp. (17.2%), potencies of quinolone agents were markedly decreased (MIC_{90}, >4 mg/L; data not shown); only carbapenems retained complete coverage of these strains.

Table 3. Antimicrobial activity of garenoxacin and selected comparison agents tested against the top five ranked Gram-positive pathogens causing SSTI in the SENTRY Program (1999-2004).[a]

Organism (rank/no. tested/prevalence)/ Antimicrobial agent	MIC (mg/L) 50%	MIC (mg/L) 90%	% by category:[b] Susceptible	% by category:[b] Resistant
P. aeruginosa (2/1,302/11.1%)				
Garenoxacin	2	>4	41.5[c]	39.5
Ciprofloxacin	≤0.25	>2	72.5	24.3
Gatifloxacin	1	>4	69.3	25.8
Levofloxacin	0.5	>4	71.0	24.7
Moxifloxacin	2	>4	-[d]	-
Cefepime	4	>16	80.0	11.4
Ceftazidime	4	>16	79.0	17.4
Gentamicin	≤2	>8	78.0	18.0
Imipenem	1	>8	81.2	12.4
Piperacillin/Tazobactam	8	>64	83.6	16.4
Tobramycin	0.5	>16	83.0	16.4
E. coli (3/1,057/9.0%)				
Garenoxacin	≤0.03	>4	78.8[c]	20.3
Ciprofloxacin	≤0.25	>2	80.1	19.8
Gatifloxacin	≤0.03	>4	80.8	14.2
Levofloxacin	≤0.03	>4	80.4	15.4
Moxifloxacin	0.06	>4	-	-
Amoxicillin/Clavulanate	8	>16	73.7	10.1
Cefepime	≤0.12	1	94.4	4.9
Cefoxitin	4	16	88.3	6.3
Ceftazidime	≤1	2	93.2	4.4 (11.5)[e]
Ceftriaxone	≤0.25	0.5	91.3	6.8 (11.1)[e]
Gentamicin	≤2	>8	86.1	12.8
Imipenem	≤0.5	≤0.5	100.0	0.0
Piperacillin/Tazobactam	2	8	93.3	3.3
Trimethoprim/Sulfamethoxazole	≤0.5	>2	73.7	26.3
Klebsiella spp. (5/564/4.8%)				
Garenoxacin	0.12	>4	83.7[c]	13.5
Ciprofloxacin	≤0.25	>2	86.9	11.3
Gatifloxacin	0.06	4	89.4	7.3
Levofloxacin	0.06	4	88.3	8.0
Moxifloxacin	0.12	>4	-	-
Amoxicillin/Clavulanate	4	>16	72.0	11.0
Cefepime	≤0.12	8	90.2	7.8
Cefoxitin	4	16	84.9	8.9
Ceftazidime	≤1	>16	83.5	13.3 (25.0)[e]
Ceftriaxone	≤0.25	>32	79.8	13.1 (23.6)[e]
Gentamicin	≤2	>8	81.0	16.9
Imipenem	≤0.5	≤0.5	100.0	0.0
Piperacillin/Tazobactam	2	>64	82.3	12.9
Trimethoprim/Sulfamethoxazole	≤0.5	>2	86.2	13.8
Enterobacter spp. (6/550/4.7%)				
Garenoxacin	0.12	>4	84.4[c]	13.5
Ciprofloxacin	≤0.25	2	89.6	8.9
Gatifloxacin	0.06	2	91.3	6.2
Levofloxacin	≤0.03	2	90.9	7.1
Moxifloxacin	0.12	>4	-	-
Amoxicillin/Clavulanate	>16	>16	3.8	94.4
Cefepime	≤0.12	4	97.3	2.0
Cefoxitin	>32	>32	2.9	94.7
Ceftazidime	≤1	>16	73.6	22.2
Ceftriaxone	≤0.25	>32	77.1	14.2
Gentamicin	≤2	8	88.9	10.2
Imipenem	≤0.5	1	99.1	0.2
Piperacillin/Tazobactam	2	64	78.7	9.6
Trimethoprim/Sulfamethoxazole	≤0.5	>2	89.5	10.5
P. mirabilis (9/298/2.5%)				
Garenoxacin	0.5	>4	78.2[c]	20.8
Ciprofloxacin	≤0.25	2	85.9	9.1
Gatifloxacin	0.12	4	86.6	8.7
Levofloxacin	0.06	2	91.6	6.7
Moxifloxacin	0.25	>4	-	-
Amoxicillin/Clavulanate	≤2	8	90.3	3.4
Cefepime	≤0.12	≤0.12	95.6	3.7
Cefoxitin	4	4	98.0	0.7
Ceftazidime	≤1	≤1	99.3	0.3 (4.0)[e]
Ceftriaxone	≤0.25	≤0.25	95.3	4.0 (5.7)[e]
Gentamicin	≤2	>8	85.9	12.1
Imipenem	1	2	99.7	0.0
Piperacillin/Tazobactam	≤0.5	1	99.7	0.0
Trimethoprim/Sulfamethoxazole	≤0.5	>2	79.9	20.1
Acinetobacter spp. (10/246/2.1%)				
Garenoxacin	4	>4	45.1	53.3
Ciprofloxacin	>2	>2	41.1	58.1
Gatifloxacin	4	>4	46.3	37.8
Levofloxacin	4	>4	45.9	41.1
Moxifloxacin	4	>4	-	-
Cefepime	16	>16	45.5	32.1
Ceftazidime	>16	>16	41.9	50.8
Gentamicin	>8	>8	39.8	56.5
Imipenem	≤0.5	>8	80.5	16.3
Piperacillin/Tazobactam	64	>64	40.7	48.0
Polymyxin B	≤1	≤1	99.2	0.8

a. Includes 3,453 isolates or 73.3% of tested Gram-negative SSTI pathogens.
b. Susceptibility breakpoint criteria of the CLSI.
c. Garenoxacin breakpoints utilized (≤1/2/4 mg/L for S/I/R) are for comparison purposes only.
d. - = no interpretive criteria.
e. Percentages in parentheses are the proportion of ESBL phenotypes using CLSI criteria.

Conclusions

- Garenoxacin was documented to be the most potent quinolone when tested against key Gram-positive pathogens (*S. aureus*, ß-haemolytic streptococci, viridans group streptococci and enterococci), and was similar in activity to these agents against other species (Enterobacteriaceae and *Acinetobacter* spp.).
- These *in vitro* data suggest that garenoxacin warrants further clinical studies in SSTI, especially against staphylococcal and streptococcal pathogens.
- As newer agents move through clinical development and into the marketplace, ongoing surveillance activities, such as those described here will be helpful in identifying the agent's particular strengths and limitations, and in tracking changes in resistance profiles as each new antimicrobial gains acceptance in clinical practice.

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