Potency and Spectrum of Garenoxacin Tested Against an International Collection of Skin and Soft Tissue Infection Pathogens: Report from the SENTRY Antimicrobial Surveillance Program (1999-2003)

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Abstract

Objective: To evaluate the spectrum and potency of garenoxacin (GRN), a novel des-F(6)-quinolone, against a large international collection (9,227) of Gram-positive and -negative bacterial pathogens that cause skin and soft tissue infections (SSTI).
Methods: Consecutive, non-duplicate bacterial isolates were collected from 1999 to 2003 from patients with documented community-acquired or nosocomial SSTI in >70 medical centers participating in the SENTRY Program in North America (36.1%), Europe (24.1%), Latin America (16.1%) and the Asia-Pacific region (23.7%). All isolates were tested using NCCLS broth microdilution methods against GRN, the currently marketed fluoroquinolones (FQ) ciprofloxacin (CIPRO), levofloxacin (LEVO), gatifloxacin (GATI) and representative comparator agents used for the empiric therapy of SSTI.
Results: The Table lists the potency and cumulative inhibition rates for GRN against the top 10 (by frequency) SSTI pathogens:

	MIC (mg/L)	% inhibited at MIC (mg/L)		
Organism (# tested)	50	≤1	2	4
S. aureus (SA; 3,790)	≤0.03	87	93	97
P. aeruginosa (PSA; 1,080)	2	41	61	70
E. coli (EC; 864)	0.03	83	84	84
Enterococcus spp. (ESP;650)	0.25	63	71	86
Klebsiella spp. (KSP; 465)	0.12	85	88	90
Enterobacter spp. (ENT; 463)	0.12	86	88	90
ß-haemolytic streptococci (BHS; 420)	0.06	100		
Coagulase neg. staphylococci (CoNS; 365)	0.12	73	86	95
P. mirabilis (PM; 238)	0.5	81	82	84
Acinetobacter spp. (ASP; 210)	2	48	50	60

Published data demonstrates that the agents causing SSTI are comprised of a distinct set of Gram-positive cocci and Gram-negative aerobic and facultative bacilli. GRN was the most potent agent tested against SA, and was at least 2-fold more potent than GATI (MIC_{50} 0.06 mg/L) and ß-fold more potent than either CIPRO or LEVO (MIC_{50} 0.25 mg/L). Furthermore, GRN was 4- to 8-fold more potent than the FQ against BHS and viridans group streptococci (VGS), and 2- to 4-fold more potent against ESP. GRN was comparable to CIPRO, LEVO and GATI against EC, KSP and ASP, but less active than these agents against PSA.
Conclusions: GRN was the most potent FQ when tested against SA, BHS, VGS and ESP, and was similar in activity to these agents against other species including EC, KSP and ASP. The in vitro data suggest that GRN maybe superior to the FQ for the treatment of SSTI infections caused by staphylococci and streptococci, warranting further clinical studies.

Introduction

Skin and soft tissue infection (SSTI) represents one of the most common community-acquired infections in all age groups. The term SSTI includes a broad range of infections, some of which can be mild, like most cases of impetigo, folliculitis, furuncles, and carbuncles; while others can be more severe (erysipelas and cellulitis). In addition, the rarer types of SSTI, such as gangrenous cellulitis and necrotizing fasciitis, have very high morbidity and mortality rates. Occasionally, a very mild case of SSTI can rapidly become a severe and life-threatening infection, especially when inappropriate initial empiric therapy is implemented or when associated with the emerging syndromes of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA). These strains often produce the Panton-Valentine leucocidin leading to serious abscess disease and elevated probability of invasive infections with high morbidity and mortality. Limited therapeutic options has highlighted the need for the development of newer agents from older antimicrobial classes (fluoroquinolones) with greater potency against Gram-positive SSTI pathogens.

Garenoxacin (formerly T-3811ME or BMS-284756) is a novel des-F(6)-quinolone that lacks the C6-position fluorine and has a unique difluoromethoxy substitution at position C8. These alternations result in a drug with improved potency against both DNA gyrases and topoisomerase IV. Garenoxacin has been described as highly active against important Gram-positive and -negative pathogens including: Enterobacteriaceae, staphylococci, streptococci (*S. pneumoniae*, viridans group species, and ß-haemolytic streptococci), *Acinetobacter* spp. and some other Gram-negative and non-fermentative bacilli, *Haemophilus influenzae*, *Moraxella catarrhalis*, atypical respiratory tract pathogens (Mycoplasmas, *C. pneumoniae*, and *Legionella* spp.), many enterococci and anaerobes, especially Gram-positive species. These features are complimented by the high probability of favorable target attainment (AUC/MIC) that has been associated with successful bacterial eradication and minimization of mutational events among indicated species (i.e. low MPC values). These elements of spectrum and potency favor garenoxacin applications for 1) community-acquired respiratory tract infections (CA-RTI; hospitalized or ambulatory patients); 2) skin and soft tissue infections (complicated with mixed flora or uncomplicated); and 3) selected community-acquired intra-abdominal infection indications.

The in vitro testing results for garenoxacin from the SENTRY Antimicrobial Surveillance Program were summarized from 1999 onward to assess the spectrum and potency versus isolates from SSTI. A total of 9,227 isolates were analyzed from results generated by the reference (National Committee for Clinical Laboratory Standards [NCCLS], currently the Clinical Laboratory Standards Institute) methods as described in document M7-A6 [2003].

Materials and Methods

Susceptibility testing. All presented MIC values were produced by broth microdilution methods (NCCLS, M6-A7) in panels produced by TREK Diagnostics (Cleveland, Ohio, USA). Mueller-Hinton broth was supplemented where indicated with 2 - 5% lysed horse blood (fastidious species including streptococci) and HTM components (*Haemophilus* species). The following NCCLS-recommended quality control (QC) strains were routinely tested: *E. coli* ATCC 25922 and 35218; *P. aeruginosa* ATCC 27583; *E. faecalis* ATCC 29212; *S. aureus* ATCC 25923 and 29213; and *S. pneumoniae* ATCC 47916. All QC results were within published MIC ranges - (CLSI, M100-S15). Approximately 35 - 40 different antimicrobial agents were processed each year with selected agents compared to garenoxacin in this presentation. A breakpoint for garenoxacin at ≤ 2 mg/L was used for comparison purposes for most species, except staphylococci where ≤ 0.12 mg/L was applied.

Bacterial strains. The organisms were consecutively collected isolates processed in a central laboratory system (JMI Laboratories, North Liberty, Iowa, USA; Women's and Children's Hospital, Adelaide, Australia; Utrecht University, Utrecht, The Netherlands) using common reference test reagents. In this investigation, the isolates were obtained from SSTI at 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). The distribution of tested species was: *S. aureus* (3,740); 31.5% oxacillin-resistant [MRSA]), *P. aeruginosa* (1,080), *E. coli* (864; 9.3 - 10.0% ESBL phenotypes), *Enterococcus* spp. (650; usually *E. faecalis*), *Klebsiella* spp. (465; including 344 *K. pneumoniae* and 98 *K. oxytoca*), 1,106 other Enterobacteriaceae (see Table 1), streptococci (493; ß-haemolytic and viridans group species) and two genus/species groups of non-fermentative Gram-negative bacilli, e.g. *Acinetobacter* spp. (210) and *S. maltophilia* (57).

The geographic distribution of the listed strains was: Asia-Pacific (23.7%), Europe (24.1%), Latin America (16.1%) and North America (36.1%).

Results

Table 1. Distribution of 9,227 bacterial pathogens isolated from skin and soft tissue infections (SSTI) monitored in the SENTRY Antimicrobial Surveillance Program (1999 - 2003).

Rank	Pathogen	No. (%)
1	*S. aureus*	3,790 (41.1)
2	*P. aeruginosa*	1,080 (11.7)
3	*E. coli*	864 (9.4)
4	Enterococci	650 (7.0)
5	*Klebsiella* spp.	465 (5.0)
6	*Enterobacter* spp.	463 (5.0)
7	ß-haemolytic streptococci	420 (4.6)
8	Coagulase-negative staphylococci	365 (4.0)
9	*P. mirabilis*	238 (2.6)
10	*Acinetobacter* spp.	210 (2.3)
11	*Serratia* spp.	160 (1.7)
12	Indole-positive *Proteae*	134 (1.5)
13	*Citrobacter* spp.	111 (1.2)
14	viridans group streptococci	73 (0.8)
15	*S. maltophilia*	57 (0.6)
	Other species	147 (1.6)

- Garenoxacin demonstrated excellent activity against both *S. aureus* (MIC_{90}, 2 mg/L) and coagulase-negative staphylococci (MIC_{90}, 4 mg/L) having a spectrum comparable to other tested fluoroquinolones. Garenoxacin was at least two-fold more potent than any other fluoroquinolone tested (ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin). These staphylococci showed 31.5 - 47.9% resistance to oxacillin (Table 2).
- *P. aeruginosa* from SSTI (Table 2) were generally less susceptible to all fluoroquinolones (68.3 - 72.7% susceptible) at published breakpoints. A total of 60.7% isolates were inhibited by garenoxacin at ≤ 2 mg/L. The most effective drugs were imipenem (81.5%), piperacillin/tazobactam (82.9%) and tobramycin (82.6%).
- The Enterobacteriaceae (*E. coli, Klebsiella* spp., *Enterobacter* spp., *P. mirabilis*) had garenoxacin susceptibility rates of 81.5 to 87.7%; rates comparable to other compounds in the same class (exception *P. mirabilis*; ranked 9th).
- Streptococci were quite susceptible to garenoxacin (MIC_{90}, 0.12 mg/L). Garenoxacin was typically ≥ two-fold more potent than gatifloxacin and other fluoroquinolones. The ß-lactams (penicillin, cephalosporins, carbapenems) were most active on a by-weight basis.
- Acinetobacters were most susceptible to garenoxacin (MIC_{50}, 2 mg/L; 50.0% susceptible), although moxifloxacin appears to be more active (MIC_{50}, 0.12 mg/L). Only carbapenems and polymyxin B had susceptibility rates at ≥ 80.0%.
- Lastly, the enterococci (650 isolates; 4th overall rank) were most susceptible to garenoxacin having 70.8% inhibition at ≤ 2 mg/L and a MIC_{50} of only 0.25 mg/L. Moxifloxacin appears to be equally active, but a CLSI breakpoint has not been established.

Table 2. Antimicrobial activity of garenoxacin and selected comparator agents tested against the top 10 pathogens causing SSTI in the SENTRY Program (1999 - 2003).[a]

	MIC (mg/L)		% by category:[b]	
Organism (rank; no. tested)/antimicrobial agent	50%	90%	Susceptible	Resistant
***S. aureus* (1; 3,790)**				
Garenoxacin	≤0.03	2	(72.5)[c]	(26.3)
Ciprofloxacin	≤0.25	>2	71.5	27.6
Gatifloxacin	0.06	4	72.9	25.3
Levofloxacin	0.25	>4	72.9	26.2
Moxifloxacin	0.06	4	72.3	20.2
Oxacillin	0.5	>8	68.5	31.5
Erythromycin	0.5	>8	59.3	40.1
Clindamycin	0.12	>8	77.7	21.9
Gentamicin	≤2	>8	84.7	14.8
Linezolid	2	2	100.0	-[d]
Quinupristin/Dalfopristin	≤0.25	0.5	99.8	0.1
Tetracycline	≤4	>8	82.7	16.9
Trimethoprim/Sulfamethoxazole	≤0.5	1	89.7	9.2
Vancomycin	1	1	100.0	0.0
***P. aeruginosa* (2; 1,080)**				
Garenoxacin	2	>4	(60.7)[e]	(29.9)
Ciprofloxacin	≤0.25	>2	72.7	24.2
Gatifloxacin	1	>4	69.3	25.7
Levofloxacin	0.5	>4	71.1	24.5
Moxifloxacin	2	>4	-	-
Cefepime	4	>16	79.5	12.2
Ceftazidime	2	>16	78.1	18.1
Gentamicin	≤2	>8	77.4	18.5
Imipenem	1	>8	81.5	13.0
Piperacillin/Tazobactam	8	>64	82.9	17.1
Tobramycin	0.5	>16	82.6	16.7
***E. coli* (3; 864)**				
Garenoxacin	≤0.03	>4	(83.6)[e]	15.7
Ciprofloxacin	≤0.25	>2	84.0	15.9
Gatifloxacin	≤0.03	>4	84.5	11.8
Levofloxacin	≤0.03	>4	84.4	12.7
Moxifloxacin	0.06	>4	-	-
Amoxicillin/Clavulanate	8	>16	74.5	10.1
Cefepime	≤0.12	0.5	95.4	3.9
Cefoxitin	4	16	89.6	6.1
Ceftazidime	≤1	≤1	94.9	2.9(10.0)[f]
Ceftriaxone	≤0.25	0.5	92.8	5.3(9.3)[f]
Gentamicin	≤2	>8	87.0	11.9
Imipenem	≤0.5	≤0.5	100.0	0.0
Piperacillin/Tazobactam	2	8	94.8	3.0
Trimethoprim/Sulfamethoxazole	≤0.5	>2	66.1	33.2
***Enterococcus* spp. (4; 650)**				
Garenoxacin	0.25	>4	(70.8)[e]	(14.0)
Ciprofloxacin	1	>2	52.9	38.6
Gatifloxacin	0.5	>4	66.0	31.8
Levofloxacin	1	>4	63.1	35.2
Moxifloxacin	0.25	>4	-	-
Ampicillin	≤2	>16	87.1	12.9
Chloramphenicol	8	>16	83.2	14.2
Gentamicin (high-level)	≤500	>1000	69.8	-
Linezolid	2	2	99.5	0.2
Teicoplanin	≤2	≤2	94.3	4.8
Vancomycin	1	4	92.5	6.8
***Klebsiella* spp. (5; 465)**				
Garenoxacin	0.12	>4	(87.5)[e]	10.1
Ciprofloxacin	≤0.25	>2	87.5	10.5
Gatifloxacin	0.06	2	90.3	5.8
Levofloxacin	0.06	4	89.0	6.5
Moxifloxacin	0.12	>4	-	-
Amoxicillin/Clavulanate	4	>16	73.8	10.8
Cefepime	≤0.12	8	91.4	6.2
Cefoxitin	4	16	86.9	7.7
Ceftazidime	≤1	>16	84.9	12.0(22.8)[f]
Ceftriaxone	≤0.25	>32	80.6	12.5(21.9)[f]
Gentamicin	≤2	>8	81.9	16.3
Imipenem	≤0.5	≤0.5	100.0	0.0
Piperacillin/Tazobactam	2	>64	84.1	11.4
Trimethoprim/Sulfamethoxazole	≤0.5	>2	76.6	20.4
***Enterobacter* spp. (6; 463)**				
Garenoxacin	0.12	>4	(87.7)[e]	10.2
Ciprofloxacin	≤0.25	1	91.1	7.7
Gatifloxacin	0.06	1	92.6	5.3
Levofloxacin	≤0.03	1	92.3	6.4
Moxifloxacin	0.06	2	-	-
Amoxicillin/Clavulanate	>16	>16	4.9	93.4
Cefepime	≤0.12	2	98.1	1.1
Cefoxitin	>32	>32	3.4	93.8
Ceftazidime	≤1	>16	75.5	20.6
Ceftriaxone	≤0.25	>32	78.3	12.8
Gentamicin	≤2	8	89.6	10.0
Imipenem	≤0.5	1	99.6	0.2
Piperacillin/Tazobactam	2	64	81.1	8.3
Trimethoprim/Sulfamethoxazole	≤0.5	>2	85.3	13.2
ß-haemolytic streptococci (7; 420)				
Garenoxacin	0.06	0.12	(100.0)[e]	(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	99.5	-
Ceftriaxone	≤0.25	≤0.25	100.0	-
Clindamycin	≤0.06	0.12	94.5	5.5
Erythromycin	≤0.06	2	85.7	14.0
Linezolid	1	1	100.0	-
Meropenem	≤0.008	0.016	100.0	-
Penicillin	≤0.016	0.06	100.0	-
Vancomycin	0.5	0.5	100.0	-
Coagulase-negative staphylococci (8; 365)				
Garenoxacin	0.12	4	(55.6)[e]	(42.5)
Ciprofloxacin	0.25	>2	56.2	41.9
Gatifloxacin	0.25	4	57.5	33.4
Levofloxacin	0.25	>4	56.2	36.7
Moxifloxacin	0.12	2	67.4	22.1
Oxacillin	2	>8	52.1	47.9
Erythromycin	>8	>8	41.4	58.4
Clindamycin	0.12	>8	69.3	29.9
Gentamicin	≤2	>8	64.4	29.0
Linezolid	1	2	100.0	-
Quinupristin/Dalfopristin	≤0.25	0.5	99.7	0.0
Tetracycline	≤4	>8	79.7	19.2
Trimethoprim/Sulfamethoxazole	≤0.5	>2	60.8	36.2
Vancomycin	2	2	100.0	0.0
***P. mirabilis* (9; 238)**				
Garenoxacin	0.5	>4	(81.5)[e]	(16.4)
Ciprofloxacin	≤0.25	2	88.2	6.7
Gatifloxacin	0.12	4	89.1	6.7
Levofloxacin	0.06	2	93.7	5.0
Moxifloxacin	0.25	>4	-	-
Amoxicillin/Clavulanate	≤2	16	89.5	3.8
Cefepime	≤0.12	≤0.12	96.6	2.5
Cefoxitin	4	4	97.9	0.4
Ceftazidime	≤1	≤1	99.6	0.4(2.9)[f]
Ceftriaxone	≤0.25	≤0.25	96.2	2.9(4.2)[f]
Gentamicin	≤2	>8	86.6	11.3
Imipenem	1	2	99.6	0.0
Piperacillin/Tazobactam	≤0.5	1	99.6	0.0
Trimethoprim/Sulfamethoxazole	≤0.5	>2	71.4	25.6
***Acinetobacter* spp. (10; 210)**				
Garenoxacin	2	>4	(50.0)[e]	(40.5)
Ciprofloxacin	>2	>2	43.8	55.2
Gatifloxacin	4	>4	49.5	35.2
Levofloxacin	4	>4	49.0	37.1
Moxifloxacin	0.12	>4	-	-
Cefepime	16	>16	46.7	31.4
Ceftazidime	16	>16	44.3	47.1
Gentamicin	>8	>8	40.0	56.7
Imipenem	≤0.5	>8	80.0	16.7
Piperacillin/Tazobactam	64	>64	42.9	46.2
Polymyxin B	≤1	≤1	98.9	1.1

a. Includes 8,545 isolates or 92.6% of tested SSTI pathogens.
b. Susceptibility breakpoint criteria of the CLSI (2005).
c. Garenoxacin breakpoint for staphylococci equivalent to peer agents was ≤ 0.12 mg/L pending PK/PD analysis.
d. - = no interpretive criteria.
e. Garenoxacin breakpoint of ≤ 2 mg/L used for comparison purposes only.
f. Percentages in parenthesis are the proportion of ESBL phenotypes.

Conclusions

- Aerobic SSTI pathogens were generally susceptible to garenoxacin including staphylococci (55.6 - 72.5% at ≤ 0.12 mg/L) and enteric bacilli such as *E. coli* and *Klebsiella* spp. (83.6 - 87.5% at ≤ 2 mg/L).
- Garenoxacin demonstrated the greatest activity versus other Gram-positive cocci such as the enterococci (MIC_{50}, 0.25 mg/L) and ß-haemolytic streptococci (MIC_{90}, 0.12 mg/L). These streptococci represented serogroup A (198) B (133), C (17), F (3) and G (62). This potency was four-fold superior to gatifloxacin and moxifloxacin (MIC_{90}, 0.25 mg/L).
- Coupled with the recognized activity of garenoxacin against anaerobic species, this documented potency against the 10 most prevalent SSTI aerobic pathogens indicates that this new fluoroquinolone could be used to treat mixed SSTI (complicated or uncomplicated). However, in hospital settings where *P. aeruginosa* may be endemic and less susceptible to garenoxacin, therapy should be based upon established treatment guidelines and susceptibility testing results.

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