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In Vitro Activity of Garenoxacin, a Novel Des-F(6)-Quinolone, Against 120,088 Clinical Isolates Collected Worldwide by the SENTRY Antimicrobial Surveillance Program (1999-2002)

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AMENDED ABSTRACT

Background: Garenoxacin (GRN), formerly BMS284756, differs from recently approved quinolones (FQ), by the lack of a fluorine at the C-6 position. We analyzed the activity of GRN in comparison to gatifloxacin (GAT), levofloxacin (LEV) and ciprofloxacin (CIP) against a worldwide organism collection.

Methods: The isolates were collected as part of the SENTRY Program in North America (47%), Europe (27%), Latin America (14%) and Asia-Pacific (12%). They were consecutively collected from > 70 sites according to specific protocols and included Gram-positive cocci (GP; 55,661 isolates), Enterobacteriaceae (ENT; 35,554), non-fermentors (NF; 13,165), *H. influenzae* (HI; 11,107) and *M. catarrhalis* (MCAT; 4,601). The isolates were tested by NCCLS broth microdilution methods. A GRN susceptible (S) breakpoint of ≤ 2 μg/ml was applied for comparison purposes only.

Results: The results of major organisms tested follows:

Organism (no. tested)	MIC$_{50}$ (μg/ml)/% S			
	GRN	GAT	LEV	CIP
Gram-positive				
S. aureus (22,982)	≤0.03/89	0.12/77	0.25/64	0.5/62
S. pneumoniae (SPN; 12,471)	0.06/>99.9	0.25/99.3	1/99.1	1/-
CoNS (7,741)	0.12/88	0.25/90	0.5/58	1/51
Enterococci (6,420)	0.5/67	1/56	2/54	2/45
ß-haemolytic streptococci (4,360)	0.06/>99.9	0.25/99.8	0.5/99.6	0.5/-
Gram-negative				
E. coli (16,138)	≤0.03/89	≤0.03/89	≤0.03/89	≤0.25/89
HI (11,107)	≤0.03/>99.9	≤0.03/>99.9	≤0.03/100	≤0.03/>99.9
P. aeruginosa (PSA; 9,510)	2/57	1/66	0.5/69	0.25/71
Klebsiella spp. (7,982)	0.12/91	0.06/93	0.06/93	≤0.25/91
MCAT (4,601)	≤0.03/100	≤0.03/100	≤0.03/100	≤0.03/100
Enterobacter spp. (4,472)	0.12/87	≤0.03/90	≤0.03/90	≤0.25/88

GRN was eight to 16-fold more potent than LEV or CIP against GP and eight-fold less potent than CIP against *P. aeruginosa*. All FQ showed similar potency and spectrum against most ENT, HI, MCAT and *Acinetobacter*. GAT and LEV (MIC$_{50}$, 1 μg/ml; 89% S) were slightly more active than GRN (MIC$_{50}$, 2 μg/ml; 67% S) and CIP (MIC$_{50}$, 2 μg/ml; 32% S) against *S. maltophilia* (1,166 strains).

Conclusions: When compared to the most commonly used FQs against over 100,000 clinical isolates worldwide, GRN showed higher activity against GP (especially SPN) and similar activity against most clinically important Gram-negative bacilli (except PSA).

INTRODUCTION

Garenoxacin (formerly BMS 284756 and T-3811) differs from recently approved quinolones by the lack of a fluorine at the C-6 position. Among the marketed quinolones, significant differences in potency and spectrum have been demonstrated. Garenoxacin has shown potent activity against a wide range of bacterial pathogens, especially multi-drug resistant Gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae* or other streptococci. In addition, garenoxacin activity against many Gram-negative organisms has been comparable to that of the current fluoroquinolones.

The SENTRY Antimicrobial Surveillance Program is a worldwide longitudinal study that has been monitoring pathogen susceptibilities and trends since 1997. The purpose of the study was to analyze the activity of garenoxacin in comparison to gatifloxacin, levofloxacin and ciprofloxacin against a large collection of organisms from six continents.

METHODS

A total of 120,088 isolates were collected by the SENTRY Program in North America (47%), Europe (27%), Latin America (14%) and Asia-Pacific-South Africa (12%) from 1999 - 2002. The rank order of pathogens was: *S. aureus* (22,982 isolates), *E. coli* (16,138), *S. pneumoniae* (12,471), *H. influenzae* (11,107), *P. aeruginosa* (9,510), *Klebsiella* spp. (7,982), coagulase-negative staphylococci (CoNS; 7,741), *Enterococcus* spp. (6,420), *M. catarrhalis* (4,601), *Enterobacter* spp. (4,472), ß-haemolytic streptococci (4,360), *Acinetobacter* spp. (2,489), *Serratia* spp. (1,935), *P. mirabilis* (1,720), viridans group streptococci (1,687), *Salmonella* spp. (1,574), *S. maltophilia* (1,166), indole-positive *Proteae* (812) and *Citrobacter* spp. (921).

Susceptibility tests were performed in two coordinating laboratories. Isolates from North America, Latin America and Europe were tested at the Jones Microbiology Institute (North Liberty, Iowa, USA); while isolates from the Asia-Pacific-South Africa region were tested at the Women's and Children's Hospital (Adelaide, Australia). The isolates were susceptibility tested by NCCLS reference broth microdilution methods against garenoxacin, gatifloxacin, levofloxacin, ciprofloxacin, among other compounds. Quality control tests and colony counts were routinely performed with *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *S. pneumoniae* ATCC 49619, *H. influenzae* ATCC 49766 and 49247, *E. coli* ATCC 25922 and 35218, and *P. aeruginosa* ATCC 27853. A garenoxacin susceptible breakpoint of ≤ 2 μg/ml was applied for comparative purposes only. All other breakpoints were those published by the NCCLS.

COMMENTS

- Garenoxacin was the most potent quinolone tested against *S. aureus* (MIC, ≤ 0.03 μg/ml; 89.3% susceptible; 22,982 isolates tested). Garenoxacin was eight-fold more potent than levofloxacin (MIC$_{50}$, 0.25 μg/ml; 64.2% susceptible) and 16-fold more potent than ciprofloxacin (MIC$_{50}$, 0.5 μg/ml; 62.4% susceptible; Table 1).
- Garenoxacin and gatifloxacin showed similar in vitro activity against CoNS (MIC$_{50}$, 0.12 and 0.25 μg/ml, respectively). Both drugs demonstrated higher potency and spectrum than levofloxacin and ciprofloxacin (Table 1).
- Garenoxacin was eight- to 32-fold more active than the other quinolones against ß-haemolytic and viridans group streptococci (more than 6,000 isolates tested; Table 1).
- The potency and spectrum of garenoxacin was similar to that of ciprofloxacin against *E. coli* (16,138 isolates), *Klebsiella* spp. (7,982 isolates), *Enterobacter* spp. (4,472 isolates) and *Salmonella* spp. (1,574 isolates; Table 2). However, reduced activity was noted for *Serratia* spp., *P. mirabilis* and other Proteae.
- Gatifloxacin (66.2% susceptibility), levofloxacin (69.4%) and ciprofloxacin (70.6%) showed similar spectrum against *P. aeruginosa* (9,510 isolates tested). However, ciprofloxacin was the most potent quinolone (MIC$_{50}$, 0.25 μg/ml) tested against this pathogen (Table 3).
- All quinolones showed similar activity against *Acinetobacter* spp. (2,489 isolates). Gatifloxacin and levofloxacin were the most active quinolones against *S. maltophilia* (1,466 isolates; Table 3).
- Garenoxacin was the most potent quinolone tested against *S. pneumoniae*. Garenoxacin (MIC$_{50/90}$, 0.06 μg/ml) was 16-fold more potent that levofloxacin (MIC$_{50/90}$, 1 μg/ml) and four- to eight-fold more potent than gatifloxacin (Table 4).
- All quinolones were highly active (MIC$_{90}$, ≤ 0.03 μg/ml) against *H. influenzae* and *M. catarrhalis* (Table 4).

Table 1. In vitro activity of garenoxacin in comparison to other quinolones tested against Gram-positive pathogens (43,190 isolates).

Organism (n)	MIC$_{50}$	MIC$_{90}$	% S	% R
S. aureus (22,982)				
Garenoxacin	≤0.03	4	89.3[a]	3.4[a]
Gatifloxacin	0.12	4	77.2	9.3
Levofloxacin	0.25	>4	64.2	23.9
Ciprofloxacin	0.5	>2	62.4	36.5
CoNS[b] (7,741)				
Garenoxacin	0.12	4	87.6[a]	4.6[a]
Gatifloxacin	0.25	4	89.8	4.6
Levofloxacin	1	>4	58.2	26.6
Ciprofloxacin	1	>2	51.5	46.7
Enterococcus spp. (6,420)				
Garenoxacin	0.5	>4	67.1[a]	17.5[a]
Gatifloxacin	1	>4	56.3	41.5
Levofloxacin	2	>4	54.2	44.4
Ciprofloxacin	2	>2	45.0	46.7
ß-haemolytic streptococci (4,360)				
Garenoxacin	0.06	0.12	99.9[a]	0.0[a]
Gatifloxacin	0.25	0.25	99.8	0.2
Levofloxacin	0.5	1	99.6	0.3
Ciprofloxacin	0.5	1	-[c]	-[c]
viridans gr. streptococci (1,687)				
Garenoxacin	0.06	0.12	99.6[a]	0.1[a]
Gatifloxacin	0.25	0.5	98.5[d]	0.9[d]
Levofloxacin	0.5	1	97.7[d]	1.8[d]
Ciprofloxacin	1	>2	-[c]	-[c]

a. A susceptible breakpoint of ≤ 2 μg/ml and a resistant breakpoint of ≥ 8 μg/ml were used for comparative purposes only.
b. CoNS = coagulase-negative staphylococci.
c. - = No breakpoint has been established by the NCCLS.
d. *S. pneumoniae* breakpoints were used for comparative purposes only.

Table 2. In vitro activity of garenoxacin in comparison to other quinolones tested against enteric Gram-negative bacilli (35,554 isolates).

Organism (n)	MIC$_{50}$	MIC$_{90}$	% S	% R
E. coli (16,138)				
Garenoxacin	≤0.03	>4	88.9[a]	10.7[a]
Gatifloxacin	≤0.03	4	89.4	7.8
Levofloxacin	≤0.03	4	89.3	8.6
Ciprofloxacin	≤0.25	>2	88.9	10.9
Klebsiella spp. (7,982)				
Garenoxacin	0.12	2	91.4[a]	6.7[a]
Gatifloxacin	0.06	1	93.4	4.2
Levofloxacin	0.06	1	93.2	4.6
Ciprofloxacin	≤0.25	1	91.5	7.0
Enterobacter spp. (4,472)				
Garenoxacin	0.12	>4	86.6[a]	10.8[a]
Gatifloxacin	≤0.03	2	90.2	7.5
Levofloxacin	≤0.03	4	89.9	8.4
Ciprofloxacin	≤0.25	2	88.2	9.9
Serratia spp. (1,935)				
Garenoxacin	≤0.03	>4	74.9[a]	13.5[a]
Gatifloxacin	0.25	2	91.8	5.0
Levofloxacin	0.12	2	92.7	5.1
Ciprofloxacin	≤0.25	2	88.5	7.5
P. mirabilis (1,720)				
Garenoxacin	0.5	>4	78.3[a]	20.0[a]
Gatifloxacin	0.12	>4	84.3	10.5
Levofloxacin	0.06	4	89.1	7.6
Ciprofloxacin	≤0.25	>2	83.1	12.7
Salmonella spp. (1,574)				
Garenoxacin	0.06	0.25	99.1[a]	0.6[a]
Gatifloxacin	≤0.03	0.12	99.4	0.6
Levofloxacin	≤0.03	0.25	99.4	0.6
Ciprofloxacin	≤0.25	≤0.25	99.3	0.6
Indole-positive *Proteae* (812)				
Garenoxacin	0.5	>4	73.0[a]	21.8[a]
Gatifloxacin	0.12	>4	80.8	16.3
Levofloxacin	0.06	>4	81.0	15.3
Ciprofloxacin	≤0.25	>2	79.2	18.5
Citrobacter spp. (921)				
Garenoxacin	0.12	4	88.1[a]	9.3[a]
Gatifloxacin	≤0.03	2	92.2	4.5
Levofloxacin	≤0.03	1	92.3	4.6
Ciprofloxacin	≤0.25	1	91.0	7.0

a. A susceptible breakpoint of ≤ 2 μg/ml and a resistant breakpoint of ≥ 8 μg/ml were used for comparative purposes only.

Table 3. In vitro activity of garenoxacin in comparison to other quinolones tested against non-fermentative Gram-negative bacilli (13,165 isolates).

Organism (n)	MIC$_{50}$	MIC$_{90}$	% S	% R
P. aeruginosa (9,510)				
Garenoxacin	2	>4	57.1[a]	32.9[a]
Gatifloxacin	1	>4	66.2	26.6
Levofloxacin	0.5	>4	69.4	24.8
Ciprofloxacin	≤0.25	>2	70.6	7.3
Acinetobacter spp. (2,489)				
Garenoxacin	4	>4	49.3[a]	42.5[a]
Gatifloxacin	4	>4	49.7	36.0
Levofloxacin	4	>4	48.9	39.3
Ciprofloxacin	>2	>2	45.2	12.7
S. maltophilia (1,166)				
Garenoxacin	2	>4	67.2[a]	16.1[a]
Gatifloxacin	1	4	88.9	5.0
Levofloxacin	1	4	88.7	5.3
Ciprofloxacin	2	>2	31.6	38.7

a. A susceptible breakpoint of ≤ 2 μg/ml and a resistant breakpoint of ≥ 8 μg/ml were used for comparative purposes only.

Table 4. In vitro activity of garenoxacin in comparison to other quinolones tested against respiratory tract pathogens (28,179 isolates).

Organism (n)	MIC$_{50}$	MIC$_{90}$	% S	% R
S. pneumoniae (12,471)				
Garenoxacin	0.06	0.06	99.9[a]	0.1[a]
Gatifloxacin	0.25	0.5	99.3	0.7
Levofloxacin	1	1	99.1	0.8
Ciprofloxacin	1	2	-[b]	3.1[c]
H. influenzae (11,107)				
Garenoxacin	≤0.03	≤0.03	99.9[a]	0.1[a]
Gatifloxacin	≤0.03	≤0.03	99.9	0.0
Levofloxacin	≤0.03	≤0.03	100.0	0.0
Ciprofloxacin	≤0.03	≤0.03	99.9	0.1
M. catarrhalis (4,601)				
Garenoxacin	≤0.03	≤0.03	100.0[a]	0.0[a]
Gatifloxacin	≤0.03	≤0.03	100.0	0.0
Levofloxacin	≤0.03	0.06	100.0	0.0
Ciprofloxacin	≤0.03	0.06	100.0	0.0

a. A susceptible breakpoint of ≤ 2 μg/ml and a resistant breakpoint of ≥ 8 μg/ml were used for comparative purposes only.
b. - = No breakpoint has been established by the NCCLS and isolates with MIC of ≥ 4 μg/ml were considered resistant for comparative purposes only.
c. Isolates with ciprofloxacin MIC ≥ 4 μg/ml.

CONCLUSIONS

- Garenoxacin was the most active quinolone against Gram-positive organisms (more than 55,000 isolates tested), especially *S. pneumoniae* (MIC$_{90}$, 0.06 μg/ml) and *S. aureus* (MIC$_{90}$, 4 μg/ml).
- Garenoxacin showed similar potency and spectrum to the other quinolones against the most frequently isolated Gram-negative species.
- Comprehensive multicenter surveillance programs remain important to continually monitor the comparative activity of older and investigational antimicrobial agents.

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