Potency of Garenoxacin, A New Des-F(6)-Quinolone, Tested Against Community-Acquired Respiratory Tract Infection Pathogens Worldwide (29,837 Strains): Report from the SENTRY Antimicrobial Surveillance Program (1999-2003)

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Abstract

Objective: To evaluate the spectrum and potency of garenoxacin (GRN; formerly BMS-284756) tested against typical community-acquired respiratory tract infection (CARTI) pathogens isolated from clinic patients emphasizing *S. pneumoniae* (SPN), *H. influenzae* (HI) and *M. catarrhalis* (MCAT). A comprehensive collection of 29,837 isolates was assessed from Europe, Asia and the Americas, each susceptibility (S) tested by reference methods in centralized laboratories.

Methods: All testing was performed by NCCLS M7-A6 (2003) methods and results were interpreted by M100-S15 (2005). The breakpoint for GRN was defined as S at ≤ 1 mg/L for comparison with fluoroquinolones (FQs): gatifloxacin (GATI) S at ≤ 1 mg/L; levofloxacin (LEVO) S at ≤ 2 mg/L (≤ 1 mg/L used for comparisons here); and moxifloxacin (MOXI) S at ≤ 1 mg/L. The QRDR regions of *gyrA, parC* and *parE* were sequenced in those strains that had a GRN MIC ≥ 0.25 mg/L and/or were R to FQs.

Results: The SPN strains (11,878) were characterized as follows: penicillin non-S at 35.1% (R at 19.4%; this rate was higher than community-acquired, hospitalized pneumonia cases); erythromycin-R at 29.7%; and ciprofloxacin (CIPRO)-R (≥ 4 mg/L; Chen et al., 1999) at 3.9% = possible QRDR mutations. HI strains (12,569) overall had ampicillin (AMP)-R at 22.8% and beta-lactamase-negative AMP-R (BLNAR) at 1.0% with 98/132 of these strains from Asia (Japan). MCAT (5,390) strains were dominantly beta-lactamase-positive (PEN-R; 95.3%). The following table lists key GRN and FQ MIC results:

	MIC (mg/L)		% inhibited at ≤ 1 mg/L			
Organism (no. tested)	50%	90%	GRN	GATI	LEVO	MOXI
SPN						
PEN-S (7,703)	0.06	0.06	99.9	99.4	97.4	99.4
PEN-I (1,865)	0.06	0.06	99.8	98.9	96.9	99.3
PEN-R (2,310)	0.06	0.06	99.9	98.2	96.4	98.4
CIPRO-R (460)	0.06	1	97.8	76.1	37.4	80.7
HI						
Amp-S (9,707)	≤0.03	≤0.03	>99.9	>99.9	>99.9	>99.9
Amp-R (2,862)	≤0.03	≤0.03	100.0	100.0	100.0	100.0
BLNAR (132)	≤0.03	≤0.03	100.0	100.0	100.0	100.0
MCAT						
PEN-S (254)	≤0.03	≤0.03	100.0	100.0	100.0	100.0
PEN-R (5,136)	≤0.03	≤0.03	100.0	100.0	100.0	100.0

FQ-R SPN strains (GRN MIC, 1 - > 4 mg/L) had multiple QRDR mutations (*gyrA* at S83F or T, *parC* at S79F or T or D83N and *parE* at I460V). One FQR HI had QRDR mutations (*gyrA* at S84L and *parC* at E88K). The overall rank order of activity versus SPN using MIC_{50} (mg/L) results was: GRN (0.06) > MOXI (0.25) > GATI (0.5) > LEVO (1) > CIPRO (2).

Conclusions: GRN was the most active quinolone tested against a global collection of 29,837 typical CARTI pathogens and was at lease 4-fold more active than MOXI against SPN isolates. GRN should be a welcome addition to our antimicrobial formularies for ambulatory care treatment of FQR and multi-drug-R species associated with CARTI.

Introduction

Respiratory tract infections (pharyngitis, sinusitis, bronchitis and pneumonia) acquired in the community setting (CA-RTI) are responsible for the greatest volume of antimicrobial use in the world. Therefore, the development of resistance that might limit the use of popularly used ß-lactams (penicillins, cephalosporins), macrolides (erythromycin, azithromycin, clarithromycin), tetracyclines, trimethoprim/sulfamethoxazole, and fluoroquinolones could have serious global consequences. Rates of penicillin (also ß-lactams) or multiple resistances in *Streptococcus pneumoniae* have reached alarming levels (> 30%), and ß-lactamase activity among *Haemophilus influenzae* or *Moraxella catarrhalis* remains at a level that compromises the use of more affordable, older penicillins. The need for broad-spectrum agents has to some degree been met by the introduction of the modern "respiratory-tract fluoroquinolones" such as gatifloxacin, gemifloxacin and moxifloxacin. However, the detection of ciprofloxacin- and levofloxacin-resistant pneumococci indicates that the search for more potent agents in the quinolone class must continue.

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 alterations resulted 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 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 CA-RTI pathogens. A total of 29,837 isolates were analyzed from results generated by the reference (National Committee for Clinical Laboratory Standards [NCCLS], currently the Clinical Laboratory Standards Institute [CLSI]) methods as described in document M7-A6 [2003].

Materials and Methods

Susceptibility testing. All MIC values were generated using broth microdilution methods (CLSI/NCCLS, M6-A7) with 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). Concurrent quality assurance was maintained via use of CLSI/NCCLS-recommended strains: *E. coli* ATCC 25922 and 35218; *P. aeruginosa* ATCC 27583; *E. faecalis* ATCC 29212; *S. aureus* ATCC 25923 and 29213; *H. influenzae* ATCC 49247 and 49766; and *S. pneumoniae* ATCC 49619. All quality control results were within published MIC ranges (CLSI/NCCLS, 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 ≤ 1 mg/L was used for comparison purposes only.

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. Isolates were derived from a wide variety of clinical sources (Program Objectives) such as: bloodstream (BSI), community-acquired or nosocomial respiratory tract sites (RTI), skin and soft tissue infections (SSTI), urinary tract infections (UTI) and selected patient populations. In this investigation, the isolates were obtained from CA-RTI at medical centers in North America (≥ 30 sites in the USA and Canada), Latin America (10 sites), Europe (≥ 30 sites) and the Asia-Pacific region (nine nations plus South Africa). The distribution of tested species was: *S. pneumoniae* (11,878 including 7,703 penicillin [PEN]-susceptible; 1,865 PEN-intermediate; 2,310 PEN-resistant; and 460 strains resistant to ciprofloxacin at ≥ 4 mg/L), *H. influenzae* (12,569 with 9,707 susceptible to ampicillin), and *M. catarrhalis* (5,390 with 5,136 PEN-resistant by ß-lactamase production). ß-lactamase-negative ampicillin-resistant *H. influenzae* strains were detected at a rate of 1.0% and then characterized as to country of origin.

Molecular methods. For those *S. pneumoniae* and *H. influenzae* isolates with elevated garenoxacin MIC values (1 - > 4 mg/L), the quinolone resistance determining regions (QRDR) of *gyrA* or *B* and *parC* or *E* were PCR amplified and sequenced.

Results

- Among the *S. pneumoniae* strains tested (11,878), the resistance rates to key antimicrobials were as follows: penicillin (≥ 2 mg/L) at 19.4%; erythromycin at 29.4%; tetracycline at 25.3% (data not shown); and trimethoprim/sulfamethoxazole at 26.5% (Table 1).
- The frequency of ampicillin resistance amongst the *H. influenzae* isolates was 22.8% with 132 ß-lactamase-negative ampicillin-resistant isolates (98 from Japan; 74.2%, Table 2). The vast majority (95.3%) of *M. catarrhalis* strains were ß-lactamase producers (Table 1).
- Garenoxacin was the most active agent against *S. pneumoniae* (MIC_{90}, 0.06 mg/L, Table 1) and was 16-fold more active than levofloxacin. More than 99.9% of pneumococci were susceptible to garenoxacin at ≤ 1 or ≤ 2 mg/L. The incidence of levofloxacin resistance among penicillin-resistant *S. pneumoniae* isolates (2,310 strains) was 1.8%.
- Penicillin (Table 1) or macrolide (Table 2) resistance did not adversely influence garenoxacin potency in pneumococci. Similarly, ß-lactamase producing isolates of *H. influenzae* (GRN MIC_{90}, ≤ 0.03 mg/L) and *M. catarrhalis* (GRN MIC_{90}, ≤ 0.03 mg/L) were as susceptible to garenoxacin as those isolates that did not produce ß-lactamases. One fluoroquinolone non-susceptible *H. influenzae* strain was detected. The isolate had two mutations in the QRDR (Table 1) and exhibited decreased susceptibility to garenoxacin.
- A comparison of garenoxacin with levofloxacin (Table 2) demonstrated that garenoxacin was 16-fold more active than levofloxacin against *S. pneumoniae*; the drugs were equally active against *H. influenzae* and *M. catarrhalis*. The majority of the ciprofloxacin-resistant pneumococci (MIC ≥ 4 mg/L) were susceptible to garenoxacin (MIC_{90} 1 mg/L); in contrast only 37.4% of these isolates were inhibited by levofloxacin at 1 mg/L.
- Table 3 details the QRDR mutations identified in those strains of *S. pneumoniae* that exhibited the highest garenoxacin MIC values (2 - > 4 mg/L; 10 of 11,878 strains or 0.08%). Multiple mutations (2 - 4; average 3.3), usually in *gyrA* and *parC,* were observed.
- Nine fluoroquinolones were studied in the SENTRY Program from 1999 – 2003. Of these nine, garenoxacin exhibited excellent potency (MIC_{90} at 0.06 mg/L) with an activity and/or spectrum that was equal or superior to currently marketed agents such as gemifloxacin, moxifloxacin, gatifloxacin, levofloxacin and ciprofloxacin (Table 4; 1,195 to 11,901 strains tested per drug).

Table 1. In vitro activity of garenoxacin compared to seven other compounds used in the therapy of community-acquired respiratory tract infections (SENTRY Program, 1999 -2003).

	MIC (mg/L)		% by category:[a]		
Organism/antimicrobial agent (no. tested)	Range	50%	90%	Susceptible	Resistant
S. pneumoniae					
Penicillin-susceptible (7,703)					
Garenoxacin	≤0.03-4	0.06	0.06	>99.9[b]	<0.1
Ciprofloxacin	≤0.016->16	1	2	-	3.4
Levofloxacin	≤0.03->4	1	1	99.3	0.6
Azithromycin	≤0.5->4	≤0.5	2	88.5	10.7
Clindamycin	≤0.25->2	≤0.25	≤0.25	94.1	5.6
Amoxicillin/Clavulanate	≤0.25-1	≤0.25	≤0.25	100.0	0.0
Cefuroxime axetil	≤0.06-8	≤0.06	0.12	99.6	0.1
Trimethoprim/Sulfamethoxazole	≤0.5->4	≤0.5	2	82.7	8.4
Penicillin-intermediate (1,865)					
Garenoxacin	≤0.03-2	0.06	0.06	>99.9	0.0
Ciprofloxacin	≤0.016->16	1	2	-	4.2
Levofloxacin	≤0.03->4	1	1	98.8	1.0
Azithromycin	≤0.5->4	≤0.5	>4	51.0	44.1
Clindamycin	≤0.25->2	≤0.25	>2	73.0	26.5
Amoxicillin/Clavulanate	≤0.25-8	≤0.25	1	99.8	0.1
Cefuroxime axetil	≤0.06->8	1	4	59.9	24.7
Trimethoprim/Sulfamethoxazole	≤0.5->4	1	>4	43.3	38.5
Penicillin-resistant (2,310)					
Garenoxacin	≤0.03->4	0.06	0.06	>99.9	<0.1
Ciprofloxacin	0.25->16	1	2	-	5.1
Levofloxacin	0.06->4	1	1	98.1	1.8
Azithromycin	≤0.5->4	4	>4	27.7	67.6
Clindamycin	≤0.25->2	≤0.25	>2	62.1	37.3
Amoxicillin/Clavulanate	≤0.25->8	2	8	74.3	12.6
Cefuroxime axetil	≤0.06->8	8	8	0.2	98.4
Trimethoprim/Sulfamethoxazole	≤0.5->4	4	>4	12.9	77.3
H. influenzae					
ß-lactamase-negative (9,839)					
Garenoxacin	≤0.03-2	≤0.03	≤0.03	>99.9[c]	0.0
Ciprofloxacin	≤0.12->2	≤0.12	≤0.12	>99.9[c]	-
Levofloxacin	≤0.03-2	≤0.03	≤0.03	>99.9[c]	-
Azithromycin	≤0.5->16	1	2	99.7	-
Clindamycin	≤0.25->2	2	>2	-	-
Amoxicillin/Clavulanate	≤0.25->8	0.5	1	99.7	0.1
Cefuroxime axetil	≤0.06->8	1	2	97.6	0.2
Trimethoprim/Sulfamethoxazole	≤0.5->4	≤0.5	>4	79.4	23.9
ß-lactamase-positive (2,730)					
Garenoxacin	≤0.03-0.25	≤0.03	≤0.03	100.0	0.0
Ciprofloxacin	≤0.12-0.25	≤0.12	≤0.12	100.0	-
Levofloxacin	≤0.03-0.25	≤0.03	≤0.03	100.0	-
Azithromycin	≤0.5->16	1	2	99.7	-
Clindamycin	≤0.25->2	>2	>2	-	-
Amoxicillin/Clavulanate	≤0.25->8	1	2	99.7	0.1
Cefuroxime axetil	≤0.06->8	1	2	98.2	0.2
Trimethoprim/Sulfamethoxazole	≤0.5->4	≤0.5	>4	72.8	23.9
M. catarrhalis					
ß-lactamase-negative (254)					
Garenoxacin	≤0.03-0.12	≤0.03	≤0.03	100.0	0.0
Ciprofloxacin	≤0.03-0.12	≤0.03	≤0.03	-	-
Levofloxacin	≤0.03-0.12	≤0.03	0.06	-	-
Azithromycin	≤0.5	≤0.5	≤0.5	-	-
Clindamycin	0.5->2	2	>2	-	-
Amoxicillin/Clavulanate	≤0.25	≤0.25	≤0.25	-	-
Cefuroxime axetil	≤0.06-1	0.25	0.5	-	-
Trimethoprim/Sulfamethoxazole	≤0.5-1	≤0.5	≤0.5	-	-
ß-lactamase-positive (5,136)					
Garenoxacin	≤0.03-0.25	≤0.03	≤0.03	100.0	0.0
Ciprofloxacin	≤0.03-0.25	≤0.03	≤0.03	-	-
Levofloxacin	≤0.03-0.25	≤0.03	0.06	-	-
Azithromycin	≤0.5-1	≤0.5	≤0.5	-	-
Clindamycin	≤0.25->2	2	>2	-	-
Amoxicillin/Clavulanate	≤0.25-1	≤0.25	≤0.25	-	-
Cefuroxime axetil	≤0.06->8	1	2	-	-
Trimethoprim/Sulfamethoxazole	≤0.5->4	≤0.5	≤0.5	-	-

a. Susceptibility as defined by the CLSI/NCCLS M100-S15, where available.
b. A susceptibility breakpoint was assigned for garenoxacin at ≤ 2 mg/L and ≥ 8 mg/L for comparison purposes only. For ciprofloxacin, a resistance-only breakpoint was used at ≥ 4 mg/L.
c. One strain resistant to ciprofloxacin by QRDR mutations of: *gyrA* (S84L) and *parC* (E88K).

Table 2. Comparative MIC distributions for garenoxacin and levofloxacin tested against selected populations of CA-RTI isolates (SENTRY Program, 1999 - 2003).

		Cum. % inhibited at MIC (mg/L):							
Organism (no. tested)	Quinolone	≤0.03	0.06	0.12	0.25	0.5	1	2	4
S. pneumoniae									
All strains (11,878)	Garenoxacin	31.5	(93.8)[a]	98.9	99.1	99.5	99.9	>99.9	>99.9
	Levofloxacin	0.2	0.2	0.4	1.1	29.7	(97.1)	99.0	99.1
Macrolide-resistant (3,531)	Garenoxacin	36.5	(92.4)	97.6	98.0	98.9	99.8	>99.9	>99.9
	Levofloxacin	0.0	0.1	0.1	0.7	33.2	(95.7)	97.7	98.0
Ciprofloxacin-resistant (460)[b]	Garenoxacin	3.3	51.3	76.5	79.8	88.3	(97.8)	99.6	99.8
	Levofloxacin	0.0	0.0	0.0	0.0	0.2	37.4	74.8	77.4
H. influenzae									
All strains (12,569)	Garenoxacin	(99.0)	99.8	>99.9	>99.9	>99.9	>99.9	100.0	-
	Levofloxacin	(99.4)	99.9	>99.9	>99.9	>99.9	>99.9	100.0	-
BLNAR (132)[c]	Garenoxacin	(98.5)	100.0	-	-	-	-	-	-
	Levofloxacin	(100.0)	-	-	-	-	-	-	-
M. catarrhalis									
All strains (5,390)	Garenoxacin	(99.5)	99.9	>99.9	100.0	-	-	-	-
	Levofloxacin	87.0	(99.8)	>99.9	100.0	-	-	-	-

a. Parenthesis indicates the MIC_{90}, if an on-scale MIC was observed.
b. Ciprofloxacin MIC at ≥ 4 mg/L.
c. Among these strains, 98 were isolated from Japanese patients (74.2%; three medical centers only).

Table 3. Most common QRDR mutations associated with elevated garenoxacin MIC values in *S. pneumoniae*.

		QRDR mutation site				
Strain	Garenoxacin MIC (mg/L)	*gyrA*	*gyrB*	*parC*	*parE*	No. mutation sites
014-656	2	S81T	-	S79T	-	2
015-1345	2	S81T	-	S79F	I460V	3
019-2947	2	-	V432D	S79F	I460V	4
				G77E		
038-2097	2	E85K	-	S79F	I460V	4
				K137N		
053-2434	2	E85K	-	S79F	I460V	3
084-5037	>4	S81F	-	S79F	-	4
		E85K		D83Y		

Table 4. Comparisons of garenoxacin and eight peer fluoroquinolones tested against *S. pneumoniae* isolates from CA-RTI (1999 - 2003).[a]

		MIC (mg/L)			%	
Rank order[b]	Fluoroquinolone (no. tested)	50%	75%	90%	≤1 mg/L	(susceptible)[c]
1.	Sitafloxacin (1,195)[d]	0.03	0.03	0.06	100.0	(-)
2.	Garenoxacin (11,878)[d]	0.06	0.06	0.06	>99.9	(-)
3.	Gemifloxacin (5,380)	≤0.12	≤0.12	≤0.12	>99.9	(99.3)
4.	Trovafloxacin (1,990)[d]	0.12	0.12	0.25	99.3	(99.3)
5.	Moxifloxacin (9,911)	0.12	0.12	0.25	99.2	(99.2)
6.	Gatifloxacin (11,878)	0.25	0.25	0.5	99.1	(99.1)
7.	Sparfloxacin (1,195)[d]	0.25	0.5	0.5	98.7	(98.2)
8.	Levofloxacin (11,878)	1	1	1	97.1	(99.0)
9.	Ciprofloxacin (11,878)	1	2	2	69.4	(-)

a. From the SENTRY Program worldwide.
b. Ranked by potency and % susceptible at published breakpoints, if available. Does not include PK/PD analyses.
c. Susceptible breakpoints of the CLSI/NCCLS (2005).
d. Investigational or withdrawn compounds.

Conclusions

- When tested against 29,837 strains of *S. pneumoniae, H. influenzae* and *M. catarrhalis* from CA-RTI, garenoxacin demonstrated a spectrum and potency that was equal or superior to currently marketed fluoroquinolones, oral ß-lactams, macrolides, clindamycin and trimethoprim/sulfamethoxazole.
- Of those *S. pneumoniae* isolates that were resistant to both ciprofloxacin and levofloxacin due to QRDR mutations, approximately 98% had garenoxacin MIC results of ≤ 1 mg/L and approximately 80% of MIC values ≤ 0.25 mg/L.
- Garenoxacin appears to be an excellent agent for oral therapy of CA-RTI, particularly for those isolates of *S. pneumoniae* that are resistant to other contemporary fluroquinolones.

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