Garenoxacin Activity and Potency against *S. pneumoniae* and *H. influenzae* Respiratory Tract Isolates (2004 - 2005): Report from a Worldwide Surveillance Network

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Abstract

Objective: To evaluate the comparative activity of garenoxacin (GRN), a novel des-F(6) quinolone, tested by reference methods against recent community-acquired respiratory tract infection (CARTI) and community acquired pneumonia (CAP) isolates. *S. pneumoniae* (SPN) and *H. influenzae* (HI) strains from Latin America (10 sites), USA (23), Europe (20), and the Far East (11) were sampled in 2004-2005.

Methods: Consecutive, non-duplicate cultures of SPN (3,042) and HI (965) were tested by CLSI reference broth microdilution methods with concurrent QC and interpretative criteria (M7-A7 and M100-S16, 2006). Comparison antimicrobials numbered >25, including: penicillin (PEN), clarithromycin (CLAR), ceftriaxone (CTRI), and 4 fluoroquinolones (FQ), ciprofloxacin (CIPRO), levofloxacin (LEVO), gatifloxacin (GATI), and moxifloxacin (MOXI). GRN susceptibility (S) was defined as MIC at <=1 mg/L for comparison purposes only. CARTI isolates came from 23 nations and CAP strains from hospitalized patients (HCAP) in 9 countries.

Results: The following table lists key study results:

	MIC_{90} (mg/L)/ %S			% non-S (R)		
Organism/source (no.)	GRN	LEVO	GATI	PEN[a]	CLAR	CTRI
SPN						
HCAP (84)	0.06/100.0	1/98.8	0.5/98.8	34.5	26.9	1.2
CARTI (2,958)	0.06/99.9	1/98.0	0.5/98.9	37.3	32.5	4.0
HI						
CARTI (965)	0.016/100.0	<=0.03/100.0	<=0.03/100.0	23.1	11.1	0.0

a. Ampicillin result for HI.

GRN activity remained unchanged compared to 1999 - 2003 results (2005 ECCMID abstract 1555 and 1565) with 99.9 and 100.0% inhibition at <=1 mg/L for SPN and HI, respectively. GRN was more potent than LEVO (16-fold), GATI (8-fold) and MOXI (4-fold) against SPN, and HCAP isolates were slightly more S than CARTI strains to nearly all agents. CTRI (96.0 - 98.8% S), cefepime (92.8 - 96.4%) and amoxicillin/clavulanate (90.5 - 91.8%) were the most active beta-lactams against SPN. PEN- and macrolide (CLAR)-R was elevated (26.9 - 37.3%) in SPN and nearly 24% of HI produced a beta-lactamase (ampicillin-R). Possible QRDR mutations (CIPRO MIC, >=4 mg/L) in SPN were noted for 1.2 - 2.8% of isolates.

Conclusions: GRN continues to exhibit the greatest activity (4- to 16-fold) compared to FQs tested against an updated (2004 - 2005) collection of CARTI and CAP isolates of SPN and HI. As FQ resistance evolves due to QRDR mutations, GRN MIC values generally remain well below potentially R levels, minimizing further selective pressure.

Introduction

Respiratory tract infections (CA-RTI; pharyngitis, sinusitis, bronchitis, and pneumonia) acquired in the community setting are responsible for the greatest amount of antimicrobial use worldwide. Therefore, the development of resistance limiting the use of popularly prescribed ß-lactams (penicillins, cephalosporins), macrolides (erythromycin, azithromycin, clarithromycin), tetracyclines (including doxycycline), trimethoprim/sulfamethoxazole, and fluoroquinolones have serious global consequences. Rates of penicillin or multidrug-resistant *Streptococcus pneumoniae* have reached alarming levels (>30%) and ß-lactamase activity among *Haemophilus influenzae* or *Moraxella catarrhalis* remains at levels that compromises the use of more affordable penicillins. The emergent need for broad-spectrum agents has been most recently met by the introduction of true "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, such as garenoxacin, must continue.

Garenoxacin 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 the Enterobacteriaceae, staphylococci, streptococci (*S. pneumoniae*, viridans group and ß-haemolytic species), *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 complemented by a favorable pharmacokinetic/pharmacodynamic profile, leading to a high AUC/MIC ratio. This high ratio results in a greater probability of favorable target attainment that has been associated with successful bacterial eradication and minimization of QRDR mutational events among indicated species (low MPC values). These elements of spectrum and potency favor garenoxacin applications for CA-RTI (hospitalized or ambulatory patients).

The in vitro testing results for garenoxacin from the SENTRY Antimicrobial Surveillance Program platform were summarized from 1999 onward to assess the spectrum and potency versus CA-RTI pathogens. Isolates were analyzed and presented at this congress in 2005 (Abstract 1555) for 1999 - 2003. All results were generated by the reference Clinical and Laboratory Standards Institute (CLSI) methods as described in documents M7-A7 (2006) and M100-S16 (2006) with the most recent 2004 - 2005 data (4,007 strains) summarized here.

Materials and Methods

Bacterial strains tested: Recent CA-RTI strains were categorized into those treated in the ambulatory setting (CA-RTI) and those requiring hospitalization (HCAP; see Table 1, *S. pneumoniae* strains only). The organisms were cultured in 2004 - 2005 from Latin America (10 medical centers), USA (23), Europe (20) and the Western-Pacific region (11). The number of strains were: *S. pneumoniae* (3,042) and *H. influenzae* (965). The CA-RTI *S. pneumoniae* and *H. influenzae* came from non-duplicated cultures in 23 nations and the HCAP from hospitalized patients in nine countries.

Susceptibility testing methods: All MIC values were generated using broth microdilution methods (CLSI M7-A7) with panels produced by TREK Diagnostics (Cleveland, Ohio, USA). Mueller-Hinton broth was supplemented where indicated with 2-5% lysed horse blood (streptococci) and HTM components (*Haemophilus*). Concurrent quality assurance was maintained via use of CLSI-recommended strains: *Escherichia coli* ATCC 25922 and 35218, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus* ATCC 2523 and 29213, *H. influenzae* ATCC 49247 and 49766, and *S. pneumoniae* ATCC 49619. All quality control results were within published MIC ranges (M100-S16) for each agent tested. More than 30 different antimicrobial agents were processed each year with selected agents (18; Table 1) compared to garenoxacin in this presentation. A breakpoint for garenoxacin susceptibility and resistance at ≤1/≥4 mg/L was used for comparison purposes only.

Results

- Compared to results previously presented (ECCMID, 2005), garenoxacin maintained high-level activity against CA-RTI and HCAP isolates of *S. pneumoniae* (99.9% at ≤ 1 mg/L in 1999 - 2003 and >99.9% for 2004 - 2005), and *H. influenzae* (100.0% at ≤ 1 mg/L for 1999 - 2005).
- Garenoxacin was 16-fold more potent than ciprofloxacin or levofloxacin versus *S. pneumoniae*, and two-to four-fold more active than moxifloxacin.
- All tested agents in the fluoroquinolone class had excellent activity against *H. influenzae* (MIC_{90}, ≤ 0.03 mg/L).
- A total of 1.2 - 2.8% of *S. pneumoniae* had elevated ciprofloxacin MICs (≥ 4 mg/L) characteristic of QRDR mutations, but <0.1% (only one strain) of isolates had a garenoxacin MIC at > 2 mg/L.
- The most compromised agents due to increasing resistance rates among *S. pneumoniae* were: penicillin (17.9 - 19.3% high-level resistance), cefuroxime axetil (21.5%), macrolides (32.2 - 36.9%), clindamycin (15.5 - 17.7%), tetracycline (11.9 - 14.8%) and trimethoprim/sulfamethoxazole (25.0 - 25.2%).

Table 1. Activity of garenoxacin and selected comparison agents tested against *S. pneumoniae* and *H. influenzae* from CA-RTI and pneumococci from patients hospitalized with CAP (4,007 strains; 2004 - 2005).

		MIC (mg/L)		
Organism/infection type (no. tested)	Antimicrobial Agent	50%	90%	% Susceptible (resistant)[a]
S. pneumoniae				
CA-RTI (2,958)	Garenoxacin	0.06	0.06	99.9 (<0.1)[b]
	Ciprofloxacin	1	2	- (2.8)[c]
	Gatifloxacin	≤0.5	≤0.5	99.0 (0.9)
	Levofloxacin	1	1	99.0 (1.0)
	Moxifloxacin	0.12	0.25	99.1 (0.4)
	Penicillin	≤0.03	2	62.7 (19.3)
	Amox/Clav[d]	≤1	2	91.8 (4.8)
	Cefuroxime axetil	≤1	8	75.7 (21.5)
	Cefepime	≤0.12	1	92.8 (0.6)
	Ceftriaxone	≤0.25	1	96.0 (0.7)
	Erythromycin	≤0.25	>8	67.2 (32.2)
	Clindamycin	≤0.25	>2	81.7 (17.7)
	Doxycycline	≤1	8	77.7 (14.8)
	TMP/SMX[d]	≤0.5	>2	65.4 (25.2)
HCAP (84)	Garenoxacin	0.06	0.06	100.0 (0.0)[b]
	Ciprofloxacin	1	2	- (1.2)[c]
	Gatifloxacin	≤0.5	≤0.5	98.8 (1.2)
	Levofloxacin	1	1	98.8 (1.2)
	Moxifloxacin	0.12	0.25	98.8 (1.2)
	Penicillin	≤0.016	2	65.5 (17.9)
	Amox/Clav[d]	≤1	2	90.5 (2.4)
	Cefepime	≤0.12	1	96.4 (0.0)
	Ceftriaxone	≤0.25	1	98.8 (0.0)
	Erythromycin	≤0.06	>8	63.1 (26.9)
	Clindamycin	≤0.25	>2	83.3 (15.5)
	Doxycycline	≤1	8	82.1 (11.9)
	TMP/SMX[d]	≤0.5	>2	61.9 (25.0)
	Vancomycin	0.25	0.5	100.0 (-)
H. influenzae				
CA-RTI (965)	Garenoxacin	≤0.008	0.016	100.0 (0.0)
	Ciprofloxacin	≤0.03	≤0.03	100.0 (0.0)
	Gatifloxacin	≤0.03	≤0.03	100.0 (0.0)
	Levofloxacin	≤0.03	≤0.03	100.0 (0.0)
	Moxifloxacin	≤0.03	≤0.03	100.0 (0.0)
	Ampicillin	≤0.5	>4	76.1 (23.1)
	Amox/Clav[d]	0.5	1	100.0 (0.0)
	Cefuroxime axetil	0.5	2	98.7 (0.1)
	Clarithromycin	8	16	88.9 (1.2)
	Chloramphenicol	≤2	≤2	98.5 (0.8)
	Rifampicin	≤0.25	0.5	99.6 (0.1)
	Doxycycline	≤1	≤1	99.4 (0.1)
	TMP/SMX[d]	≤0.5	>4	79.4 (18.4)

a. CLSI (2006) interpretive criteria.
b. For comparison purposes, garenoxacin breakpoints were defined at ≤1/≥4 mg/L.
c. Proportion of all isolates with MIC at ≥ 4 mg/L indicating possible QRDR mutations.
d. Amox/Clav = amoxicillin/clavulanic acid (2:1) and TMP/SMX = trimethoprim/sulfamethoxazole (1:19).

Conclusions

- Garenoxacin has maintained high in vitro activity when tested against CA-RTI and HCAP isolates of *S. pneumoniae* (MIC_{90}, 0.06 mg/L) from a worldwide sample collection (2004 - 2005).
- Garenoxacin was also very active (MIC_{90}, ≤ 0.03 mg/L) against all isolates of *H. influenzae* from CA-RTI.
- Garenoxacin continues to be an excellent candidate for treatment of CA-RTI and HCAP caused by *S. pneumoniae* or *H. influenzae* that have resistances to other orally administered agents, including previously introduced fluoroquinolones.

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