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Comparative Activity of Garenoxacin (BMS 284756), a Novel Desfluoroquinolone, Tested Against 13,704 Isolates From Community-Acquired Respiratory Tract Infections: Results From the SENTRY Antimicrobial Surveillance Program

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ABSTRACT

Background: Emerging resistances to orally administered antimicrobials have escalated among bacterial pathogens (*Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*) causing community-acquired respiratory tract infections (CARTI). More compounds that are potent and clinically tolerated appear needed. The spectrum and potency of garenoxacin, formerly BMS 284756, was assessed against a worldwide collection of CARTI isolates from a longitudinal surveillance network, the SENTRY Antimicrobial Surveillance Program.
Methods: A total of 13,704 strains of *H. influenzae, M. catarrhalis*, and *S. pneumoniae* was tested by reference methods and compared to numerous other agents. Nearly all (95.8%) *M. catarrhalis* were penicillin-resistant (R), 23.3% of *H. influenzae* were ampicillin-R and 19.2% of *S. pneumoniae* had MICs ≥ 2 µg/ml to penicillin. The distribution of strains by monitored geographic region was: Asia-Pacific (n = 1,434), Europe (n = 3,231), Latin America (n = 1,296), and North America (n = 7,743).
Results: Garenoxacin was very active against the three monitored species with MIC_{90} values of ≤ 0.06 µg/ml. Garenoxacin and other quinolones were equally active against Gram-negative pathogens (except moxifloxacin which was 2- to 4-fold less potent versus *M. catarrhalis*), but against pneumococci the rank order of potency (MIC_{50} in µg/ml) was: gemifloxacin (0.015) > garenoxacin (0.06) > trovafloxacin = moxifloxacin (MOXI; 0.12) > gatifloxacin (0.25) > levofloxacin (LEVO) = ciprofloxacin (CIPRO; 1). Trends toward resistance worldwide included LEVO/CIPRO-R (MIC, ≥ 4 µg/ml) increases from 0.9/1.5% (1999) to 1.0/6.8% (2001). A single *S. pneumoniae* strain had a garenoxacin MIC of > 2 µg/ml (0.02%) compared to R for LEVO and MOXI at 0.8%. The highest quinolone-R was observed in the Asia-Pacific and North American regions.
Conclusions: Garenoxacin, a new desfluoroquinolone with improved safety, was documented to be active (MIC, ≤ 1 µg/ml) against > 99.9% of all CARTI pathogen isolates in the four geographic regions of the SENTRY Program. Evolving R to other classes appears to position this investigational desfluoroquinolone as a potential treatment option for future clinical use in ambulatory patients.

INTRODUCTION

Community-acquired respiratory tract infections (CARTI) account for more than one-third of doctor's office visits and a majority of antimicrobial prescriptions are used for the treatment of this indication. Empiric oral therapy is most often used and therefore, broad-spectrum antimicrobials are most often preferred. During the past decade, several fluoroquinolones have been developed with a variety of molecular substitutions that have increased the activity against pathogens primarily suspected of causing CARTI. The increased utilization of quinolones in general has produced increasing resistance rates among several key human pathogens. To date, the prevalence of fastidious respiratory pathogens resistant to quinolones remains low. However, the resistance rates to older quinolones has increased and a continued trend of resistance to newer quinolones has been shown.

Garenoxacin (formerly BMS 284756 and T-3811) is a des-fluoro(6)-quinolone with potent in vitro activity against many Gram-positive and -negative organisms. Its overall spectrum of activity is superior to older quinolones such as ciprofloxacin and levofloxacin and comparable to newer agents like moxifloxacin and gatifloxacin. In vitro studies have shown desfluoroquinolones have lower toxicity in mice and high bioavailability.

In this study, we compare the in vitro activity of garenoxacin to several orally administered agents including other quinolones, *ß-lactams*, macrolides, clindamycin, Synercid®, and trimethoprim/sulfamethoxazole against a large collection of recent isolates of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. These organisms were collected from patients diagnosed with CARTI in the SENTRY Antimicrobial Surveillance Program during 1999 to 2001 from medical centers throughout the world. All tests were performed using reference methods.

MATERIALS AND METHODS

Organisms tested. The bacterial isolates tested in this study were collected by more than 60 medical centers in North America, Latin America, Europe and Asia-Pacific regions during 1999 to 2001 as part of the SENTRY Antimicrobial Surveillance Program. A total of 13,704 strains derived from patients diagnosed with CARTI consisted of 5,974 *H. influenzae* (23.3% ampicillin-resistant, MIC, ≥2 µg/ml), 2,409 *M. catarrhalis* (>95% ß-lactamase-positive) and 5,321 *S. pneumoniae* (36.3% penicillins non-susceptible). These strains were forwarded to the monitoring sites (Iowa, USA and Adelaide, Australia) where identifications were confirmed. (Tables 1 and 2).

Table 1. Distribution of 13,704 isolates by species among the four monitored SENTRY Antimicrobial Surveillance Program regions (1999-2001).

Program year	Organism tested	Region: Asia-Pacific	Europe	Latin America	North America
1999	*H. influenzae*	220	211	197	1096
	M. catarrhalis	113	91	87	542
	S. pneumoniae	255	213	257	1201
2000	*H. influenzae*	328	680	264	1198
	M. catarrhalis	159	285	48	525
	S. pneumoniae	359	536	245	1102
2001	*H. influenzae*	NT[a]	668	104	1008
	M. catarrhalis	NT	142	26	391
	S. pneumoniae	NT	405	68	680

a. NT = not tested.

Table 2. Characteristics of the tested populations of respiratory tract pathogens.

Population (no. tested)	Defining features
H. influenzae (5,974)	23.3% ampicillin resistance 22.8% trimethoprim/sulfamethoxazole resistance
M. catarrhalis (2,409)	95.8% ß-lactamase producers
S. pneumoniae (5,321)	36.3% non-susceptibility to penicillins 28.4% macrolide resistance (15.4% M-phenotypes) 1.4% ceftriaxone resistance 0.3% cefepime resistance <1.0% quinolone resistance

Antimicrobial agents. Garenoxacin was provided by Bristol-Myers Squibb (Princeton, NJ, USA) and the comparison compounds were obtained from their respective manufacturers.

Susceptibility testing. All strains were tested using the reference broth microdilution methods (NCCLS) in validated dry-form trays (TREK Diagnostics, Westlake, OH, USA). More than 30 antimicrobials were tested (17 reported here). After inoculation, the trays were incubated in ambient air at 35ºC for 16 to 20 hours and minimum inhibitory concentration (MIC) endpoints were determined. NCCLS [2002] susceptibility interpretations were utilized for all comparison compounds and ≤2 µg/ml was applied for garenoxacin, the breakpoint used for levofloxacin.

RESULTS

- Garenoxacin, along with the other quinolones tested, demonstrated the most potent activity against *H. influenzae* (MIC_{50}, ≤0.008 - ≤0.03 µg/ml; 99.9 - 100.0% susceptible), *M. catarrhalis* (MIC_{50}, ≤0.008 - <0.03 µg/ml; 100.0% susceptible), and *S. pneumoniae* (MIC_{50}, 0.015 - 1 µg/ml; 99.1 - 99.9% susceptible). (Table 3).

Table 3. Antimicrobial activity of garenoxacin (formerly BMS 284756) and 16 comparison agents tested by reference methods against fastidious respiratory tract infection isolates.

Antimicrobial agent	$MIC_{50/90}$ in µg/ml (% susceptible)[a] for: *H. influenzae* (n=5,974)	*M. catarrhalis* (n=2,409)	*S. pneumoniae* (n=5,321)
Ampicillin	≤0.5/>4 (76.7)	NT[b]	NT
Penicillin	NT	>4/>4 (4.2)	≤0.03/2 (63.7)
Amoxicillin/Clavulanate	0.5/1 (99.7)	≤0.25/≤0.25 (100.0)	0.25/2 (95.1)
Ceftriaxone	≤0.008/≤0.008 (>99.9)	0.25/0.5 (100.0)	0.03/1 (94.0)
Cefepime	≤0.06/0.12 (>99.9)	0.5/2 (98.8)	≤0.06/1 (95.7)
Clarithromycin	8/16 (87.3)	≤0.25/≤0.25 (100.0)	NT
Erythromycin	NT	NT	≤0.25/>32 (70.8)
Clindamycin	NT	NT	≤0.25/4 (86.5)
Quinupristin/Dalfopristin	NT	NT	0.5/0.5 (99.7)
Trimethoprim/Sulfamethoxazole	≤0.5/>4 (77.2)	≤0.5/≤0.5 (97.5)	≤0.5/>4 (61.9)
Ciprofloxacin	≤0.03/≤0.03 (>99.9)	≤0.03/≤0.03 (100.0)	1/2 (-)[c]
Garenoxacin[d]	≤0.03/≤0.03 (100.0)	≤0.03/≤0.03 (100.0)	0.06/0.06 (>99.9)
Gatifloxacin	≤0.03/≤0.03 (100.0)	≤0.03/≤0.03 (100.0	0.25/0.5 (99.2)
Levofloxacin	≤0.03/≤0.03 (100.0)	≤0.03/≤0.03 (100.0)	1/1 (99.1)
Moxifloxacin	≤0.03/≤0.03 (>99.9)	0.06/0.06 (100.0)	0.12/0.25 (99.2)
Trovafloxacin	≤0.03/≤0.03 (100.0)	≤0.03/≤0.03 (100.0)	0.12/0.25 (99.4)

a. Susceptibility as defined by the NCCLS [2002].
b. NT = not tested.
c. - = no interpretive criteria have been suggested [NCCLS, 2002].
d. Garenoxacin susceptibility defined as a MIC of ≤2 µg/ml (as for levofloxacin) [NCCLS, 2002].
e. An MIC of ≤0.25 µg/ml was defined as susceptible due to more limited bioavailability.

- Rank order for quinolone activity against the pneumococci was: gemifloxacin (MIC_{50}, 0.015 µg/ml) > garenoxacin (MIC_{50}, 0.06 µg/ml) > moxifloxacin = trovafloxacin (MIC_{50}, 0.12 µg/ml) > gatifloxacin (MIC_{50}, 0.25 µg/ml) > levofloxacin = ciprofloxacin (MIC_{50}, 1 µg/ml).

- Rank order for susceptibilities against the pneumococci was: garenoxacin (100.0%) > gemifloxacin (99.7%) > trovafloxacin (99.4%) > gatifloxacin = moxifloxacin (99.2%) > levofloxacin (99.1%).

- Ciprofloxacin showed a 4.5-fold increase in resistance among *S. pneumoniae* over the three year period, from 1.5% in 1999 to 6.8% in 2001. (Table 4).

Table 4. Trends in the susceptibility to 4 quinolones of 5,321 *S. pneumoniae* isolates in the SENTRY Program from community-acquired respiratory tract infections for 1999 through 2001 worldwide.

Quinolone tested	% of isolates with MIC at ≥4 µg/ml for:[a] 1999	2000	2001
Ciprofloxacin	1.5	3.5	6.8
Garenoxacin	0.0	<0.1[b]	0.0
Gatifloxacin	0.9	0.8	0.8
Levofloxacin	0.9	1.0	1.0

a. Resistance as defined by Chen et al. [1999] or by the NCCLS [2002].
b. One strain (0.02%) with a MIC of 4 µg/ml; >99.9% of strains were inhibited at ≤1 µg/ml.

CONCLUSIONS

- Garenoxacin possesses almost complete (99.9%) activity against isolates obtained from all geographical regions of the SENTRY Program (1999-2001).
- The activity of ciprofloxacin during the past three years has eroded and its spectrum against *S. pneumoniae* has become more compromised. (Table 4).
- Longitudinal surveillance programs must be continued to track the quinolone class in order to monitor evolving resistance patterns and direct future treatment options.

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