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Comparison of In Vitro Activities of Gatifloxacin and Ciprofloxacin against Four Taxa of Rapidly Growing Mycobacteria

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By using current NCCLS broth microdilution methods, we found that gatifloxacin inhibited 90% of the isolates of the *Mycobacterium fortuitum* group at ≤0.12 μg/ml and 90% of the *Mycobacterium chelonae* isolates at ≤4 μg/ml. Gatifloxacin was generally fourfold more active than ciprofloxacin. We recommend that both gatifloxacin and ciprofloxacin be tested routinely against rapidly growing mycobacteria.

The fluoroquinolones have become increasingly important in the treatment of infections due to mycobacteria. Previous studies involving a wide variety of clinical bacterial isolates and the new 8-methoxy quinolone, gatifloxacin, have shown that gatifloxacin is more active than ciprofloxacin against untreated strains (1, 5) and that its activity (MIC) is less affected overall by mutations responsible for increasing quinolone resistance. Thus, we undertook a comparative study of the in vitro susceptibilities of the rapidly growing mycobacteria (RGM) to gatifloxacin and ciprofloxacin.

(A portion of this study was presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Ill., 16 to 19 December 2001.)

We tested ciprofloxacin and gatifloxacin against 124 random clinical isolates of RGM. Isolates included *Mycobacterium abscessus* (24 isolates), *M. chelonae* (32 isolates), the *M. fortuitum* group (39 isolates, including 20 isolates of *M. fortuitum,* 7 isolates of *M. peregrinum,* 3 isolates of *M. mageritense,* 4 isolates of sorbitol-positive *M. fortuitum* third biovariant, and 5 isolates of sorbitol-negative *M. fortuitum* third biovariant), *M. smegmatis* group (3 isolates of *M. wolinskyi* and 2 isolates each of *M. smegmatis* sensu stricto and *M. goodii*) (2), *M. immunogenum* (2 isolates) (16), and *M. mucogenicum* (20 isolates). Susceptibilities were determined only once for each isolate.

The American Type Culture Collection (ATCC) strains of RGM studied included *M. fortuitum* ATCC 6841^T, *M. peregrinum* ATCC 14467^T, *M. peregrinum* ATCC 700686, *M. abscessus* ATCC 19977^T, *M. chelonae* ATCC 35752^T, *M. smegmatis* sensu stricto ATCC 19420^T, *M. wolinskyi* ATCC 700010^T, *M. goodii* ATCC 700504^T, sorbitol-positive *M. fortuitum* third biovariant ATCC 49403, and sorbitol-negative *M. fortuitum* third biovariant ATCC 49404.

RGM were identified by using conventional methods, including drug susceptibility patterns (15), carbohydrate utilization tests, and PCR restriction enzyme analysis of a 439-bp sequence (Telenti fragment) of the 65-kDa *hsp* gene (8, 10).

MICs were determined by use of the NCCLS-approved broth microdilution technique (6, 7). MICs of gatifloxacin were 0.12 to 32 μg/ml, while those of ciprofloxacin were 0.12 to 16 μg/ml (one lot number of panels used contained concentrations of ciprofloxacin of ≤0.25 to 16 μg/ml). The MIC breakpoints indicating susceptibility, moderate susceptibility (intermediate), and resistance to gatifloxacin were ≤2, 4, and ≥8 μg/ml, and those for ciprofloxacin were ≤1, 2, and ≥4 μg/ml (the NCCLS breakpoints for *Enterobacteriaceae* and *Staphylococcus* species) (6). Gatifloxacin breakpoints for RGM have not yet been addressed by the NCCLS (7).

For quality control tests, *Staphylococcus aureus* ATCC 29213 and *Escherichia coli* ATCC 25922 were used. Acceptable MIC ranges for *S. aureus* ATCC 29213 are 0.03 to 0.12 and 0.12 to 0.5 μg/ml for gatifloxacin and ciprofloxacin, respectively. Acceptable MIC ranges for *E. coli* ATCC 25922 are 0.008 to 0.03 and 0.004 to 0.016 μg/ml for gatifloxacin and ciprofloxacin, respectively (6).

Results for the major species (groups) of pathogenic RGM are shown in Tables 1 and 2. Generally, the MICs of gatifloxacin for all of the RGM except *M. abscessus* were 1 to 4 dilutions lower than those of ciprofloxacin.

TABLE 1. Comparison of ranges, MIC_{50}s, MIC_{90}s, and percentages of gatifloxacin- and ciprofloxacin-susceptible mycobacteria

Species and drug	No. of isolates tested[b]	MIC (μg/ml)[a]			% Susceptible
		Range	50%	90%	
M. abscessus	24				
Gatifloxacin		2–>32	16	>32	10
Ciprofloxacin		8–>16	16	>16	0
M. chelonae	32				
Gatifloxacin		≤0.12–8	1	4	96
Ciprofloxacin		0.25–>16	4	>16	8
M. fortuitum group	39				
Gatifloxacin		≤0.12–0.5	≤0.12	≤0.12	100
Ciprofloxacin		≤0.12–2	0.25	1	100
M. mucogenicum	20				
Gatifloxacin		≤0.12–0.5	≤0.25	≤0.25	100
Ciprofloxacin		≤0.25–1	0.5	0.5	100

[a] The MIC resistance breakpoints were ≥8 μg/ml for gatifloxacin and ≥4 μg/ml for ciprofloxacin (6, 7).
[b] A total of 115 isolates were tested.

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TABLE 2. Comparison of susceptibilities of RGM to gatifloxacin and ciprofloxacin at specified MICs

Species and drug	No. of isolates tested[a]	No. (cumulative %) of isolates susceptible at an MIC (μg/ml) of:									
		≤0.12[b]	≤0.25[a]	0.5	1	2	4	8	16	>16	32	>32
M. abscessus	24											
Gatifloxacin					1 (4)	2 (13)	2 (21)	4 (38)	6 (63)		6 (88)	3 (100)
Ciprofloxacin						3 (12)	1 (15)	3 (27)	3 (38)	16 (100)		
M. chelonae	32											
Gatifloxacin		1 (3)		2 (9)	10 (41)	12 (78)	6 (97)	1 (100)				
Ciprofloxacin			1 (3)			1 (6)	17 (59)	6 (78)	3 (88)	4 (100)		
M. fortuitum group	39											
Gatifloxacin		38 (97)		1 (100)								
Ciprofloxacin		13 (33)	11 (62)	8 (82)	4 (92)	3 (100)						
M. mucogenicum	20											
Gatifloxacin		8 (40)	10 (90)	2 (100)								
Ciprofloxacin		1 (5)	7 (40)	11 (95)	1 (100)							

[a] A total of 115 isolates were tested.
[b] The two lowest MICs reflect different lot numbers of panels used.

For the *M. fortuitum* group, 39 of 39 (100%) of the isolates were susceptible to gatifloxacin at MICs of ≤0.5 μg/ml, whereas only 32 of 39 (82%) were susceptible to ciprofloxacin at ≤0.5 μg/ml (Table 2).

Of the *M. chelonae* isolates, 31 of 32 (97%) were susceptible or intermediate to gatifloxacin at an MIC of ≤4 μg/ml, compared to 1 of 32 (6%) to ciprofloxacin at 2 μg/ml and 17 of 32 (59%) to ciprofloxacin at 4 μg/ml.

Of the 24 isolates of *M. abscessus* tested against gatifloxacin, only 21% were intermediate or susceptible, while 12% of the same isolates tested against ciprofloxacin were such.

The gatifloxacin MICs for all seven isolates of the three members of the *M. smegmatis* group (*M. smegmatis* sensu stricto [3], *M. wolinskyi* [2], and *M. goodii* [2]) were ≤0.12 μg/ml (data not shown). The MICs required for 50% inhibition (MIC_{50}s) of *M. smegmatis* sensu stricto, *M. goodii*, and *M. wolinskyi* were 1, ≤0.12, and 1 μg/ml, respectively (data not shown).

The ciprofloxacin and gatifloxacin MIC test results for 10 mycobacterial ATCC isolates are shown in Table 3. Quality control results were within the acceptable ranges defined by the NCCLS (6, 7).

TABLE 3. MICs of gatifloxacin and ciprofloxacin for RGM reference strains

Strain	MIC (μg/ml)	
	Gatifloxacin	Ciprofloxacin
M. fortuitum group		
M. fortuitum ATCC 6841^T	≤0.12	≤0.12
M. peregrinum ATCC 14467^T	≤0.12	≤0.12
M. peregrinum ATCC 700686[a]	≤0.12	0.25
M. fortuitum third biovariant		
ATCC 49403 (sorbitol positive)	≤0.12	0.25
ATCC 49404 (sorbitol negative)	≤0.12	0.5
M. abscessus ATCC 19977^T	4	>16
M. chelonae ATCC 35752^T	≤0.12	0.25
M. smegmatis sensu stricto ATCC 19420^T	≤0.12	0.5
M. wolinskyi ATCC 700010	≤0.12	0.5
M. goodii ATCC 700504	≤0.12	≤0.12

[a] NCCLS-recommended MIC control strain.

The only oral drugs currently available for *M. chelonae* that inhibit >90% isolates at clinically active levels are the macrolides (clarithromycin or azithromycin) (3, 12) and linezolid (4, 13). Clarithromycin is the drug of choice for disease caused by *M. chelonae*, but monotherapy has a significant risk for mutational resistance (estimated to be 10 to 15%) in the setting of disseminated cutaneous disease in immunosuppressed individuals (9, 14). Linezolid use is limited by its high cost and concerns for long-term hematologic toxicity (4, 13). On the basis of the present results, gatifloxacin is the third oral agent to inhibit >90% of *M. chelonae* isolates at clinically achievable levels.

Currently there are no clinical data available for results of treatment with gatifloxacin for infections caused by RGM.

The NCCLS has recommended that the fluoroquinolone ciprofloxacin be tested against the RGM (7) but clearly has not predicted gatifloxacin activity against *M. chelonae*. We recommend that both gatifloxacin and ciprofloxacin be routinely tested against the RGM at the concentrations in broth previously noted.

Since the gatifloxacin MICs for the *M. fortuitum* group isolates are lower than those of ciprofloxacin, these isolates may be less likely to develop clinical resistance to gatifloxacin following a single mutational event. As this resistance is a problem with *M. fortuitum* and the earlier fluoroquinolones, the use of monotherapy with the *M. fortuitum* group is precluded (11).

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REFERENCES

1. **Bauernfiend, A.** 1997. Comparison of the antibacterial activities of the quinolones Bay 12–039, gatifloxacin (AM 1155), trovafloxacin, clinafloxacin, levofloxacin and ciprofloxacin. J. Antimicrob. Chemother. **40:**639–651.
2. **Brown, B. A., B. Springer, V. A. Steingrube, R. W. Wilson, G. E. Pfyffer, M. J. Garcia, M. C. Menendez, B. Rodriguez-Salgado, K. C. Jost, S. H. Chiu, G. O. Onyi, E. C. Böttger, and R. J. Wallace, Jr.** 1999. Description of *Mycobacterium wolinskyi* and *Mycobacterium goodii*, two new rapidly growing species related to *Mycobacterium smegmatis* and associated with human wound infections: a cooperative study from the International Working Group on Mycobacterial Taxonomy. Int. J. Syst. Bacteriol. **49:**1493–1511.

3. **Brown, B. A., R. J. Wallace, Jr., G. O. Onyi, V. De Rosas, and R. J. Wallace III.** 1992. Activities of four macrolides, including clarithromycin, against *Mycobacterium fortuitum*, *Mycobacterium chelonae*, and *M. chelonae*-like organisms. Antimicrob. Agents Chemother. **36:**180–184.
4. **Brown-Elliott, B. A., R. J. Wallace, Jr., R. Blinkhorn, C. J. Crist, and L. M. Mann.** 2001. Successful treatment of disseminated *Mycobacterium chelonae* infection with linezolid. Clin. Infect. Dis. **33:**1433–1434.
5. **Jones, R. N., M. A. Pfaller, and The SENTRY Antimicrobial Surveillance Program Participants Group.** 2001. Can antimicrobial susceptibility testing results for ciprofloxacin or levofloxacin predict susceptibility to a newer fluoroquinolone, gatifloxacin?: report from the SENTRY Antimicrobial Surveillance Program (1997–1999). Diagn. Microbiol. Infect. Dis. **39:**237–243.
6. **NCCLS.** 2002. Performance standards for antimicrobial susceptibility testing. Twelfth Informational Supplement, M100-S12. NCCLS, Wayne, Pa.
7. **NCCLS.** 2000. Susceptibility testing of mycobacteria, nocardia and other aerobic actinomycetes. Tentative standard M24-T2, 2nd ed. NCCLS, Wayne, Pa.
8. **Steingrube, V. A., J. L. Gibson, B. A. Brown, Y. Zhang, R. W. Wilson, M. Rajagopalan, and R. J. Wallace, Jr.** 1995. PCR amplification and restriction endonuclease analysis of a 65-kilodalton heat shock protein gene sequence for taxonomic separation of rapidly growing mycobacteria. J. Clin. Microbiol. **33:**149–153.
9. **Tebas, P., F. Sultan, R. J. Wallace, Jr., and V. Fraser.** 1995. Rapid development of resistance to clarithromycin following monotherapy for disseminated *Mycobacterium chelonae* infection in a heart transplant patient. Clin. Infect. Dis. **20:**443–444.
10. **Telenti, A., F. Marchesi, M. Balz, F. Bally, E. C. Böttger, and T. Bodmer.** 1993. Rapid identification of mycobacteria to the species level by polymerase chain reaction and restriction enzyme analysis. J. Clin. Microbiol. **31:**175–178.
11. **Wallace, R. J., Jr., G. Bedsole, G. Sumter, C. V. Sanders, L. C. Steele, B. A. Brown, J. Smith, and D. R. Graham.** 1990. Activities of ciprofloxacin and ofloxacin against rapidly growing mycobacteria with demonstration of acquired resistance following single-drug therapy. Antimicrob. Agents Chemother. **34:**65–70.
12. **Wallace, R. J., Jr., B. A. Brown, and G. Onyi.** 1992. Skin, soft tissue, and bone infections due to *Mycobacterium chelonae* subspecies *chelonae*—importance of prior corticosteroid therapy, frequency of disseminated infections, and resistance to oral antimicrobials other than clarithromycin. J. Infect. Dis. **166:**405–412.
13. **Wallace, R. J., Jr., B. A. Brown-Elliott, S. C. Ward, C. J. Crist, L. B. Mann, and R. W. Wilson.** 2001. Activities of linezolid against rapidly growing mycobacteria. Antimicrob. Agents Chemother. **45:**764–767.
14. **Wallace, R. J., Jr., A. Meier, B. A. Brown, Y. Zhang, P. Sander, G. O. Onyi, and E. C. Böttger.** 1996. Genetic basis for clarithromycin resistance among isolates of *Mycobacterium chelonae* and *Mycobacterium abscessus*. Antimicrob. Agents Chemother. **40:**1676–1681.
15. **Wallace, R. J., Jr., J. M. Swenson, and V. A. Silcox.** 1985. The rapidly growing mycobacteria: characterization and susceptibility testing. Antimicrob. Newsl. **2:**85–92.
16. **Wilson, R. W., V. A. Steingrube, E. C. Böttger, B. Springer, B. A. Brown-Elliott, V. Vincent, K. C. Jost Jr., Y. Zhang, M. J. Garcia, S. H. Chiu, G. O. Onyi, H. Rossmoore, D. R. Nash, and R. J.Wallace, Jr.** 2001. *Mycobacterium immunogenum* sp. nov., a novel species related to *Mycobacterium abscessus* and associated with clinical disease, pseudo-outbreaks, and contaminated metalworking fluids: an international cooperative study on mycobacterial taxonomy. Int. J. Syst. Evol. Microbiol. **51:**1751–1764.