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In Vitro Activities of BAY Y3118, Ciprofloxacin, Ofloxacin, and Fleroxacin against Gram-Positive and Gram-Negative Pathogens from Respiratory Tract and Soft Tissue Infections

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BAY Y3118 was highly active against *Moraxella catarrhalis*, *Haemophilus influenzae*, *Legionella pneumophila*, *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus* (except quinolone-resistant, methicillin-resistant *S. aureus*), *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus pneumoniae* (MIC for 90% of strains tested [MIC_{90}], 0.063 μg/ml). For *Enterococcus faecalis* and *Corynebacterium jeikeium*, MIC_{90}s were 4 and 2 μg/ml, respectively. BAY Y3118 was as active as ciprofloxacin against *Pseudomonas aeruginosa* (MIC_{90}, 0.5 μg/ml) and had potent activity against *Bacteroides fragilis* (MIC_{90}, 0.5 μg/ml).

During recent years, a number of fluoroquinolones have been developed and several have been proven clinically efficacious for the treatment of infections caused by gram-negative facultative pathogens, *Chlamydia* sp., *Mycoplasma* sp., and methicillin-susceptible *Staphylococcus aureus* (3, 4, 6, 11). Most experience has been obtained with ciprofloxacin, ofloxacin, and pefloxacin. Since the introduction of these drugs, however, development of resistance to them has been reported for *S. aureus*, *Pseudomonas aeruginosa*, and some members of the family *Enterobacteriaceae*, e.g., *Klebsiella* sp. and *Serratia* sp. (10). Several newer quinolones have been evaluated in vitro against gram-positive bacteria, but improved activity against gram-positive bacteria has often been found to associate with decreased activity against gram-negative bacteria (2).

BAY Y3118 is a new fluoroquinolone which appears to be as active as ciprofloxacin in vitro against gram-negative and many gram-positive and anaerobic bacteria. We studied the in vitro activity of BAY Y3118 against 408 gram-positive and gram-negative respiratory pathogens from community- and hospital-acquired pneumonia and gram-positive pathogens isolated from soft tissue and intravascular infections.

A total of 408 isolates were studied (Table 1); all but 7 of 20 *Legionella* strains were clinical isolates from patients with respiratory tract infections, soft tissue infections, and catheter-related infections. Eighty percent of all strains were obtained from patients hospitalized in the University Hospital of Nijmegen; the other strains were isolated from patients hospitalized in the University Hospitals of Rotterdam and Utrecht, the Canisius-Wilhelmina Hospital of Nijmegen, and the Medical Centre of Leeuwarden between 1 January 1991 and 1 July 1992. The 21 mucoid *P. aeruginosa* strains were isolated from patients with cystic fibrosis.

MICs were determined in duplicate by using a routine broth dilution method in microtiter plates, according to the recommendations of the National Committee for Clinical Laboratory Standards (5) and the European Study Group (7). Media used were Iso-Sensitest broth (Oxoid CM 491) supplemented with 2% lysed horse blood and IsoVitaleX (2.5%; BBL 1187) for *Corynebacterium jeikeium*, *Haemophilus influenzae*, and *Bacteroides fragilis* and buffered starch-yeast extract broth according to the directions of Saito et al. (8) for *Legionella pneumophila*.

Antimicrobial stock solutions were prepared by dissolving powdered BAY Y3118, ciprofloxacin, and ofloxacin in water and powdered fleroxacin in 0.1 N NaOH. BAY Y3118 and ciprofloxacin were provided by Bayer AG (Leverkusen, Germany), ofloxacin was provided by Hoechst Pharma (Amsterdam, The Netherlands), and fleroxacin was provided by Hoffmann-La Roche (Basel, Switzerland).

The microtiter plates were filled with 100 μl of double-concentrated antibiotic test solution in each well. The inocula were prepared according to the direct colony suspension method as recommended by the National Committee for Clinical Laboratory Standards (5). Several colonies (at least four) of overnight cultures grown on blood agar (lysed horse blood agar with IsoVitaleX or buffered charcoal-yeast extract agar) were added to 3 ml of sterile 0.85% NaCl to a McFarland turbidity standard of 0.5 (1.5×10^8 CFU/ml) and further diluted in 10 ml of double-concentrated test broth to a final organism concentration of 3×10^6 to 5×10^6 CFU/ml. Each well was inoculated with 100 μl of this suspension (final inoculum size, 1.5×10^6 to 2.5×10^6 CFU/ml). The inoculum size and purity were controlled by plating 1 μl of the bacterial suspension on appropriate media. The plates with aerobic and facultative bacteria were incubated at 37°C; plates with *B. fragilis* were incubated at 37°C in anaerobic jars with 5% CO_2, 10% H_2, and 85% N_2. All plates were judged for growth after 24 and 48 h of incubation.

The MIC was defined as the lowest concentration preventing visible growth in the test medium. Control strains used were *Escherichia coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 29213, and *Enterococcus faecalis* ATCC 29212.

The comparative activities of the clinical isolates and control strains are given in Table 1. BAY Y3118 was the most active quinolone against all strains tested, followed by ciprofloxacin, ofloxacin, and fleroxacin.

Gram-positive organisms. BAY Y3118 was at least 15 times more active than ciprofloxacin, ofloxacin, and fleroxacin against *S. aureus*, methicillin-resistant *Staphylococcus*

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TABLE 1. Antibacterial activities of BAY Y3118, ciprofloxacin, ofloxacin, and fleroxacin against 408 clinical pathogens

Bacterial species (*n*)	Drug[a]	MIC (mg/liter)[b]		
		Range	50%	90%
S. aureus				
Methicillin susceptible (20)	BAY	0.016–0.063	0.032	0.032
	CIP	0.25–2	0.5	0.5
	OFL	0.25–1	0.5	0.5
	FLE	0.5–2	1	1
Methicillin resistant (10)[c]	BAY	0.016–2	0.032	2
	CIP	0.25–>32	1	>32
	OFL	0.25–>32	1	16
	FLE	0.5–>32	2	>32
S. epidermidis (methicillin resistant, 30)	BAY	0.016–16	0.063	0.5
	CIP	0.25–≥32	0.5	≥32
	OFL	0.5–≥32	1	16
	FLE	0.5–≥32	1	≥32
S. pyogenes (20)	BAY	0.032–0.125	0.063	0.063
	CIP	0.25–2	0.5	1
	OFL	0.5–4	1	2
	FLE	2–>32	4	8
S. agalactiae (20)	BAY	0.032–0.125	0.063	0.063
	CIP	0.5–2	1	2
	OFL	1–4	2	2
	FLE	4–16	8	16
S. pneumoniae (penicillin resistant, 13; penicillin susceptible, 17)	BAY	0.032–0.125	0.032	0.063
	CIP	0.5–4	1	2
	OFL	1–2	2	2
	FLE	2–8	2	4
E. faecalis (30)	BAY	0.125–8	0.25	4
	CIP	0.125–>32	2	>32
	OFL	2–>32	4	>32
	FLE	4–>32	8	>32
E. faecium (22)	BAY	0.25–≥32	8	16
	CIP	2–≥32	16	≥32
	OFL	2–≥32	16	≥32
	FLE	2–≥32	≥32	≥32
C. jeikeium (18)	BAY	0.25–4	1	2
	CIP	16–≥32	≥32	≥32
	OFL	16–≥32	≥32	≥32
	FLE	≥32	≥32	≥32
M. catarrhalis (20)	BAY	0.016–0.063	0.032	0.032
	CIP	0.125–0.25	0.25	0.25
	OFL	0.125–0.25	0.125	0.25
	FLE	0.25–0.5	0.25	0.5
H. influenzae (20)	BAY	0.004–0.032	0.008	0.016
	CIP	0.016–0.063	0.032	0.032
	OFL	0.032–0.063	0.063	0.063
	FLE	0.063–0.125	0.063	0.125
L. pneumophila (20)	BAY	0.008–0.016	0.008	0.016
	CIP	0.016–0.032	0.032	0.032
	OFL	0.032–0.063	0.032	0.062
	FLE	0.032–0.063	0.032	0.032
P. aeruginosa				
Nonmucoid (21)	BAY	0.063–4	0.25	0.5
	CIP	0.063–4	0.125	0.5
	OFL	0.25–16	0.5	2
	FLE	0.25–≥32	1	2
Mucoid (21)	BAY	0.032–1	0.25	0.5
	CIP	0.063–1	0.125	0.5
	OFL	0.125–4	0.5	2
	FLE	0.125–4	1	2
Acinetobacter sp. (20)	BAY	0.008–0.5	0.032	0.5
	CIP	0.125–≥32	0.25	4
	OFL	0.125–16	0.25	4
	FLE	0.25–≥32	0.5	16
E. coli (16)	BAY	0.008–0.25	0.016	0.063
	CIP	0.032–2	0.032	0.25
	OFL	0.063–2	0.125	0.5
	FLE	0.125–8	0.125	1
E. cloacae (15)	BAY	0.016–0.5	0.032	0.5
	CIP	0.016–2	0.032	1
	OFL	0.063–16	0.125	2
	FLE	0.125–16	0.125	4
K. pneumoniae (16)	BAY	0.016–0.125	0.032	0.063
	CIP	0.016–0.25	0.063	0.25
	OFL	0.063–1	0.125	0.5
	FLE	0.125–1	0.25	1
S. marcescens (21)	BAY	0.016–1	0.25	0.5
	CIP	0.063–8	0.25	2
	OFL	0.125–16	1.0	4
	FLE	0.125–16	0.5	4
B. fragilis (20)	BAY	0.063–0.5	0.125	0.5
	CIP	4–≥32	4	8
	OFL	2–16	4	8
	FLE	8–16	8	16
Control strains				
S. aureus ATCC 29213	BAY	0.016		
	CIP	0.5		
	OFL	0.5		
	FLE	0.5		
E. faecalis ATCC 29212	BAY	0.125		
	CIP	1		
	OFL	2		
	FLE	4		
E. coli ATCC 25922	BAY	0.008		
	CIP	0.032		
	OFL	0.063		
	FLE	0.063		
P. aeruginosa ATCC 27853	BAY	0.25		
	CIP	0.25		
	OFL	1		
	FLE	2		

[a] BAY, BAY Y3118; CIP, ciprofloxacin; OFL, ofloxacin; FLE, fleroxacin.
[b] 50% and 90%, MICs for 50 and 90% of isolates, respectively.
[c] Three strains were ciprofloxacin resistant (MIC, >32 μg/ml).

epidermidis, *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus pneumoniae*. Seven of ten methicillin-resistant *S. aureus* strains were as susceptible as the methicillin-susceptible *S. aureus* strains to BAY Y3118, with MICs for 90% of isolates tested of 0.032 μg/ml, but the three methicillin- and quinolone-resistant *S. aureus* strains were inhibited only by 1 μg/ml (one strain) or 2 μg/ml (two strains). These three methicillin- and quinolone-resistant *S. aureus* strains were resistant to ciprofloxacin, ofloxacin, and fleroxacin, with MICs 16 to >32 μg/ml. Thirty methicillin resistant *S. epidermidis* strains (resistant to penicillin; methicillin; narrow-, expanded-, and broad-spectrum cephalosporins; and gentamicin) were susceptible to BAY Y3118 (MIC for 90% of isolates, 0.5 μg/ml) but not to the other quinolones. Both penicillin-resistant and penicillin-susceptible *S. pneumoniae* strains were susceptible to BAY Y3118; they were less susceptible to the other quinolones.

BAY Y3118 was the only quinolone showing activity against *E. faecalis* and *C. jeikeium*, with 50% of the strains susceptible to 0.25 and 1.0 μg/ml, respectively.

Gram-negative organisms. BAY Y3118 was about 10 times more active against *Moraxella catarrhalis* than was ciprofloxacin. The activity of BAY Y3118 against *H. influenzae* was in the same range as that of ciprofloxacin and four to eight times greater than that of ofloxacin and fleroxacin;

β-lactamase-producing and -nonproducing strains were equally susceptible. All quinolones were extremely active against *L. pneumophila*.

BAY Y3118 was at least four times more active against members of the *Enterobacteriaceae* than were ciprofloxacin and ofloxacin and eight or more times more active than was fleroxacin. BAY Y3118 and ciprofloxacin showed comparable activities against *P. aeruginosa*. There was no difference in activity against mucoid or nonmucoid strains.

BAY Y3118 was the most active quinolone against *B. fragilis*, with a MIC for 90% of strains of 0.5 μg/ml.

Compared with ciprofloxacin, ofloxacin, and fleroxacin, BAY Y3118 showed higher activity against all bacteria tested except *P. aeruginosa*, which showed comparable susceptibility to ciprofloxacin. The most interesting characteristic of BAY Y3118 was its high activity against gram-positive bacteria and *B. fragilis*.

Streptococci, pneumococci, and staphylococci all showed a high susceptibility to BAY Y3118. Like others, we found methicillin-resistant *S. aureus* strains less susceptible to ciprofloxacin, ofloxacin, and fleroxacin (1), although the number of strains tested was low. A matter of concern was the finding that three methicillin- and quinolone-resistant *S. aureus* strains resistant to the three compared quinolones were also less susceptible to BAY Y3118. This could imply that this quinolone also cannot overcome resistance by methicillin-resistant *S. aureus*.

Enterococcal infections have become increasingly important. Most enterococci tested were isolated from our intensive care units, where ciprofloxacin is often used. In 3 years of the use of ciprofloxacin, enterococcal resistance rose from 10 to >90% in some of our wards. Similar reports have come from others (9). Only 50% of the *E. faecalis* strains were susceptible to the new test drug, and these strains were generally susceptible to ciprofloxacin (MIC, 0.125 to 2 μg/ml); for strains resistant to ciprofloxacin, MICs of BAY Y3118 were 2 to 4 μg/ml, suggesting that one must be aware of cross-resistance among enterococci. None of the *Enterococcus faecium* strains were susceptible to BAY Y3118.

A number of gram-negative organisms may be responsible for hospital-acquired pneumonia. Among them, *Klebsiella pneumoniae*, *Enterobacter* strains, *Serratia marcescens*, and *P. aeruginosa* predominate. Resistance of these strains to quinolones has been reported (10), and we also found a rise in the MIC of ciprofloxacin during the years we used this drug for the treatment of hospital-acquired pneumonia. Therefore, we tested the activity of BAY Y3118 against these problem strains, and *E. coli* served as the representative for other members of the *Enterobacteriaceae*. The in vitro activity of BAY Y3118 against *E. coli* and *K. pneumoniae* was excellent; *Enterobacter cloacae* and *S. marcescens* strains were less susceptible to BAY Y3118, as they were also to ciprofloxacin. This combined decreased susceptibility must be the result of ciprofloxacin use in our intensive care wards and may reflect cross-resistance between these two drugs.

In conclusion, BAY Y3118 has a high activity against a number of common pathogens associated with respiratory tract and soft tissue infections, with an improved activity against gram-positive species and *B. fragilis* compared with that of the older fluoroquinolones.

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