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BRIEF REPORT

In vitro antimicrobial activity of moxifloxacin against bacterial strains isolated from blood of neutropenic cancer patients

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The use of fluoroquinolones has increased in neutropenic cancer patients over the past two decades. With respect to empiric treatment of fever in neutropenic patients, the poor activity of older quinolones against gram-positive cocci prompted physicians to add specific anti-gram-positive agents to provide better activity against streptococci, which are frequently isolated from these patients. The efficacy and safety of oral antibiotic regimens that include fluoroquinolones for the treatment of low-risk febrile neutropenic patients have been documented in two large studies [1, 2]. The widespread use of fluoroquinolones as prophylactic agents in cancer patients has been associated with the occurrence of resistance in *E. coli* and coagulase-negative staphylococci, organisms which are most often responsible for bacteremia in these patients [3].

Moxifloxacin is an 8-methoxyquinolone that has enhanced activity against gram-positive bacteria relative to ciprofloxacin and other older fluoroquinolones. Oral moxifloxacin is 90% bioavailable, and its mean half-life of 12 h allows once-a-day dosing. Peak serum concentrations of 3.2–4.5 μg/ml have been achieved following oral doses of 400 mg of moxifloxacin, and the agent is widely distributed throughout the body [4]. The aim of the present study was to assess the in vitro activity of moxifloxacin against gram-positive and gram-negative bacteria isolated from the blood of neutropenic cancer patients and to compare it with other fluoroquinolones and reference antibiotics.

The collection of bacterial strains isolated from the blood of febrile neutropenic cancer patients randomized in two trials conducted by the Infectious Diseases Group of the European Organization for Research and Treatment of Cancer (EORTC-IDG) between 1993 and 2000 [5, 6] yielded 152 gram-positive isolates, including 71 coagulase-negative staphylococci, 29 *S. aureus*, 19 *S. mitis*, 19 *S. oralis*, and 14 *E. faecalis*, and 85 gram-negative strains, including 44 *E. coli*, 30 *K. pneumoniae* and 11 *P. aeruginosa*. These strains were used in the present study. Bacterial identification was confirmed at the Microbiological Reference Center (CHUV, Lausanne) using standardized methods [7].

Minimal inhibitory concentrations (MICs) of four fluoroquinolones (moxifloxacin, levofloxacin, gatifloxacin, ciprofloxacin), as well as cefepime, meropenem, amikacin, vancomycin, penicillin for streptococci and oxacillin for staphylococci were determined using a microbroth dilution

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Table 1 In vitro activity of moxifloxacin and comparative agents against gram-positive and gram-negative bacteria

Organism	Antibiotic	MIC50 (μg/ml)	MIC90 (μg/ml)	Range (μg/ml)	Susceptible (%)
CNS (*n*=71)	Moxifloxacin	1	2	0.016–16	45
	Levofloxacin	2	8	0.016–>64	42
	Gatifloxacin	2	4	0.032–16	45
	Ciprofloxacin	8	64	0.016–>64	42
	Oxacillin	4	>64	0.016–>64	49
	Cefepime	8	64	0.016–>64	54
	Meropenem	4	32	0.016–>64	51
	Vancomycin	2	2	0.125–>64	96
S. aureus (*n*=29)	Moxifloxacin	0.064	0.125	0.016–64	90
	Levofloxacin	0.125	0.25	0.064–32	90
	Gatifloxacin	0.032	0.125	0.032–32	90
	Ciprofloxacin	0.25	1	0.125–16	90
	Oxacillin	0.5	1	0.125–>64	90
	Cefepime	4	4	2–>64	90
	Meropenem	0.125	0.5	0.016–32	90
	Vancomycin	1	1	0.125–1	100
S. oralis (*n*=20)	Moxifloxacin	0.25	0.5	0.125–16	90
	Levofloxacin	1	2	0.125–64	90
	Gatifloxacin	0.5	2	0.25–32	79
	Ciprofloxacin	2	8	0.016–32	75
	Penicillin G	0.016	0.064	0.016–0.25	95
	Cefepime	0.25	0.5	0.016–2	95
	Meropenem	0.016	0.016	0.016–0.5	100
	Vancomycin	0.25	0.5	0.016–0.5	100
S. mitis (*n*=19)	Moxifloxacin	0.25	0.5	0.064–8	95
	Levofloxacin	1	2	0.125–32	95
	Gatifloxacin	0.5	2	0.125–16	90
	Ciprofloxacin	1	16	0.016–16	63
	Penicillin G	0.016	0.5	0.016–64	84
	Cefepime	0.064	1	0.016–2	78
	Meropenem	0.016	0.25	0.016–1	95
	Vancomycin	0.25	0.25	0.016–0.5	100
E. faecalis (*n*=14)	Moxifloxacin	0.5	8	0.125–32	71
	Levofloxacin	2	64	0.25–>64	79
	Gatifloxacin	1	16	0.125–32	64
	Ciprofloxacin	2	32	0.25–>64	33
	Penicillin G	2	4	0.25–8	100
	Meropenem	4	8	1–16	87
	Vancomycin	1	2	0.5–2	100
	Amikacin	1	2	0.5–2	–
E. coli (*n*=44)	Moxifloxacin	0.016	16	0.016–32	80
	Levofloxacin	0.016	8	0.016–64	80
	Gatifloxacin	0.032	8	0.032–32	80
	Ciprofloxacin	0.016	16	0.016–>64	80
	Ceftazidime	0.25	0.5	0.064–32	98
	Cefepime	0.25	2	0.064–8	100
	Meropenem	0.064	0.25	0.016–0.5	100
	Amikacin	4	8	1–8	100
K. pneumoniae (*n*=30)	Moxifloxacin	0.064	0.125	0.064–0.25	100
	Levofloxacin	0.064	0.064	0.016–0.125	100
	Gatifloxacin	0.032	0.032	0.032–0.125	100
	Ciprofloxacin	0.016	0.016	0.016–0.064	100
	Ceftazidime	0.25	8	0.125–64	96
	Cefepime	0.125	4	0.016–8	100
	Meropenem	0.25	0.5	0.016–0.5	100
	Amikacin	2	4	1–16	100

Table 1 (continued)

Organism	Antibiotic	MIC50 (μg/ml)	MIC90 (μg/ml)	Range (μg/ml)	Susceptible (%)
P. aeruginosa (*n*=11)	Moxifloxacin	1	64	0.25–64	64
	Levofloxacin	0.25	16	0.25–64	82
	Gatifloxacin	0.5	32	0.25–32	82
	Ciprofloxacin	0.125	8	0.016–32	82
	Ceftazidime	2	128	2–128	82
	Cefepime	4	128	2–128	73
	Meropenem	2	8	1–64	64
	Amikacin	1	8	0.5–16	100

CNS coagulase-negative staphylococci

technique according to methods recommended by the Clinical and Laboratory Standards Institute (CLSI) [8]. For all antibiotics tested, the MIC breakpoints recommended by the CLSI were used. Since CLSI did not provide MIC breakpoints for moxifloxacin against any organisms other than staphylococci (<0.5 μg/ml for susceptibility), the MIC breakpoints used for moxifloxacin against all other organisms were <1 μg/ml for susceptibility, >2 μg/ml for resistance [9]. Quality control was performed by testing American Type Culture Collection (ATCC) strains *E. coli* 25922 and 35218, *S. aureus* 29213, *E. faecalis* 29212 and *P. aeruginosa* 27853.

Moxifloxacin displayed excellent in vitro activity against staphylococci and viridans streptococci, and compared with all other quinolones, it had the lowest MIC90 against coagulase-negative staphylococci, *S. aureus*, *S. oralis* and *S. mitis* (Table 1). The better activity against viridans streptococci is particularly interesting, and might reduce the need to add a beta-lactam for the oral treatment of fever in low-risk neutropenic patients. Compared with ciprofloxacin, moxifloxacin exhibits increased, but still only relatively modest activity against enterococci.

Against *E. coli*, the MIC_{90} of all fluoroquinolones tested was between 8 and 16 μg/ml: 9 of 44 isolates were highly resistant. These highly resistant organisms were isolated from nine patients hospitalized in six different centers. Six of the nine patients with fluoroquinolone-resistant *E. coli* had received quinolone prophylaxis before the occurrence of the bacteremic episode. In contrast, none of 35 patients infected with fluoroquinolone-susceptible *E. coli* strains had received fluoroquinolone prophylaxis (Fisher's test $p<0.001$). Thus, as previously described in EORTC-IDG trials, infections due to fluoroquinolone-resistant *E. coli* still occur in high-risk patients who receive fluoroquinolone prophylaxis, even though its use decreased from 52% in the trial performed over 1993–1994 [5] to 33% in the trial performed over 1997–2000 [6]. Regarding other gram-negative isolates, moxifloxacin is highly active against *Klebsiella* spp and was less active than ciprofloxacin against *P. aeruginosa*.

Rolston et al. [10] tested the in vitro activity of moxifloxacin against 900 strains isolated from cancer patients: two thirds of these strains were bloodstream isolates. As in the present study, moxifloxacin was the most active fluoroquinolone against coagulase-negative staphylococci, *S. aureus* and viridans streptococci. These researchers also reported fluoroquinolone-resistant *E. coli* related to previous prophylaxis and lower in vitro activity of moxifloxacin against *P. aeruginosa* compared with ciprofloxacin.

The susceptibility of the EORTC-IDG strains to various antibiotics commonly used in neutropenic patients has been tested. As shown for bacteria isolated from neutropenic patients in US cancer centers [11], the highest rates of susceptibility were observed with cefepime and meropenem, which are active against 100% of viridans streptococci, *E. coli* and *Klebsiella* spp. Amikacin is active against all gram-negative bacteria including *P. aeruginosa*, and ceftazidime is active against the vast majority of *E. coli*, *Klebsiella* spp and *P. aeruginosa*.

In conclusion, this study confirms that moxifloxacin exhibits increased in vitro activity relative to older fluoroquinolones against gram-positive bacteria isolated from the blood of neutropenic patients. In areas with low fluoroquinolone resistance among Enterobacteriaceae, these findings could support the use of single-drug oral regimens in low-risk febrile neutropenic patients. This in turn might provide a potential benefit in terms of compliance, especially for outpatients. Although the moderate in vitro activity of moxifloxacin against *P. aeruginosa* might be a potential problem, this non-fermentative bacteria is currently isolated only infrequently from the blood of low-risk neutropenic cancer patients. Since the emergence of resistant *E. coli* was observed in patients receiving fluoroquinolone prophylaxis, this practice should be avoided in low-risk neutropenic patients as it might limit the use of fluoroquinolones as oral therapeutic agents.

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