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In Vitro Activities of DX-619 and Comparison Quinolones against Gram-Positive Cocci

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The in vitro activity of the novel quinolone DX-619 was compared to those of currently available quinolones against U.S. clinical isolates of *Staphylococcus aureus*, coagulase-negative staphylococci, *Enterococcus* spp., *Streptococcus pyogenes*, and *Streptococcus pneumoniae*. DX-619 was the most potent quinolone overall, indicating possible utility as an anti-gram-positive quinolone.

Currently available quinolones are clinically efficacious for many infections caused by gram-positive pathogens if the pathogens are wild-type in their quinolone resistance-determining regions but may lack useful activity against isolates that have developed resistance as a consequence of previous quinolone exposure (2, 7, 10). Recalcitrant gram-positive cocci, including staphylococci (4, 9), enterococci (8), and pneumococci (5, 11), may be resistant to multiple classes of antibiotics in addition to quinolones. DX-619 is a novel, des-fluoro quinolone with enhanced anti-gram-positive activity (6). The current study was designed to evaluate the in vitro activity of DX-619 against 228 clinical isolates of aerobically growing gram-positive cocci from U.S. medical centers, using gatifloxacin, moxifloxacin, levofloxacin, and ciprofloxacin as comparator agents.

The isolates comprised oxacillin-susceptible and -resistant *Staphylococcus aureus* and coagulase-negative staphylococci, *Enterococcus* spp., *Streptococcus pyogenes*, and *Streptococcus pneumoniae*. Where possible, the isolates were chosen to exhibit various levels of quinolone resistance. They were not random clinical isolates. MICs were determined by the agar dilution method according to CLSI guidelines (3), using Mueller-Hinton agar (Oxoid, Basingstoke, United Kingdom) and doubling dilutions of DX-619, ciprofloxacin, moxifloxacin, gatifloxacin, and levofloxacin. Penicillin, oxacillin, and vancomycin were also tested as required to determine the resistances to these agents of isolates of *S. pneumoniae*, staphylococci, and enterococci, respectively. In susceptibility testing with *S. pneumoniae* and *S. pyogenes*, 5% sheep blood (Colorado Serum Co., Denver, CO) was added. Plates were inoculated with a Steers replicator to produce an inoculum of 10^4 CFU per spot and incubated at 37°C for 24 h. *S. pneumoniae* and *S. pyogenes* were incubated in 5% CO_2. Strains were categorized as susceptible or resistant based upon CLSI criteria. Antibiotic susceptibility was also performed on the CLSI-recommended quality control strains *S. pneumoniae* ATCC 49619, *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Pseudomonas aeruginosa* ATCC 27853, and *Escherichia coli* ATCC 25922.

The activities of the study drugs are summarized in Table 1, which shows MIC ranges and the concentrations that inhibited 50% and 90% of the isolates. DX-619 was the most potent agent, inhibiting all isolates at 4 μg/ml, compared to moxifloxacin (32 μg/ml), gatifloxacin (64 μg/ml), levofloxacin (128 μg/ml), and ciprofloxacin (>256 μg/ml). Based on activity at the MIC_{90} level, DX-619 was 32- to 512-fold more potent than the comparators against oxacillin-susceptible *S. aureus*, 16- to 1,024-fold more potent against oxacillin-resistant *S. aureus*, 8- to 32-fold more potent against oxacillin-susceptible coagulase-negative staphylococci, 16- to 1,024-fold more potent against oxacillin-resistant coagulase-negative staphylococci, 16- to >128-fold more potent against vancomycin-resistant enterococci, 16- to 64-fold more potent against *S. pyogenes*, 32- to 512-fold more potent against all *S. pneumoniae* isolates, and 32- to 256-fold more potent against 18 penicillin-resistant isolates. It was particularly potent (MIC ≤ 1 μg/ml) against staphylococci that were highly resistant to ciprofloxacin (MIC > 256 μg/ml). These findings were consistent with those reported for Japanese isolates by Fujikawa et al. (6) and also those reported for staphylococci by Bogdanovich et al. (1).

Overall, DX-619 is a novel quinolone with potent in vitro activity against a wide range of gram-positive pathogens. Its attributes of greatest potential are its high potency against oxacillin-resistant staphylococci and penicillin-resistant pneumococci. There is a growing need for effective new therapies for the increasing number of infections caused by these pathogens. Further studies, including those of toxicity, human pharmacokinetics, and therapeutic efficacy, are warranted.

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TABLE 1. Susceptibilities of clinical isolates to DX-619 and comparison agents

Organism	No. of strains	Antibiotic	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	% Susceptibility[a]
Oxacillin-susceptible *Staphylococcus aureus*	24	DX-619	0.004–0.25	0.015	0.06	ND
		Ciprofloxacin	0.25–256	1	32	63
		Levofloxacin	0.12–16	0.25	4	79
		Moxifloxacin	0.03–2	0.06	2	ND
		Gatifloxacin	0.06–8	0.25	2	92
Oxacillin-resistant *Staphylococcus aureus*	37	DX-619	0.004–1	0.12	0.25	ND
		Ciprofloxacin	0.25–>256	32	256	16
		Levofloxacin	0.12–64	8	32	22
		Moxifloxacin	0.03–8	2	4	ND
		Gatifloxacin	0.12–32	4	16	30
Oxacillin-susceptible coagulase-negative staphylococci	18	DX-619	0.007–0.015	0.015	0.015	ND
		Ciprofloxacin	0.12–0.5	0.25	0.5	100
		Levofloxacin	0.12–0.5	0.25	0.5	100
		Moxifloxacin	0.03–0.12	0.12	0.12	ND
		Gatifloxacin	0.12–0.25	0.25	0.25	100
Oxacillin-resistant coagulase-negative staphylococci	43	DX-619	0.007–0.5	0.06	0.25	ND
		Ciprofloxacin	0.25–>256	4	256	30
		Levofloxacin	0.12–32	4	32	47
		Moxifloxacin	0.03–8	1	4	ND
		Gatifloxacin	0.12–16	1	4	72
Enterococcus spp. (non-vancomycin resistant)	9	DX-619	0.03–4	NA[b]	NA	ND
		Ciprofloxacin	0.5–>256	NA	NA	55
		Levofloxacin	1–128	NA	NA	55
		Moxifloxacin	0.12–32	NA	NA	ND
		Gatifloxacin	0.25–64	NA	NA	77
Enterococcus spp. (vancomycin resistant)	13	DX-619	0.03–4	0.25	2	ND
		Ciprofloxacin	0.5–>256	4	>256	8
		Levofloxacin	0.5–128	4	128	15
		Moxifloxacin	0.12–32	2	32	ND
		Gatifloxacin	0.25–64	4	64	46
Streptococcus pyogenes	23	DX-619	0.007–0.015	0.007	0.015	ND
		Ciprofloxacin	0.25–1	0.5	0.5	ND
		Levofloxacin	0.25–1	0.5	1	100
		Moxifloxacin	0.12–0.25	0.25	0.25	ND
		Gatifloxacin	0.12–0.25	0.25	0.25	100
Streptococcus pneumoniae (all isolates)	61	DX-619	0.002–0.06	0.007	0.03	ND
		Ciprofloxacin	0.5–64	2	16	ND
		Levofloxacin	0.5–32	1	4	89
		Moxifloxacin	0.06–8	0.25	1	90
		Gatifloxacin	0.12–8	0.5	1	90
Streptococcus pneumoniae (penicillin resistant)	18	DX-619	0.002–0.007	0.007	0.007	ND
		Ciprofloxacin	0.5–4	1	2	ND
		Levofloxacin	0.5–1	1	1	100
		Moxifloxacin	0.06–0.5	0.12	0.25	100
		Gatifloxacin	0.12–0.5	0.25	0.5	100

[a] Calculated using CLSI criteria. ND, not determined (CLSI susceptibility criteria unavailable).
[b] NA, not applicable.

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