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In Vitro Activities of the New Ketolide HMR 3647 (Telithromycin) in Comparison with Those of Eight Other Antibiotics against Viridans Group Streptococci Isolated from Blood of Neutropenic Patients with Cancer

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The in vitro activities of the ketolide telithromycin and eight other antibiotics were tested against 77 strains of viridans group streptococci isolated from blood samples of neutropenic patients. Thirty-one (40.3%) of the strains were resistant to penicillin G, and 27 (35.1%) were resistant to erythromycin A. Telithromycin (MIC range of ≤0.03 to 1 μg/ml) was the most active antimicrobial tested. These data suggest that telithromycin could be useful for treatment of viridans group streptococcal bacteremia in neutropenic patients with cancer.

Viridans group streptococci are now recognized as a major cause of bacteremia in neutropenic patients with cancer (3, 11, 12, 16). Importantly, viridans group streptococcal bacteremia may be complicated by hypotension, septic shock, and adult respiratory distress syndrome, which have a high mortality rate (5, 7, 18, 29). Oral penicillin V or roxythromycin added to a fluoroquinolone have resulted in significant reductions of viridans group streptococcal bacteremia (20, 22). However, the increasing incidence of isolation of viridans group streptococci resistant to penicillin and macrolides compromises the current utility of these antibiotics (1, 2, 9, 14, 30). Indeed, there have been reports of bacteremias due to penicillin-resistant strains developing in patients receiving prophylaxis with a combination of quinolone and penicillin (7; V. Krcmery and J. Trupl, Letter, Lancet 346:1362–1363, 1995). On the other hand, the emergence of strains of viridans group streptococci resistant to multiple antibiotics has complicated the treatment of infections caused by these organisms. Thus, there is a need for antimicrobial agents against viridans group streptococci.

HMR 3647 (telithromycin) is a new, semisynthetic 14-membered-ring agent belonging to a new chemical family, the ketolides, which have shown promising in vitro activity against a range of microorganisms (4, 15, 19, 23, 26, 28).

The aim of this study was to compare the susceptibilities to telithromycin of 77 viridans group streptococci isolated consecutively from blood samples of neutropenic patients with cancer with their susceptibilities to eight other antibiotics, in order to determine the potential of telithromycin against these organisms.

(This study was partially presented at the 9th European Congress of Clinical Microbiology and Infectious Diseases, Berlin, Germany, March 1999 [F. Alcaide, M. A. Benítez, J. Carratalà, F. Gudiol, J. Liñares, and R. Martín, abstr. P174, p. 131].)

A total of 77 strains of viridans group streptococci isolated from the blood samples of adult neutropenic patients with cancer (<500 granulocytes/mm^3) were tested for antimicrobial susceptibilities. Only one isolate per patient was tested. Alpha-hemolytic and nonhemolytic streptococci were identified to species level according to standard methods (27). Colony morphology was evaluated, and pure cultures were tested for production of acid from trehalose, sorbitol, lactose, mannitol, sucrose, inulin, raffinose, glycerol, arabinose, maltose, and sorbose. Isolates were additionally tested for reaction in esculin agar and bile esculin agar, growth in 6.5% sodium chloride broth, ammonia production from arginine, pyruvate utilization, sodium hippurate hydrolysis, and hydrolysis of starch. We used the taxonomy and nomenclature system proposed by Coykendall (13) and updated by Bruckner and Colonna (8), which includes five groups: *Streptococcus mitis, S. sanguis, S. milleri, S. salivarius*, and *S. mutans*.

The following antibiotics were tested: HMR 3647 (telithromycin; Hoechst-Marion-Roussel, Romainville, France); penicillin G (C.E.P.A., S.A., Madrid, Spain); cefotaxime (Roussel Ibérica S.A., Madrid, Spain); erythromycin A (Abbott Laboratories, North Chicago, Ill.); clindamycin (Pharmacia & Upjohn, Barcelona, Spain); vancomycin (Eli Lilly & Co., Indianapolis, Ind.); chloramphenicol and co-trimoxazole (Sigma-Aldrich Quimica, S.A., Madrid, Spain); and ciprofloxacin (Bayer, West Haven, Conn.). For each antibiotic, the MIC was determined by the microdilution method, using cation-adjusted Mueller-Hinton broth supplemented with lysed horse blood (final concentration, 2.5%) as recommended by the National Committee for Clinical Laboratory Standards (NCCLS) (24). The inoculum was prepared by suspending several colonies from an overnight blood agar culture in sterile 0.9% saline and adjusting the turbidity to 0.5 McFarland standard. The suspension was further diluted to provide a final concentration of bacteria of 5×10^5 CFU/ml in each well of the microdilution trays. The plates were covered with plastic tape and incubated

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TABLE 1. In vitro activities of telithromycin and eight other antibiotics against viridans group streptococci (n = 77) isolated from blood samples of neutropenic cancer patients by erythromycin A susceptibility

Antibiotic	Type of streptococcus[a]	MIC (μg/ml)[b]		
		Range	50%	90%
Erythromycin A	All strains	≤0.03–128	0.12	>128
	S	≤0.03–0.12	≤0.03	0.06
	R	1–>128	4	>128
Penicillin G	All strains	≤0.03–16	0.12	4
	S	≤0.03–8	0.06	4
	R	≤0.03–16	2	4
Cefotaxime	All strains	≤0.03–16	0.25	4
	S	≤0.03–8	0.06	2
	R	≤0.03–16	1	4
Clindamycin	All strains	≤0.03–>128	0.12	>128
	S	≤0.03–2	0.12	0.5
	R	≤0.03–>128	1	>128
Vancomycin	All strains	≤0.25–1	0.5	1
	S	≤0.25–1	0.5	1
	R	≤0.25–1	0.5	1
Chloramphenicol	All strains	≤2–8	4	4
	S	≤2–4	4	4
	R	≤2–8	4	8
Co-trimoxazole	All strains	≤0.5–8	1	4
	S	≤0.5–4	0.5	4
	R	≤0.5–8	2	4
Ciprofloxacin	All strains	≤0.12–>128	2	4
	S	≤0.12–16	2	4
	R	1–>32	4	8
Telithromycin	All strains	≤0.03–2	≤0.03	0.25
	S	≤0.03–0.06	≤0.03	≤0.03
	R	≤0.03–2	0.06	1

[a] S, viridans group streptococci (n = 50) susceptible to erythromycin A (MIC, ≤0.25 μg/ml); R, viridans group streptococci (n = 27) resistant to erythromycin A (MIC, ≥0.5 μg/ml).
[b] 50% and 90%, MIC_{50} and MIC_{90}, respectively.

TABLE 2. In vitro activities of telithromycin and eight other antibiotics against viridans group streptococci (n = 77) isolated from blood samples of neutropenic cancer patients by penicillin G susceptibility

Antibiotic	Type of streptococcus[a]	MIC (μg/ml)[b]		
		Range	50%	90%
Penicillin G	S	≤0.03–0.12	0.06	0.12
	IR	0.25–2	1	2
	HR	4–16	4	8
Erythromycin A	S	≤0.03–>128	0.06	4
	IR	≤0.03–>128	0.5	>128
	HR	≤0.03–>128	2	>128
Cefotaxime	S	≤0.03–1	0.06	0.25
	IR	≤0.03–2	1	2
	HR	1–16	4	8
Clindamycin	S	≤0.03–>128	0.12	0.5
	IR	≤0.03–>128	0.5	>128
	HR	≤0.03–>128	0.12	>128
Vancomycin	S	≤0.25–1	0.5	1
	IR	0.5–1	0.5	1
	HR	0.5–1	0.5	1
Chloramphenicol	S	≤2–8	4	4
	IR	≤2–8	4	8
	HR	≤2–8	4	4
Co-trimoxazole	S	≤0.5–4	≤0.5	4
	IR	≤0.5–8	2	4
	HR	≤0.5–8	4	4
Ciprofloxacin	S	≤0.12–16	2	4
	IR	0.5–8	2	8
	HR	1–>32	4	>32
Telithromycin	S	≤0.03–2	≤0.03	0.06
	IR	≤0.03–0.5	≤0.03	0.25
	HR	≤0.03–2	≤0.03	0.25

[a] S, viridans group streptococci (n = 46) susceptible to penicillin G (MIC, ≤0.03 to 0.12 μg/ml); IR, viridans group streptococci (n = 13) intermediately resistant to penicillin G (MIC, 0.25 to 2 μg/ml); HR, viridans group streptococci (n = 18) highly resistant to penicillin G (MIC, ≥4 μg/ml).
[b] 50% and 90%, MIC_{50} and MIC_{90}, respectively.

at 35°C for 20 to 24 h. The MIC was defined as the lowest concentration of antibiotic which inhibited visible growth. Strains were classified for erythromycin A and penicillin G susceptibilities according to NCCLS criteria (25). *Streptococcus pneumoniae* ATCC 49619, *Staphylococcus aureus* ATCC 29213, and *Enterococcus faecalis* ATCC 29212 were used for quality control.

The distribution of viridans group streptococci for species isolated was 60 *S. mitis* strains, 6 *S. sanguis* strains, 6 *S. salivarius* strains, 4 *S. milleri* strains, and 1 *S. mutans* strain.

The susceptibility testing results are shown in Tables 1 and 2. Thirty-one (40.3%) of the 77 viridans group streptococcal isolates showed decreased susceptibility to penicillin G (MIC range, 0.25 to 16 μg/ml), 13 (16.9%) were intermediately resistant, and 18 (23.4%) were highly resistant. The strains were classified in two groups according to their erythromycin A susceptibility: 50 (64.9%) were susceptible, and 27 (35.1%) were resistant; 26% of the erythromycin-susceptible strains and 66.7% of the highly resistant strains were penicillin resistant (chi-square test, 10.42; $P < 0.01$).

S. mitis, in addition to being the most frequently isolated species (77.9%), showed the highest rates of resistance to penicillin G (43.5%) and erythromycin A (38.5%). Regarding the other species, the resistance to penicillin G was found in four of six *S. sanguis* strains and in one of six *S. salivarius* strains.

The ketolide telithromycin was the most active antimicrobial tested, followed by vancomycin. All erythromycin-resistant strains were inhibited at 1 μg of telithromycin per ml or less. The MIC at which 50% of the strains were inhibited (MIC_{50}) and MIC_{90} of telithromycin for these strains were, respectively, 5 and 2 dilutions lower than the MIC_{50} and MIC_{90} of erythromycin A. In addition, the MIC_{50} and MIC_{90} of this ketolide for intermediately and highly penicillin-resistant strains were ≤0.03 and 0.25 μg/ml, respectively.

The increasing incidence of viridans group streptococcal bacteremia in neutropenic patients observed in many institu-

tions and the emergence of serious complications and resistance to antibiotics are of great concern (6, 17, 21). Our data show that the current rates of penicillin G and erythromycin A resistance among viridans group streptococci isolated from blood samples of neutropenic patients clearly limit the usefulness of these drugs. *S. mitis*, which is the most frequently isolated species and the one most often linked to the occurrence of complications, shows the highest rate of resistance (9, 10). Our study shows that telithromycin has a good level of in vitro activity against viridans group streptococci, including strains that are highly penicillin G and erythromycin A resistant. According to these findings, telithromycin could be useful for the treatment of viridans group streptococcal bacteremia in neutropenic patients with cancer.

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