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In Vitro Activities of the Ketolide HMR 3647 against Recent Gram-Positive Clinical Isolates and *Haemophilus influenzae*

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The ketolide HMR 3647 (previously RU 66647) was evaluated against 2,563 recent clinical isolates of gram-positive pathogens and 200 *Haemophilus influenzae* isolates. HMR 3647 was active against macrolide-resistant streptococci, including pneumococci, but was not active against macrolide- or lincosamide-resistant staphylococci. Against *H. influenzae*, the potency of HMR 3647 was similar to that of azithromycin.

Ketolides are new semisynthetic 14-membered ring macrolides that differ from erythromycin A in that a 3-keto group is substituted for L-cladinose on the erythronolide A ring (1). They exhibit an antimicrobial spectrum comparable to erythromycin A, but for gram-positive cocci, ketolide MICs tend to be significantly lower than those of erythromycin A (2, 4, 5, 7, 8, 10). They are active against some anaerobic bacteria (6). Macrolide-resistant strains of *Streptococcus pneumoniae* are susceptible to the ketolides (4, 5, 10). HMR 3647 (previously RU 66647) is the ketolide that was selected for further evaluation in clinical studies. In this report, we describe the in vitro activity of HMR 3647 against 2,563 consecutive gram-positive clinical isolates collected from 10 North American medical centers and 200 stock cultures of *Haemophilus influenzae*.

The 10 North American medical centers that contributed consecutive clinical isolates for this study are listed in the appendix. A total of 2,563 recent gram-positive clinical isolates, each from a different patient, was collected during the first quarter of 1997. The species or major groups of microorganisms are described in Table 1. In addition, 200 stock cultures of *H. influenzae* (84 ampicillin-susceptible cultures, 27 ampicillin-resistant and β-lactamase-negative cultures, and 89 β-lactamase-positive cultures) were also tested.

All isolates were subjected to in vitro antimicrobial susceptibility tests by the broth microdilution procedure as recommended by the National Committee for Clinical Laboratory Standards (9). All test trays were incubated at 35°C without added CO_2. For testing streptococci, the cation-adjusted Mueller-Hinton broth was supplemented with 2 to 3% lysed horse blood. For testing *H. influenzae* isolates, freshly prepared Haemophilus Test Medium (HTM) broth was used. HMR 3647 was provided by Hoechst Marion Roussel. The other drugs, used for comparison, were procured from their respective U.S. manufacturers or purchased from Sigma Chemical Company, St. Louis, Mo. Only breakpoint concentrations of penicillin or oxacillin and vancomycin were tested. Concentrations of HMR 3647, erythromycin A, and clindamycin ranged from 0.12 to 16 μg/ml. Azithromycin and clarithromycin were tested only against *H. influenzae*, at concentrations ranging from 0.12 to 32 μg/ml.

When the broth microdilution trays were first prepared, they were validated by testing standard quality control organisms in triplicate. Those control strains were again tested on each day that a set of tests was initiated. Controls included *Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus* ATCC 29213, and *Streptococcus pneumoniae* ATCC 49619. The MICs of erythromycin and clindamycin were all within accepted control limits (9). The MICs of azithromycin and clarithromycin (diluted in HTM broth) were also within control limits when tested against *H. influenzae* ATCC 49247 (9).

Table 1 summarizes the MIC data of HMR 3647, erythromycin A, and clindamycin (and of azithromycin and clarithromycin for *H. influenzae*). By comparing geometric mean MICs, we defined the relative potency of drugs tested against *H. influenzae* to be as follows: azithromycin > HMR 3647 > clarithromycin. The difference between azithromycin and HMR 3647 was marginal. HMR 3647, erythromycin A, and clindamycin showed little useful activity against oxacillin-resistant staphylococci and vancomycin-resistant enterococci. Against most species, the ketolide was substantially more potent than erythromycin A. The frequency of off-scale MICs at either end of the range of concentrations tested precludes accurate assessment of the magnitude of differences between MICs. For different species, median MICs of HMR 3647 and erythromycin A differed by a magnitude of 0- to 64-fold.

The MICs of HMR 3647 for erythromycin-resistant staphylococci and enterococci were greater than those for erythromycin-susceptible strains (Table 2). In the case of streptococci, over 90% of the HMR 3647 MICs were ≤0.25 μg/ml regardless of erythromycin A or clindamycin resistance patterns. Two of 175 (1%) *Streptococcus pyogenes* isolates were resistant to erythromycin (MICs, 2.0 and 4.0 μg/ml), but both strains were susceptible to clindamycin and to HMR 3647. Over 95% of the erythromycin-resistant or clindamycin-resistant pneumococci and other streptococci were susceptible to 1.0 μg of HMR 3647 per ml. However, for *E. faecalis*, 1 μg of HMR 3647 per ml inhibited only 74% of the erythromycin-resistant strains and 87% of the clindamycin-resistant strains. The majority of erythromycin-resistant staphylococci and *Enterococcus faecium* isolates were also resistant to HMR 3647 (Table 2).

All clindamycin-resistant isolates were also resistant to erythromycin A, but the reverse was not true. The clindamycin-resistant strains were not as susceptible to HMR 3647 as the clindamycin-susceptible strains were (Table 2). This was particularly true of staphylococci and enterococci. Only 26% of the 185 clindamycin-resistant *S. aureus* strains were susceptible to 1 μg of HMR 3647 per ml, and only 3% of 138 clindamycin-resistant coagulase-negative staphylococci were susceptible to

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TABLE 1. Comparative susceptibility of recent gram-positive clinical isolates and *H. influenzae* stock cultures to HMR 3647, erythromycin A, and clindamycin[a]

Microorganism	No. of isolates tested	Antimicrobial agent	MIC (μg/ml)		
			Range	50%	90%
Enterococcus faecalis	359	HMR 3647	≤0.12–>16	≤0.12	2.0
		Erythromycin	≤0.12–>16	4.0	>16
		Clindamycin	≤0.12–>16	16	>16
Enterococcus faecium					
Vancomycin susceptible	55	HMR 3647	≤0.12–8.0	2.0	8.0
		Erythromycin	≤0.12–>16	>16	>16
		Clindamycin	≤0.12–>16	>16	>16
Vancomycin resistant	39	HMR 3647	≤0.12–>16	4.0	8.0
		Erythromycin	2.0–>16	>16	>16
		Clindamycin	≤0.12–>16	>16	>16
Enterococcus: other species[b]	38	HMR 3647	≤0.12–>16	≤0.12	8.0
		Erythromycin	≤0.12–>16	16	>16
		Clindamycin	≤0.12–>16	16	>16
Staphylococcus aureus					
Oxacillin susceptible	316	HMR 3647	≤0.12–>16	≤0.12	≤0.12
		Erythromycin	≤0.12–>16	0.5	>16
		Clindamycin	≤0.12–>16	≤0.12	0.25
Oxacillin resistant	199	HMR 3647	≤0.12–>16	>16	>16
		Erythromycin	≤0.12–>16	>16	>16
		Clindamycin	≤0.12–>16	>16	>16
Coagulase-negative *Staphylococcus*					
Oxacillin susceptible	218	HMR 3647	≤0.12–>16	≤0.12	0.5
		Erythromycin	≤0.12–>16	0.25	>16
		Clindamycin	≤0.12–>16	≤0.12	0.25
Oxacillin resistant	259	HMR 3647	≤0.12–>16	0.25	>16
		Erythromycin	≤0.12–>16	>16	>16
		Clindamycin	≤0.12–>16	0.25	>16
Streptococcus pyogenes	175	HMR 3647	≤0.12–≤0.12	≤0.12	≤0.12
		Erythromycin	≤0.12–4.0	≤0.12	≤0.12
		Clindamycin	≤0.12–≤0.12	≤0.12	≤0.12
Streptococcus agalactiae	90	HMR 3647	≤0.12–1.0	≤0.12	≤0.12
		Erythromycin	≤0.12–>16	≤0.12	1.0
		Clindamycin	≤0.12–>16	≤0.12	≤0.12
Streptococcus pneumoniae					
Penicillin susceptible	358	HMR 3647	≤0.12–0.25	≤0.12	≤0.12
		Erythromycin	≤0.12–>16	≤0.12	≤0.12
		Clindamycin	≤0.12–>16	≤0.12	≤0.12
Penicillin intermediate	82	HMR 3647	≤0.12–0.5	≤0.12	0.25
		Erythromycin	≤0.12–>16	≤0.12	4.0
		Clindamycin	≤0.12–>16	≤0.12	≤0.12
Penicillin resistant	105	HMR 3647	≤0.12–0.5	≤0.12	≤0.12
		Erythromycin	≤0.12–>16	0.5	>16
		Clindamycin	≤0.12–>16	≤0.12	>16
Streptococcus viridans group	125	HMR 3647	≤0.12–0.5	≤0.12	≤0.12
		Erythromycin	≤0.12–>16	0.25	16
		Clindamycin	≤0.12–>16	≤0.12	8.0
Streptococcus: other species[c]	62	HMR 3647	≤0.12–4.0	≤0.12	≤0.12
		Erythromycin	≤0.12–>16	≤0.12	8.0
		Clindamycin	≤0.12–>16	≤0.12	≤0.12
Corynebacterium species[d]	29	HMR 3647	≤0.12–>16	≤0.12	>16
		Erythromycin	≤0.12–>16	8.0	>16
		Clindamycin	≤0.12–>16	>16	>16
Other gram-positive species[e]	54	HMR 3647	≤0.12–>16	≤0.12	≤0.12
		Erythromycin	≤0.12–>16	≤0.12	1.0
		Clindamycin	≤0.12–>16	≤0.12	1.0
Haemophilus influenzae					
Ampicillin susceptible, β-lactamase negative	84	HMR 3647	0.25–8.0	2.0	4.0
		Clarithromycin	0.25–32	4.0	16
		Azithromycin	0.12–4.0	1.0	2.0
Ampicillin resistant, β-lactamase negative	27	HMR 3647	0.12–4.0	2.0	4.0
		Clarithromycin	0.25–32	8.0	16
		Azithromycin	0.12–2.0	1.0	2.0
Ampicillin resistant, β-lactamase positive	89	HMR 3647	0.25–8.0	2.0	4.0
		Clarithromycin	0.25–>32	4.0	8.0
		Azithromycin	0.12–4.0	1.0	2.0

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TABLE 2. In vitro activity of HMR 3647 against macrolide- and lincosamide-resistant bacterial isolates

Microorganism (total no. of isolates tested)	Resistance phenotype[a]	No. of isolates[b]	HMR 3647 MIC (μg/ml)		% of isolates for which MIC was ≤1.0 μg/ml[c]
			50%	90%	
Staphylococcus aureus (515)	Ery^s	265	≤0.12	≤0.12	100
	Ery^r	249	2.0	8.0	23
	Clin^s	330	≤0.12	≤0.12	100
	Clin^r	185	>16	>16	26
Coagulase-negative *Staphylococcus* spp. (477)	Ery^s	198	≤0.12	≤0.12	100
	Ery^r	276	0.5	>16	51
	Clin^s	335	≤0.12	0.25	100
	Clin^r	138	>16	>16	3
Streptococcus pneumoniae (545)	Ery^s	445	≤0.12	≤0.12	100
	Ery^i	37	≤0.12	≤0.12	100
	Ery^r	63	≤0.12	0.25	100
	Clin^s	514	≤0.12	≤0.12	100
	Clin^r	30	≤0.12	≤0.12	100
Nonpneumococcal *Streptococcus* spp. (452)	Ery^s	349	≤0.12	≤0.12	100
	Ery^i	51	≤0.12	≤0.12	100
	Ery^r	52	≤0.12	0.25	98
	Clin^s	427	≤0.12	≤0.12	100
	Clin^r	24	≤0.12	≤0.12	96
Enterococcus faecalis (359)	Ery^s	58	≤0.12	≤0.12	100
	Ery^i	140	≤0.12	≤0.12	100
	Ery^r	161	0.25	4.0	94
	Clin^i	30	≤0.12	≤0.12	97
	Clin^r	324	≤0.12	2.0	87
Enterococcus faecium (94)	Ery^i	20	≤0.12	≤0.12	100
	Ery^r	74	4.0	8.0	14
	Clin^s	16	≤0.12	≤0.12	100
	Clin^r	76	2.0	8.0	23

[a] Strains were susceptible (s), intermediately susceptible (i), or resistant (r) to erythromycin (Ery) or clindamycin (Clin). For both drugs, MIC breakpoints for susceptibility and resistance, respectively, were ≤4.0 and ≥16 μg/ml for tests of enterococci, ≤4.0 and ≥32 μg/ml for tests of staphylococci, and ≤0.5 and ≥2.0 μg/ml for tests of pneumococci and other streptococci.

[b] Phenotypes that were represented by fewer than 10 isolates are excluded from this table.

[c] Percent of strains susceptible to ≤1.0 μg of HMR 3647 per ml.

the same concentration of HMR 3647. On the other hand, clindamycin-resistant pneumococci were uniformly susceptible to HMR 3647, as were 96% of the clindamycin-resistant nonpneumococcal streptococci. That is particularly noteworthy because the majority of clindamycin-resistant pneumococci are also resistant to penicillin G and are often resistant to many other unrelated drugs (3).

In summary, for a sample of 2,563 recent gram-positive clinical isolates, HMR 3647 demonstrated significantly greater activity than erythromycin A or clindamycin, particularly against erythromycin- and penicillin-resistant *S. pneumoniae* and other streptococci. Additional studies with 200 *H. influenzae* isolates demonstrated that azithromycin and HMR 3647 were similar in potency and that clarithromycin was substantially less potent. Such differences in the in vitro potency of these drugs do not necessarily predict differences in their clinical efficacy, but HMR 3647 is likely to be a valuable addition to the macrolide-lincosamide-streptogramin B class of drugs.

APPENDIX

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[a] For *H. influenzae* strains, drugs used for comparison with HMR 3647 were clarithromycin and azithromycin.

[b] Includes 17 *E. avium*, 3 *E. casseliflavus*, 1 *E. cecorum*, 10 *E. durans*, 2 *E. raffinosus*, and 5 *E. gallinarum* isolates.

[c] Includes 1 *S. anginosus*, 8 *S. bovis*, 3 *S. constellatus*, 1 *S. intermedius*, 19 *S. mitis*, 2 *S. milleri*, 2 *S. mutans*, 7 *S. sanguis*, 3 serogroup C, 1 serogroup F, and 8 serogroup G isolates and 7 *Streptococcus* isolates with no species identified.

[d] Includes 15 *C. jeikeium*, 2 *C. minutissimum*, 1 *C. striatum*, 2 group 2, 1 group ANF-1, 1 group ANF-3, 1 *C. aquaticum*, and 1 *C. urealyticum* isolate and 5 *Corynebacterium* isolates with no species identified.

[e] Includes 1 *Aerococcus viridans*, 7 *Bacillus* spp., 2 *Gemella* spp., 5 *Lactobacillus* spp., 2 *Leuconostoc* spp., 4 *Listeria monocytogenes*, 2 *Micrococcus* spp., 1 *Pediococcus* spp., 1 *Rhodococcus* spp., and 29 *Stomatococcus* spp.