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In Vitro Evaluation of a Novel Ketolide Antimicrobial Agent, RU-64004

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Ketolides, a novel macrolide subclass, possess a mode of action that is similar to that of structurally related macrolide-lincosamide-streptogramin (MLS) compounds. By using reference in vitro tests, the in vitro activity of RU-64004 was compared to those of six other MLS compounds against more than 800 clinical pathogens, including 356 gram-positive organisms. The spectrum of activity of the ketolide was most similar to that of clindamycin versus staphylococci and streptococci and superior to those of all macrolides tested against oxacillin-resistant staphylococci and vancomycin-resistant (*vanA*, *vanB*, and *vanC*) enterococcal isolates. The activity of the ketolide was greater than those of the macrolides, azalides, or clindamycin tested against vancomycin-susceptible enterococci (MICs at which 90% of isolates are inhibited [MIC_{90}s], 0.25 to 4 μg/ml), penicillin-resistant pneumococci (MIC_{90}, 0.25 μg/ml), and most beta-hemolytic streptococci. All *Streptococcus pneumoniae* and beta-hemolytic streptococcus strains were inhibited by ketolide concentrations of ≤0.25 μg/ml. Against 165 erythromycin-resistant strains, RU-64004 inhibited (MICs, ≤0.5 μg/ml) approximately one-third of staphylococci, all streptococci, and slightly more than one-half of the enterococci. Quinupristin-dalfopristin (a streptogramin combination) was active against all tested isolates with the exception of non-*Enterococcus faecium* enterococci, against which the ketolide exhibited greater potency (MIC_{50}s, 0.03 to 2 μg/ml). The ketolide was also active against *Haemophilus influenzae* (MIC_{90}, 2 μg/ml), *Moraxella catarrhalis* (MIC_{90}, 0.12 μg/ml), pathogenic *Neisseria* spp. (MIC_{90}, 0.5 μg/ml), and many gram-positive anaerobes (MIC_{90}, 0.5 μg/ml). RU-64004 may enhance the role of macrolide drugs in the treatment of some serious infections caused by MLS-resistant gram-positive organisms.

Infections with gram-positive organisms are becoming an area of major concern due to their increased incidence and the high-level resistance profiles common among several species causing serious invasive disease (9, 10, 17, 18, 20, 26–28). This has led to extensive research for new drug entities (everninomycins, fluoroquinolones, glycylcyclines, and oxazolidinones) to circumvent or limit the emerging problem (17, 18, 27, 28).

Ketolides are a new class of macrolide-like antimicrobial agents (1). Instead of the cladinose moiety, these agents have a 2-keto structure which appears to increase their stability in a weakly acidic environment (1). Their mechanism of action is similar to that of the macrolides, which consists of binding to the 50S ribosomal subunit and inhibition of bacterial protein synthesis (6). They also penetrate well into phagocytic elements (2). Ketolides show in vitro activity against multidrug-resistant, gram-positive organisms, including staphylococci, enterococci, and pneumococci (13, 15, 30), anaerobes (12), *Haemophilus* spp. (3, 11, 24), *Helicobacter pylori* (8), pathogenic *Neisseria* spp. (14), *Chlamydia* spp. (16), *Legionella* spp. (7), *Mycoplasma* spp. (25), and some mycobacteria (29). In the present study we compared the in vitro activity (21–23) of a new ketolide, RU-64004, with those of six other macrolide-lincosamide-streptogram in B class compounds against more than 800 recent clinical isolates.

MATERIALS AND METHODS

A total of 356 clinical isolates of gram-positive organisms were examined. Included in the organism profile were oxacillin-resistant and -susceptible *Staphylococcus* spp., penicillin-resistant and -susceptible *Streptococcus* spp., and *Enterococcus* strains susceptible or resistant to vancomycin (see Table 1). More than four hundred gram-negative strains were tested to further define the spectrum of activity of the ketolide (see Table 2 and data not shown). The activities of the ketolide against a selected group of erythromycin-susceptible or -resistant *Staphylococcus* spp., *Streptococcus* spp., and *Enterococcus* spp. were also investigated (see Table 3).

RU-64004 and roxithromycin were obtained from Roussel Uclaf (Romainville, France), and the comparison compounds were provided by Abbott Laboratories (North Chicago, Ill.), Pfizer, Inc. (New York, N.Y.), Upjohn + Pharmacia (Kalamazoo, Mich.), Rhone-Poulenc Rorer (Collegeville, Pa.), and Sigma Chemical Co. (St. Louis, Mo.). All agents were supplied as standard laboratory powders, solubilized according to the manufacturers' instructions, and diluted to appropriate concentrations and placed into 96-well broth microdilution trays provided by Prepared Media Laboratories (Tualatin, Oreg.) for testing the majority of the species or into agar-based medium for testing anaerobes and *Neisseria gonorrhoeae* (21, 22).

Microdilution MICs were determined with Mueller-Hinton broth supplemented with lysed horse blood when testing *Haemophilus influenzae* and *Streptococcus* spp. Agar dilution MICs were determined in brucella agar supplemented with 5% sheep blood for anaerobes and in GC agar medium supplemented with a defined XV factor for *N. gonorrhoeae* (21, 22). The MIC was defined as the lowest concentration of antimicrobial agent inhibiting visible growth after 16 h of incubation for rapidly growing species and 24 h of incubation for more fastidious species. Trays and agar plates were incubated overnight in ambient air or in an increased CO_2 environment (5%) for fastidious species and for gonococci at 35°C, as specified by the National Committee for Clinical Laboratory Standards (NCCLS) (21). Standard quality control strains included *Streptococcus pneumoniae* ATCC 49619, *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *N. gonorrhoeae* ATCC 49226, and *Bacteroides fragilis* ATCC 25285. The fact that the results obtained were in the NCCLS quality control ranges validated the test procedures and reagents that were used.

RESULTS AND DISCUSSION

The results of susceptibility testing for 356 gram-positive pathogens are presented in Table 1. RU-64004 was active against oxacillin-susceptible *S. aureus* and *Staphylococcus epidermidis* (MICs at which 90% of isolates are inhibited [MIC_{90}s], 0.06 to 0.12 μg/ml). The inhibition rate (MICs, ≤0.5

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TABLE 1. Activity of RU-64004 compared to those of six macrolide-lincosamide-streptogramin compounds and vancomycin against gram-positive organisms

Organism(s) (no. of isolates tested)	Antimicrobial agent	MIC (μg/ml)			% Inhibited[a]
		50%	90%	Range	
Staphylococcus aureus					
Oxacillin susceptible (66)	RU-64004	0.06	0.06	0.015–>16	94 (94)
	Erythromycin	0.5	>8	0.25–>8	86
	Clarithromycin	0.25	8	0.25–>8	88
	Roxithromycin	1	>8	0.5–>8	89
	Azithromycin	2	>8	1–>8	70
	Clindamycin	≤0.25	≤0.25	≤0.25–>16	95
	Quinu-Dalfo[b]	0.25	0.5	≤0.12–0.5	100
	Vancomycin	0.5	0.5	0.25–1	100
Oxacillin resistant (50)	RU-64004	>16	>16	0.03–>16	34 (34)
	Erythromycin	>8	>8	0.5–>8	6
	Clarithromycin	>8	>8	0.25–>8	6
	Roxithromycin	>8	>8	1–>8	6
	Azithromycin	>8	>8	2–>8	4
	Clindamycin	>16	>16	0.25–>16	34
	Quinu-Dalfo	0.5	0.5	0.25–1	100
	Vancomycin	0.5	1	0.5–2	100
Staphylococcus epidermidis					
Oxacillin susceptible (23)	RU-64004	0.06	0.12	0.03–>16	91 (91)
	Erythromycin	0.25	>8	0.25–>8	74
	Clarithromycin	0.25	>8	0.25–>8	74
	Roxithromycin	0.5	>8	0.5–>8	74
	Azithromycin	1	>8	0.5–>8	70
	Clindamycin	≤0.25	≤0.25	≤0.25–>16	91
	Quinu-Dalfo	≤0.12	≤0.12	≤0.12–0.25	100
	Vancomycin	1	1	0.25–2	100
Oxacillin resistant (27)	RU-64004	>16	>16	0.06–>16	19 (19)
	Erythromycin	>8	>8	1–>8	0
	Clarithromycin	>8	>8	0.5–>8	4
	Roxithromycin	>8	>8	2–>8	4
	Azithromycin	>8	>8	4–>8	0
	Clindamycin	>16	>16	≤0.25–>16	19
	Quinu-Dalfo	0.25	0.25	≤0.12–0.5	100
	Vancomycin	1	2	1–2	100
Staphylococcus haemolyticus					
Oxacillin susceptible (7)	RU-64004	0.03		0.03–16	86 (86)
	Erythromycin	0.25		0.25–>8	71
	Clarithromycin	0.25		0.12–>8	57
	Roxithromycin	0.5		0.5–>8	71
	Azithromycin	0.5		0.5–>8	57
	Clindamycin	≤0.25		≤0.25–>16	86
	Quinu-Dalfo	0.25		≤0.12–0.5	100
	Vancomycin	0.5		0.25–1	100
Oxacillin resistant (13)	RU-64006	0.06	>16	0.03–>16	62 (62)
	Erythromycin	0.5	>8	0.5–>8	54
	Clarithromycin	0.25	>8	0.25–>8	54
	Roxithromycin	1	>8	1–>8	54
	Azithromycin	4	>8	1–>8	46
	Clindamycin	≤0.25	>16	≤0.25–>16	62
	Quinu-Dalfo	0.25	0.25	≤0.12–0.5	100
	Vancomycin	1	2	1–2	100
Coagulase-negative *Staphylococcus* spp. (20)[c]	RU-64004	0.06	16	0.015–>16	80 (80)
	Erythromycin	0.25	>8	0.12–>8	55
	Clarithromycin	0.25	>8	0.12–>8	55
	Roxithromycin	0.5	>8	0.25–>8	55
	Azithromycin	2	>8	0.5–>8	50
	Clindamycin	≤0.25	>16	≤0.25–>16	80
	Quinu-Dalfo	0.25	0.5	≤0.12–1	100
	Vancomycin	0.5	1	0.25–2	100

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TABLE 1—*Continued*

Organism(s) (no. of isolates tested)	Antimicrobial agent	MIC (μg/ml)			% Inhibited[a]
		50%	90%	Range	
Streptococcus spp.					
Serogroup A (20)	RU-64004	≤0.008	≤0.008	≤0.008	100 (100)
	Erythromycin	≤0.06	≤0.06	≤0.06	100
	Clarithromycin	≤0.06	≤0.06	≤0.06	100
	Roxithromycin	0.12	0.25	≤0.06–0.25	100
	Azithromycin	0.25	0.25	≤0.06–0.25	100
	Clindamycin	≤0.25	≤0.25	≤0.25	100
	Quinu-Dalfo	≤0.12	0.25	≤0.12–0.5	100
	Vancomycin	0.25	0.25	0.25	100
Serogroup B (20)	RU-64004	≤0.008	≤0.008	≤0.008	100 (100)
	Erythromycin	≤0.06	≤0.06	≤0.06	100
	Clarithromycin	≤0.06	≤0.06	≤0.06	100
	Roxithromycin	0.12	0.25	0.12–0.25	100
	Azithromycin	0.25	0.5	0.12–0.5	100
	Clindamycin	≤0.25	≤0.25	≤0.25	100
	Quinu-Dalfo	0.25	0.25	0.25	100
	Vancomycin	0.25	0.25	0.25	100
Serogroup C (10)	RU-64004	≤0.008	0.015	≤0.008–0.25	100 (100)
	Erythromycin	≤0.06	>8	≤0.06–>8	80
	Clarithromycin	≤0.06	8	≤0.06–>8	80
	Roxithromycin	≤0.06	0.25	≤0.06–>8	80
	Azithromycin	0.12	>8	≤0.06–>8	80
	Clindamycin	≤0.25	≤0.25	≤0.25–>8	90
	Quinu-Dalfo	0.25	0.5	0.25–0.5	100
	Vancomycin	0.25	0.25	0.25–0.5	100
Serogroup G (10)	RU-64004	≤0.008	0.015	≤0.008–0.06	100 (100)
	Erythromycin	≤0.06	>8	≤0.06–>8	70
	Clarithromycin	≤0.06	4	≤0.06–4	70
	Roxithromycin	0.25	>8	0.12–>8	70
	Azithromycin	0.5	>8	0.25–>8	70
	Clindamycin	≤0.25	≤0.25	≤0.25–>16	90
	Quinu-Dalfo	0.25	0.5	0.25–0.5	100
	Vancomycin	0.25	0.5	≤0.12–0.5	100
Streptococcus pneumoniae					
Penicillin susceptible (15)	RU-64004	≤0.008	≤0.008	≤0.008	100 (100)
	Erythromycin	≤0.06	≤0.06	≤0.06	100
	Clarithromycin	≤0.06	≤0.06	≤0.06	100
	Roxithromycin	≤0.06	0.12	≤0.06–0.12	100
	Azithromycin	0.25	0.25	0.12–0.5	100
	Clindamycin	≤0.25	≤0.25	≤0.25	100
	Quinu-Dalfo	0.25	0.5	0.25–0.5	100
	Vancomycin	0.25	0.25	≤0.12–0.5	100
Penicillin resistant (15)	RU-64004	0.03	0.25	≤0.008–0.25	100 (100)
	Erythromycin	>8	>8	≤0.06–>8	7
	Clarithromycin	>8	>8	≤0.06–>8	7
	Roxithromycin	>8	>8	0.12–>8	7
	Azithromycin	>8	>8	0.5–>8	7
	Clindamycin	≤0.25	>16	≤0.25–>16	53
	Quinu-Dalfo	0.5	0.5	0.25–1	100
	Vancomycin	0.25	0.25	≤0.12–0.25	100
Enterococcus faecalis					
Vancomycin susceptible (10)	RU-64004	0.03	0.25	0.015–0.5	100 (100)
	Erythromycin	1	>8	0.5–>8	20
	Clarithromycin	1	>8	0.25–>8	70
	Roxithromycin	4	>8	2–>8	20
	Azithromycin	8	>8	2–>8	20
	Clindamycin	>16	>16	16–>16	0
	Quinu-Dalfo	4	8	4–8	60

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TABLE 1—*Continued*

Organism(s) (no. of isolates tested)	Antimicrobial agent	MIC (μg/ml)			% Inhibited[a]
		50%	90%	Range	
Vancomycin resistant (10)	RU-64004	2	8	0.015–8	20 (60)
	Erythromycin	>8	>8	2–>8	0
	Clarithromycin	>8	>8	2–>8	10
	Roxithromycin	>8	>8	8–>8	0
	Azithromycin	>8	>8	>8	0
	Clindamycin	>16	>16	>16	0
	Quinu-Dalfo	8	16	4–>16	30
Enterococcus faecium					
Vancomycin susceptible (10)	RU-64004	0.03	4	0.015–8	60 (80)
	Erythromycin	8	>8	0.25–>8	10
	Clarithromycin	4	>8	0.12–>8	20
	Roxithromycin	>8	>8	0.12–>8	10
	Azithromycin	>8	>8	0.25–>8	10
	Clindamycin	16	>16	≤0.25–>16	10
	Quinu-Dalfo	2	2	0.25–2	100
Vancomycin resistant (10)	RU-64004	4	8	0.015–8	10 (10)
	Erythromycin	>8	>8	4–>8	0
	Clarithromycin	>8	>8	4–>8	0
	Roxithromycin	>8	>8	>8	0
	Azithromycin	>8	>8	>8	0
	Clindamycin	>16	>16	≤0.25–>16	10
	Quinu-Dalfo	0.5	0.5	0.5	100
Enterococcus spp. (20)	RU-64004	0.06	1	0.03–2	85 (100)
	Erythromycin	4	>8	0.12–>8	35
	Clarithromycin	4	>8	≤0.06–>8	40
	Roxithromycin	8	>8	0.25–>8	35
	Azithromycin	>8	>8	0.25–>8	35
	Clindamycin	16	>16	8–>16	0
	Quinu-Dalfo[b]	2	8	0.25–16	80
	Vancomycin	4	4	0.25–4	100

[a] Inhibition breakpoints defined by NCCLS (23) or by previously cited, peer-reviewed publications (10). For the ketolide, two MICs (≤0.5 and ≤2 μg/ml) were used to define the MIC distributions. The percentage data in parentheses are for the ≤2-μg/ml concentration.

[b] Quinu-Dalfo, quinupristin-dalfopristin, tested at a 30:70 ratio. The MIC listed is a total for both components.

[c] Includes *S. auricularis* (two strains), *S. capitus* (two strains), *S. connii* (two strains), *S. hominis* (four strains), *S. saprophyticus* (four strains), *S. sciurii* (two strains), *S. simulans* (two strains), and *S. warneri* (two strains). Five strains were oxacillin resistant.

μg/ml) for the ketolide was higher (34%) than those for azithromycin (4%), erythromycin (6%), clarithromycin (6%), and roxithromycin (6%) but was comparable to that for clindamycin (34%) against oxacillin-resistant *S. aureus* when using the NCCLS breakpoint MICs (23). Only 19% of oxacillin-resistant *S. epidermidis* strains were inhibited by RU-64004 at either concentration (≤0.5 and 2 μg/ml) used to define the MICs. The ketolide had a superior overall antistaphylococcal effect compared to those of the three macrolides and the azalide against the 206 organisms tested. The MIC_{50}s of RU-64004 were consistently ≥2 $\log_2$ dilution steps lower compared to those of azithromycin, erythromycin, clarithromycin, roxithromycin, quinupristin-dalfopristin, and vancomycin. However, all strains of oxacillin-susceptible or -resistant *Staphylococcus* spp. were susceptible to quinupristin-dalfopristin and vancomycin (23).

All serogroup A and B *Streptococcus* spp. were very susceptible to the agents tested, and all were inhibited by the ketolide at concentrations of ≤0.008 μg/ml. The serogroup C and G *Streptococcus* spp. were slightly less inhibited by RU-64004 (MIC_{90}s, 0.015 μg/ml). The ketolide had activity against the beta-hemolytic strains that were resistant to erythromycin, clarithromycin, roxithromycin, and clindamycin (70 to 90% susceptibility range). The MIC_{90}s of the ketolide were generally lower (more than eightfold when MICs were on-scale) than those of the macrolides, quinupristin-dalfopristin, and vancomycin. The activity of RU-64004 against both penicillin-susceptible and -resistant *S. pneumoniae* strains was complete and comparable to those of vancomycin and quinupristin-dalfopristin. The MIC_{50}s and MIC_{90}s of the ketolide were higher for the penicillin-resistant pneumococci (MIC_{50}, 0.03 μg/ml) than for the penicillin-susceptible strains, which were all inhibited by RU-64004 at ≤0.008 μg/ml. The vast majority of penicillin-resistant pneumococci were also resistant to erythromycin, clarithromycin, roxithromycin, and azithromycin but were inhibited by the ketolide.

Whereas all vancomycin-susceptible *E. faecalis* strains were inhibited by RU-64004 at concentrations of ≤0.5 μg/ml, only 20% of the vancomycin-resistant *E. faecalis* strains were inhibited at that level. The activity and antibacterial spectrum of the ketolide appeared to be better than those of the other macrolide-lincosamide antimicrobial agents tested. RU-64004 had inhibitory activity against more than 50% (MIC_{50}, 0.03 μg/ml) of the vancomycin-susceptible *Enterococcus faecium* strains, and this activity was superior to those of the macrolides tested (10 to 20% susceptibility) and clindamycin (10% susceptibili-

TABLE 2. Activities of RU-64004 against 155 fastidious strains, including *H. influenzae*, *M. catarrhalis*, pathogenic *Neisseria* species, and selected anaerobic gram-negative and -positive bacteria

Organism(s) (no. of isolates tested)	MIC (μg/ml)		
	50%	90%	Range
H. influenzae (50)[a]	2	2	0.03–4
M. catarrhalis (30)	0.06	0.12	0.03–0.12
N. gonorrhoeae (30)[b]	0.25	0.5	0.06–0.5
N. meningitidis (10)	≤0.008	0.5	≤0.008–0.5
Neisseria spp. (10)[c]	1	4	0.25–4
Anaerobic species (25)[d]	0.06	0.5	0.03–2

[a] Includes beta-lactamase-positive ($n = 20$), beta-lactamase-negative ($n = 20$), and chromosomally mediated ampicillin-resistant ($n = 10$) strains.
[b] Includes penicillin-susceptible ($n = 10$), beta-lactamase positive ($n = 10$), and chromosomally mediated penicillin-resistant ($n = 10$) strains.
[c] Strains included *N. subflava* ($n = 4$), *N. sicca* ($n = 4$), and *N. mucosa* ($n = 2$).
[d] Strains included *Clostridium* spp. ($n = 10$), *Prevotella* spp. ($n = 5$), and *Peptostreptococcus* spp. ($n = 10$).

ty). For the remaining *Enterococcus* spp. (Table 1), the ketolide inhibited all strains at ≤2 μg/ml, a result indicating that its antibacterial spectrum is the same as that of vancomycin (MIC_{90}, 4 μg/ml).

Table 2 lists the activities of RU-64004 against representative gram-negative fastidious species (155 strains). At least 90% of the strains of *H. influenzae* tested were inhibited by RU-64004 at ≤2 μg/ml. Against *H. influenzae* this agent appears to possess better activity than that reported for clarithromycin and activity comparable to that of azithromycin. The MIC_{90} of RU-64004 for *Moraxella catarrhalis* strains was 0.12 μg/ml. *N. gonorrhoeae* and *Neisseria meningitidis* were very susceptible to the ketolide (MIC_{90}s, 0.5 μg/ml). *Neisseria* spp. other than the gonococci and *N. meningitidis* showed significantly decreased susceptibility to the ketolide (MIC_{90}, 4 μg/ml; range, 0.25 to 4 μg/ml). RU-64004 demonstrated acceptable activity against the anaerobic strains tested (MIC_{90}, 0.5 μg/ml), which included *Clostridium* spp., *Prevotella* spp., and *Peptostreptococcus* spp., but it was inactive against the *B. fragilis* group (data not shown). Furthermore, RU-64004 had no activity (MIC_{50}, >8 μg/ml) when it was tested against representatives of 27 species (305 strains) of gram-negative bacilli. RU-64004 MICs were ≤2 μg/ml for fewer than 1% of strains tested.

TABLE 3. Activities of RU-64004 against erythromycin-susceptible and -resistant populations of *S. aureus*, coagulase-negative staphylococci, pneumococci, and *Enterococcus* spp.

Organism(s)	Erythromycin susceptibility (no. of isolates tested)[a]	MIC (μg/ml)		% Inhibited at concn (μg/ml) of:	
		50%	90%	≤0.5	≤2
S. aureus	Susceptible (60)	0.06	0.06	100	100
	Resistant (56)[b]	16	>16	36[c]	36[c]
Coagulase-negative staphylococci	Susceptible (41)	0.03	0.06	100	100
	Resistant (49)[b]	16	>16	31[c]	31[c]
S. pneumoniae	Susceptible (16)	≤0.008	≤0.008	100	100
	Resistant (14)[b]	0.03	0.06	100	100
Enterococci	Susceptible (10)	0.015	0.015	100	100
	Resistant (46)	0.25	8	57	72

[a] Defined by the criteria of the NCCLS (23). Cross-resistance among azithromycin, clarithromycin, and roxithromycin was near complete (≥95%).
[b] The same rates were observed for clindamycin.
[c] All strains were susceptible to quinupristin-dalfopristin.

The data in Table 3 indicate that the activities of RU-64004 against erythromycin-resistant *S. aureus* and coagulase-negative *Staphylococcus* spp. were in the range of 31 to 36% when the ketolide breakpoint was used at ≤0.5 μg/ml. Erythromycin-resistant *S. pneumoniae* strains were inhibited by the ketolide at ≤0.5 μg/ml. Among the erythromycin-resistant enterococci, approximately one-half of the strains were inhibited by RU-64004 at ≤0.5 μg/ml and a slightly greater number (72%) were inhibited by the drug at ≤2 μg/ml. The ketolide MIC_{50}s and MIC_{90}s for the erythromycin-resistant organisms (MIC_{50} range, 0.03 to >16 μg/ml; MIC_{90} range, 0.06 to >16 μg/ml) were elevated in comparison to those for the erythromycin-susceptible strains.

The novel ketolide RU-64004 appears to offer a potential alternative for treating penicillin- and erythromycin-resistant *S. pneumoniae* strains. This agent also has in vitro activity greater than those of the macrolides against *Staphylococcus* spp., a feature that makes RU-64004 essentially equal to clindamycin. The streptococcal coverage of RU-64004 was complete, but for vancomycin-resistant *E. faecalis* and both vancomycin-susceptible and -resistant *E. faecium* strains, the potential spectrum of activity of quinupristin-dalfopristin was equal to or superior to that of RU-64004. These results are consistent with those of early in vitro studies with RU-64004 (3–5, 11–15). In vivo studies with animal models have shown quite promising results, especially against infections caused by macrolide-resistant strains (5). Furthermore, ketolides appear to be less affected by the adverse influences of variations in pH and inoculum concentration and of medium type (4), and the potency of ketolides appears to be enhanced by human serum components (4). Further investigations are required to assess the clinical value of RU-64004, its organ safety profile (19), and its pharmacodynamic features.

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