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In Vitro Evaluation of Three New Macrolide Antimicrobial Agents, RU28965, RU29065, and RU29702, and Comparisons with Other Orally Administered Drugs

RONALD N. JONES,[1]* ARTHUR L. BARRY,[2] AND C. THORNSBERRY[3]

Kaiser Foundation Laboratories (Oregon Region), Clackamas, Oregon 97015[1]; The Clinical Microbiology Institute, Tualatin, Oregon 97062[2]; and Centers for Disease Control, Atlanta, Georgia 30333[3]

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Three new macrolide drugs (RU28965, RU29065, and RU29702) were compared in vitro with erythromycin and five other orally administered antimicrobical agents by using 733 recent clinical isolates. All of the investigational macrolides had a spectrum very similar to that of erythromycin, but with slightly higher (two- to fourfold) minimum inhibitory concentrations against *Haemophilus influenzae*, staphylococci, and streptococci including *Streptococcus faecalis*. RU29065 and RU29702 were more active than erythromycin against *Neisseria gonorrhoeae* and *Neisseria meningitidis*. The drugs appeared to be predominantly bacteriastatic and were ineffective against gram-negative bacilli, and their minimum inhibitory concentrations were greatly increased by high inoculum concentrations. Cross-resistance between the macrolides was nearly complete, favoring the use of a single agent for in vitro susceptibility test if in vivo therapeutic differences are not observed.

Macrolide antimicrobial agents have been widely used for over two decades as treatment of infections caused by susceptible gram-positive pathogens. The principal applications of these drugs appear to be as secondary choices to penicillins in less serious outpatient infectious diseases and for pneumococcal lower respiratory infections among penicillin-allergic inpatients. More recently, erythromycin has become indicated for *Legionella* and some chlamydial or *Mycoplasma* spp. diseases. To date, the newer macrolides that have been investigated in the United States have not offered a significantly wider antimicrobial spectrum, increased potency, or superior pharmacokinetic characteristics (3, 6, 13, 14).

This report presents the in vitro evaluation of three new macrolide antimicrobics (RU28965, RU29065, and RU29702) that are said to possess superior pharmacokinetic qualities compared with that of erythromycin (publication in press, Roussel-UCLAF). Since each of these drugs have an extended serum half-life after rapid absorption from the gastrointestinal tract, we choose to compare their antimicrobial activities with currently available and some investigational oral drugs. Additional studies of the effect of inoculum density on the macrolide minimum inhibitory concentrations (MICs), their minimal bactericidal concentrations (MBCs), and cross-resistance comparisons are also presented.

MATERIALS AND METHODS

Antimicrobial agents. RU28965, RU29065, and RU29702 (Fig. 1) were supplied by Hoechst-Roussel Pharmaceuticals, Inc., Somerville, N.J. The remaining reference antimicrobial agents were kindly provided as follows: cefaclor from Eli Lilly Research Laboratories, Indianapolis, Ind.; erythromycin from Abbott Laboratories, North Chicago, Ill.; clindamycin from The Upjohn Co., Kalamazoo, Mich., dicloxacillin from Bristol Laboratories, Syracuse, N.Y.; ampicillin from Beecham Laboratories, Bristol, Tenn.; and SCH 29482 from Schering Corp., Kenilworth, N.J.

Bacterial isolates. A total of 733 recent (1982) clinical bacterial isolates were collected by the three collaborating laboratories or were provided by T. L. Gavan, The Cleveland Clinic Foundation, Cleveland, Ohio; E. Hugh Gerlach, St. Francis Hospital, Wichita, Kans.; and P. C. Fuchs, St. Vincent Hospital, Portland, Oreg. The above isolates were typical strains, except for resistant *Haemophilus influenzae* and *Neisseria gonorrhoeae* isolates having known β-lactamase or chloramphenicol resistance mechanisms. Most of the isolates were tested by two or more of the collaborating laboratories (mainly the Centers for Disease Control and the Clinical Microbiology Institute) in a manner previously reported (2, 6, 7).

These isolates included 260 strains of the *Enterobacteriaceae*, 194 strains of non-*Enterobacteriaceae* gram-negative bacilli, and 279 strains of gram-positive and gram-negative cocci (Table 1, 2, and 3).

Antimicrobial susceptibility tests. Broth microdilution tests were used throughout this study, following the M7-T procedure specified by the National Committee for Clinical Laboratory Standards (2, 6, 7, 9).

TABLE 1. Antimicrobial activity of three new macrolide antibiotics compared with six other orally administered drugs against 192 recent clinical isolates of gram-positive cocci

Organism (no. tested)	Antimicrobial agent	MIC (μg/ml)			% Susceptible[a]
		Geometric mean MIC	For 90% of strains	Range	
Staphylococcus aureus					
Penicillin susceptible (20)	RU28965	1.23	2.0	0.5–2.0	100.0
	RU29065	1.18	2.0	0.5–2.0	100.0
	RU29702	1.45	2.0	1.0–2.0	100.0
	Erythromycin	0.61	1.0	0.25–1.0	100.0
	Clindamycin	0.06	0.12	0.06–0.12	100.0
	Dicloxacillin	0.10	0.12	0.06–0.25	100.0
	Cefaclor	0.86	1.0	0.25–2.0	100.0
	SCH29482	0.07	0.12	0.06–0.12	100.0
Penicillin resistant (27)	RU28965	0.82	1.0	0.5–2.0	100.0
	RU29065	0.83	1.0	0.5–2.0	100.0
	RU29702	1.07	2.0	0.5–2.0	100.0
	Erythromycin	0.39	0.5	0.25–2.0	100.0
	Clindamycin	0.14	0.25	0.12–0.25	100.0
	Dicloxacillin	0.19	0.25	0.06–0.5	100.0
	Cefaclor	2.13	4.0	0.5–8.0	100.0
	SCH29482	0.06	0.06	0.06–0.5	100.0
Methicillin resistant (10)	RU28965	>32	>32	1.0–>32	11.1
	RU29065	>32	>32	1.0–>32	11.1
	RU29702	>32	>32	1.0–>32	11.1
	Erythromycin	>32	>32	0.5–>32	11.1
	Clindamycin	>32	>32	0.12–>32	11.1
	Dicloxacillin[b]	0.24[b]	0.5[b]	0.12–0.5[b]	100.0[b]
	Cefaclor	13.9	32	1.0–32	33.3
	SCH29482	0.13	0.25	0.06–0.25	100.0
Staphylococcus epidermidis					
Penicillin susceptible (9)	RU28965	0.69	2.0	0.25–2.0	100.0
	RU29065	0.67	2.0	0.25–2.0	100.0
	RU29702	0.69	2.0	0.25–2.0	100.0
	Erythromycin	0.29	0.5	0.12–0.5	100.0
	Clindamycin	0.11	0.12	0.06–0.12	100.0
	Dicloxacillin	0.42	1.0	0.06–1.0	100.0
	Cefaclor	1.23	4.0	0.06–4.0	100.0
	SCH29482	0.36	2.0	0.06–2.0	100.0
Penicillin resistant (6)	RU28965	0.5	0.5	0.5	100.0
	RU29065	0.38	0.5	0.25–0.5	100.0
	RU29702	0.58	1.0	0.5–1.0	100.0
	Erythromycin	0.25	0.25	0.25	100.0
	Clindamycin	0.10	0.12	0.06–0.12	100.0
	Dicloxacillin	0.10	0.5	0.12–0.5	100.0
	Cefaclor	0.50	0.5	0.5	100.0
	SCH29482	0.08	0.12	0.06	100.0
Staphylococcus spp.					
Erythromycin resistant (21)[c]	RU28965	>32	>32	16–>32	0.0
	RU29065	>32	>32	32–>32	0.0
	RU29702	>32	>32	16–>32	0.0
	Clindamycin	>32	>32	0.06–>32	28.6
	Dicloxacillin	11.1	>32	0.06–>32	81.0
	Cefaclor	17.3	32	0.12–>32	52.4
	SCH29482	6.30	2.0	0.06–>32	90.0
Streptococcus faecalis					
Erythromycin susceptible (22)	RU28965	3.77	4.0	1.0–8.0	90.9
	RU29065	2.61	4.0	0.5–4.0	100.0
	RU29702	3.34	4.0	0.5–8.0	95.5
	Erythromycin	1.03	2.0	0.25–2.0	100.0
	Cefaclor	26.5	32	8.0–>32	4.5
	SCH29482	4.11	8.0	0.5–8.0	90.9

TABLE 1—*Continued*

Organism (no. tested)	Antimicrobial agent	MIC (μg/ml)			% Susceptible[a]
		Geometric mean MIC	For 90% of strains	Range	
	Ampicillin	0.48	0.5	0.12–0.5	100.0
Erythromycin resistant (10)	RU28965	>32	>32	32–>32	0.0
	RU29065	>32	>32	>32	0.0
	RU29702	>32	>32	>32	0.0
	Cefaclor	32.0	32	16–>32	0.0
	SCH29482	5.60	8.0	4.0–8.0	60.0
	Ampicillin	0.5	0.5	0.5	100.0
Streptococcus pneumoniae (26)	RU28965	0.11[d]	0.12	≤0.06–>32	92.3
	RU29065	≤0.06[d]	≤0.06	≤0.06–>32	92.3
	RU29702	0.07[d]	0.12	≤0.06–>32	92.3
	Erythromycin	≤0.06[d]	≤0.06	≤0.06–>32	92.3
	Clindamycin	0.26	0.12	≤0.06–4.0	100.0
	Dicloxacillin	5.69	16	0.12–>32	53.8
	Cefaclor	1.63	2.0	0.25–16	96.2
	SCH29482	1.32	0.5	≤0.12–4.0	100.0
Streptococcus pyogenes (21)	RU28965	0.10[d]	16	≤0.06–>32	76.2
	RU29065	≤0.06[d]	8.0	≤0.06–>32	85.7
	RU29702	0.07[d]	8.0	≤0.06–>32	85.7
	Erythromycin	0.08[d]	4.0	≤0.06–>32	90.5
	Clindamycin	0.07	0.12	≤0.06–>32	95.2
	Dicloxacillin	0.09	0.12	≤0.06–0.5	100.0
	Cefaclor	0.16	0.25	≤0.06–1.0	100.0
	SCH29482	0.13	≤0.12	≤0.12–0.25	100.0
Streptococcus agalactiae (20)	RU28965	0.11	0.12	0.12–0.25	100.0
	RU29065	≤0.06	0.12	≤0.06–0.12	100.0
	RU29702	≤0.06	0.12	≤0.06–0.12	100.0
	Erythromycin	≤0.06	≤0.06	≤0.06–0.12	100.0
	Clindamycin	≤0.06	≤0.06	≤0.06	100.0
	Dicloxacillin	0.68	1.0	0.25–2.0	100.0
	Cefaclor	0.58	1.0	≤0.06–2.0	100.0
	SCH29482	≤0.12	≤0.12	≤0.12–0.25	100.0

[a] Susceptible MIC was ≤4.0 μg/ml for all drugs, except dicloxacillin (≤2.0 μg/ml) and cefaclor (≤8.0 μg/ml). Breakpoints are based on National Committee for Clinical Laboratory Standards tentative standard M7-T (9).

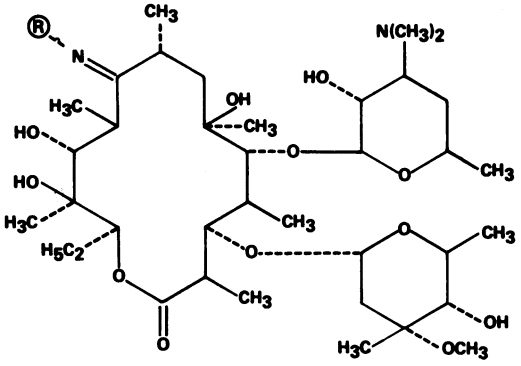
[b] Note low MIC values that point out poor predictive value of dicloxacillin MICs as indication of methicillin resistance.

[c] Includes penicillin-susceptible *S. aureus* (three strains), penicillin-resistant *S. epidermidis* (eight strains), penicillin-susceptible *S. epidermidis* (one strain), and methicillin-resistant *S. aureus* (nine strains).

[d] Geometric mean derived from macrolide-susceptible isolates only, thus providing a more reliable comparison of activity.

The test trays were prepared commercially (Prepared Media Laboratory, Tualatin, Oreg.) with a single lot of Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) supplemented with 50 μg of calcium per ml and 25 μg of magnesium per ml and were distributed to the testing laboratories. The frozen test panels were then held at −43°C or less until needed. Before use the trays were thawed at room temperature (approximately 20 min) and inoculated with disposable replicators delivering 5 μl of inoculum to each well. The final inoculum was approximately 5×10^5 CFU/ml. For the testing of *H. influenzae*, *N. meningitidis*, and fastidious streptococci (*Streptococcus pyogenes*, *S. agalactiae*, and *S. pneumoniae*), the inoculum was standardized in Mueller-Hinton broth containing 5% lysed rabbit blood; 0.1 ml of this adjusted cell suspension was added to each microdilution well, giving a final concentration of 5×10^5 CFU/ml. The *N. gonorrhoeae* strains were tested on agar media by methods previously described (1–3, 6). The MIC was recorded as the lowest concentration totally inhibiting visible bacterial growth (clear well or agar surface) after 18 h of incubation at 35°C.

The MBC was determined by subculturing 5% of the volume in each well to an antimicrobial agent-free blood agar plate. After incubating the subcultures 48 h, the MBC was determined as the lowest concentration yielding no more than 0.1% survival of the initial inoculum (99.9% killing). The MBC interpretive criteria of Pearson et al. (10) were employed throughout



Macrolide	®
RU 28965	$H_3CO(CH_2)_2OCH_2O$–
RU 29065	$(H_3C)_2N–CH_2–CH_2–O$–
RU 29702	$Et_2N–CH_2–CH_2O$–

FIG. 1. Structural features of macrolides RU28965, RU29065, and RU29702.

this study phase. The 40 selected strains that were used to determine MBC values were also tested with inocula of 10^3, 10^5, and 10^7 CFU/ml to determine the effect of altering inoculum density on the macrolide MIC values.

RESULTS

The spectrum of activity of the three new macrolides was compared with that of other orally administered drugs (Table 1). Compounds RU28965 and RU29065 were more active against methicillin-susceptible *Staphylococcus aureus* than was RU29702, yet erythromycin was approximately twice as potent as the new drugs. The oral penem SCH29482 was the most active, and cefaclor was the least inhibitory (by weight) against *S. aureus*. Only SCH29482 and dicloxacillin showed in vitro activity against methicillin-resistant strains of *S. aureus*. Since the dicloxacillin results are considered a false-susceptible artifact of the in vitro test method, the data for the other β-lactams (cefaclor and SCH29482) must be considered suspect. A general trend toward greater macrolide susceptibility (lower MICs) was noted among the *S. aureus* and *Staphylococcus epidermidis* isolates producing penicillinase compared with penicillin-susceptible strains. Lower geometric mean macrolide MICs were found for the *S. epidermidis* strains (0.25 to 0.69 μg/ml) compared with the tested isolates of *S. aureus* (0.39 to 1.45 μg/ml). All staphylococcal strains susceptible to methicillin were inhibited by the four macrolide drugs at ≤2.0 μg/ml. Like the methicillin-resistant *S. aureus* strains, the erythromycin-resistant *Staphylococcus* spp. were not inhibited by clinically significant concentrations of the new macrolide drugs, clindamycin, or cefaclor. Elevated SCH29482 MICs were also encountered for the macrolide-resistant staphylococci.

RU29065 was the most active new macrolide against *Streptococcus faecalis*, but two- to threefold less active than erythromycin and approximately twofold more potent than SCH29482. Enterococci resistant to erythromycin were also not inhibited by RU28965, RU29065, RU29702, or cefaclor. These *S. faecalis* strains were also resistant to clindamycin and dicloxacillin (data not shown). Pneumococci and the β-hemolytic *Streptococcus* spp. were very susceptible to all four macrolides (geometric mean MICs, ≤0.06 to 0.11 μg/ml), again RU29065 seemed to be the most active new drug, followed by RU29702 and RU28965. Erythromycin remained the most active macrolid against the three nonenterococcal *Streptococcus* spp. Only RU28965 among the new drugs had <85% inhibition of any gram-positive species at ≤4.0 μg/ml, e.g., 76.2% inhibition of *S. pyogenes* isolates.

A more limited spectrum was found for the three new macrolides against the gram-negative strains tested (Table 2). Marginal anti-*Haemophilus* spp. inhibition was identified for all four macrolides. Erythromycin was most active (50% MIC [MIC_{50}], 2.0 μg/ml) against ampicillin-resistant and -susceptible strains of *H. influenzae*. The other drugs had an activity ranking of RU29065 > RU29702 > RU28965. All four macrolides showed acceptable inhibitory qualities against the *Neisseria* spp. (all MIC_{90} values, ≤2.0 μg/ml). All of the macrolides were ineffective on the *Enterobacteriaceae* and the nonenteric, gram-negative bacilli (Table 2). Only a minority of strains of *Acinetobacter* spp. and *Pseudomonas stutzeri* were inhibited by concentrations of RU29065, RU29702, and erythromycin that might be achieved in urine or perhaps by topical administration. Only RU29065 and RU29702 showed susceptible-range MIC_{50} values (≤4.0 μg/ml) against *A. calcoaceticus* subsp. *lwoffi*.

Forty gram-positive strains (five species) were tested against the macrolides for their bactericidal activity and the influence of increasing inoculum density on the MIC (Table 3). All four organism groupings from the two genera demonstrate similar findings: minimal influence on the MICs by an inoculum increases from 10^3 to 10^5 CFU/ml, a profound inoculum effect (≥64-fold increase) when the inoculum concentrations reached 10^7 CFU/ml, and MBC values elevated above the corresponding MIC result. The later

TABLE 2. Comparative antimicrobial activity of four macrolide drugs against *Haemophilus influenzae*, *Neisseria* spp., and 332 other gram-negative organisms[a]

Organism (no. tested)	RU28965		RU29065		RU29702		Erythromycin	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Haemophilus influenzae								
Ampicillin susceptible (30)	8.0	16	4.0	8.0	4.0	8.0	2.0	4.0
Ampicillin resistant (31)	8.0	16	4.0	8.0	8.0	8.0	2.0	4.0
Neisseria gonorrhoeae								
Penicillin susceptible (31)	0.5	2.0	0.12	0.25	≤0.06	0.25	0.5	1.0
Penicillin resistant (30)	0.5	1.0	0.12	0.12	≤0.06	0.25	0.25	1.0
Neisseria meningitidis (26)	0.12	0.5	≤0.06	0.12	≤0.06	0.25	0.25	0.5
Acinetobacter calcoaceticus								
Subsp. *anitratus* (13)	>32	>32	16	16	16	32	16	32
Subsp. *lwoffi* (5)	>32	>32	2.0	16	4.0	16	16	32
Pseudomonas stutzeri (9)	>32	>32	16	>32	32	>32	4.0	>32
Other non-*Enterobacteriaceae* (45)[b]	>32	>32	>32	>32	>32	>32	>32	>32
Enterobacter agglomerans (20)	>32	>32	16	>32	32	>32	>32	>32
Other *Enterobacteriaceae* (240)[c]	>32	>32	>32	>32	>32	>32	>32	>32

[a] MICs are given in micrograms per milliliter inhibitory 50 and 90% of tested strains.

[b] Includes *P. aeruginosa* (25 strains), *P. fluorescens* (11 strains), and *P. maltophilia* (9 strains).

[c] Includes *Citrobacter diversus* (18 strains), *C. freundii* (21 strains), *E. coli* (27 strains), *Enterobacter aerogenes* (20 strains), *E. cloacae* (20 strains), *Klebsiella* spp. (27 strains), *Proteus mirabilis* (27 strains), *P. vulgaris* (10 strains), *Providencia rettgeri* (20 strains), *P. stuartii* (20 strains), and *Serratia marcescens* (30 strains).

finding is consistent with other macrolide drugs (erythromycin, rosaramicin, or josamycin), but the MBC increase may be as low as 2-fold (erythromycin versus *S. faecium-durans* and the three new macrolides versus *S. epidermidis*) or as high as 32-fold.

Table 4 demonstrates a "nearly complete" cross-resistance between the new drugs and erythromycin against the gram positive strains tested. Using the disk test susceptible breakpoints or MIC correlates of the National Committee for Clinical Laboratory Standards (≤2.0 μg/ml as susceptible and ≥8.0 μg/ml as resistant), we found 90.1 to 94.3% absolute agreement between the drugs. The RU29065 data most closely correlated to erythromycin, showing no major discrepancies (false-susceptible or false-resistant) and only 5.7% minor interpretive errors. The RU28965-erythromycin and RU29702-erythromycin comparisons, respectively,

TABLE 3. Comparison of the MIC and the MBC of four macrolides and demonstration of the effect of increasing inoculum concentration on their MIC results

Organism (no. tested)	Macrolide	MIC_{50} (μg/ml) at indicated inoculum (log_{10} CFU/ml)			MBC_{50} (μg/ml) at inoculum of 10^5 CFU/ml)
		10^3	10^5	10^7	
S. aureus (10)[a]	RU28965	0.12	0.5	>32	16
	RU29065	0.25	0.5	>32	16
	RU29702	0.25	0.5	>32	8.0
	Erythromycin	0.06	0.25	>32	4.0
S. epidermidis (10)[a]	RU28965	0.25	0.5	>32	1.0
	RU29065	0.12	0.5	>32	1.0
	RU29702	0.25	0.5	>32	1.0
	Erythromycin	0.12	0.25	>32	1.0
S. faecalis (10)	RU28965	2.0	4.0	>32	>32
	RU29065	2.0	2.0	>32	32
	RU29702	2.0	2.0	>32	16
	Erythromycin	1.0	1.0	>32	16
S. faecium-durans (10)	RU28965	2.0	4.0	>32	>32
	RU29065	1.0	2.0	>32	8.0
	RU29702	2.0	2.0	>32	8.0
	Erythromycin	1.0	1.0	>32	2.0

[a] Half of the strains tested produced penicillinase.

TABLE 4. Macrolide cross-resistance comparing the new drugs and erythromycin against 192 strains of gram-positive cocci[a]

Antimicrobial agent	MIC (μg/ml)	No. cross-resistant (% of total) with erythromycin MIC (μg/ml):		
		≤2.0	4.0	≥8.0
RU28965	≤2.0	129 (67.2)		
	4.0	14 (7.3)		
	≥8.0	4 (2.1)	1 (0.5)	44 (22.9)
RU29065	≤2.0	137 (71.4)		
	4.0	10 (5.2)		
	≥8.0		1 (0.5)	44 (22.9)
RU29702	≤2.0	132 (68.8)		
	4.0	14 (7.3)		
	≥8.0	1 (0.5)	1 (0.5)	44 (22.9)

[a] Includes all strains listed in Table 1.

produced 2.1 and 0.5% of strains susceptible to erythromycin, but resistant to the new macrolides. These serious (very major) errors as well as the great proportion of the minor discrepancies were found among strains of *S. faecalis* and *S. pyogenes*. By applying the M7-T criteria of the National Committee for Clinical Laboratory Standards (9), the major error rates would be 2.6, 0.5, and 1.0% for the erythromycin comparisons with RU28965, RU29065, and RU29702, respectively. This assumes that the erythromycin breakpoints could be applied to the new drugs.

DISCUSSION

The three new macrolide antimicrobial agents appear very comparable to erythromycin in their spectrum of antimicrobial activity. Our data compare favorably to those received from the manufacturer (Roussel-UCLAF, 1982), where the *S. aureus* geometric mean MICs were 0.64, 0.35, 0.31, and 0.28 to 0.39 μg/ml for RU28965, RU29065, RU29702, and erythromycin, respectively. The geometric mean MIC data for the same drugs in *S. faecalis* were 1.65, 0.23, 0.24, and 0.24 to 0.64 μg/ml, respectively. In most instances erythromycin was slightly more potent than the most active of the new drugs, RU29065. RU29065 was consistently more active or equal in its in vitro efficacy compared with RU28965 or RU29702 against all gram-positive cocci, *H. influenzae*, *Neisseria* spp., and some of the gram-negative bacilli. A total of 15% of *Enterobacter agglomerans*, 22% of *Acinetobacter* spp., and 22% of *P. stutzeri* strains had RU29065 MICs ≤4.0 μg/ml.

These results are similar to those reported for other investigational macrolides such as rosaramicin (formerly rosamicin) and josamycin (3, 6, 14). Recently studied macrolide drugs have generally been only comparable to erythromycin in antimicrobial activity against the major gram-positive pathogens (6, 14), yet seem to offer promise against genital infections because of high potency against *N. gonorrhoeae*, chlamydia, and mycoplasma (3, 6) and their elevated concentrations in various body tissues (6, 13). These drugs were found to be predominantly bacteristatic, with MBCs at inoculum concentrations of 10^5 CFU/ml of 1.0 to >32 μg/ml. These results were consistent with those previously reported for rosaramicin (6) and josamycin (14).

The findings of lower macrolide MICs against the penicillinase-producing *Staphylococcus* spp. was an unexpected finding and is unexplained. The SCH29482 MICs tested against methicillin-resistant *S. aureus* were quite different from that previously published (2). Variable SCH29482 activity has been reported for the MRSA strains; European studies (8, 11) have generally demonstrated marked inhibitory activity (MIC_{90}, 0.25 to 0.46 μg/ml), and the United States investigations (2, 5, 12) have showed a lack of significant activity (MIC_{90}, >32 to ≥256 μg/ml).

Cross-resistance comparisons among the macrolides have previously found nearly complete interpretive agreement between erythromycin, rosaramicin, and josamycin allowing for pharmacological differences (3, 6, 14). In this study, we demonstrate a very high degree of cross-resistance between erythromycin and three new macrolides. In vitro susceptibility testing with erythromycin may be acceptable to predict clinical or bacteriological responses (or both) to these drugs.

RU28965, RU29065, and RU29702 appear to be promising new macrolides with long serum half-lives that possess antimicrobial activity very similar to erythromycin. Their characteristics against *Neisseria* spp., *Haemophilus* spp., and the majority of gram-positive cocci warrants continued in vitro and in vivo studies. Areas yet to be explored would include interactions with other commonly used drugs (4); activity against *Legionella* spp. (manuscript in preparation), chlamydia, and mycoplasma; and drug levels in various body tissues or fluids.

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