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MINIREVIEWS

New Directions for Macrolide Antibiotics: Structural Modifications and In Vitro Activity

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Erythromycin is an old and well-established antimicrobial agent which has assumed greater therapeutic importance because of its activity against increasingly prevalent pathogens such as *Legionella*, *Campylobacter*, and *Chlamydia* spp. (1, 13, 59, 79). It is generally perceived within the infectious disease community as a safe and effective antibiotic. These circumstances have prompted research groups throughout the world to continue exploration for novel modifications of erythromycin which would improve upon the therapeutic properties of the parent compound. During the past few years, several new derivatives of erythromycin have been identified during preclinical evaluation as sufficiently promising to warrant clinical investigations.

Although erythromycin is the only member of the large class of macrolide antibiotics to have achieved significant clinical utility in the United States, several macrolides other than erythromycin have been developed and used in other countries (58). These macrolides differ from erythromycin in the size and/or substitution pattern of the lactone ring system; in recent years, new derivatives of these other macrolides have also been prepared and evaluated for clinical utility. Pertinent properties and clinical results for all of these new macrolide derivatives are summarized in this minireview.

CHEMISTRY OF MACROLIDES

Degradation of erythromycin. Erythromycin is well-known to decompose under acidic conditions to first yield its 8,9-anhydro-6,9-hemiketal and subsequently its 6,9; 9,12-spiroketal (Fig. 1) (49). Neither of these decomposition products possesses any significant antimicrobial activity, although the anhydrohemiketal has been suggested as the principal agent responsible for many of the gastrointestinal side effects of erythromycin therapy (63).

Passage of erythromycin through the stomach can result in substantial acid-catalyzed degradation (and loss of antibiotic activity). Considerable success in protecting erythromycin from decomposition in the stomach has been achieved by using highly water insoluble salts (e.g., lauryl sulfate or stearate) or acid-stable enteric coatings. A new example of the former approach is erythromycin acistrate (2′-*O*-acetylerythromycin stearate); a thorough review of this product has just appeared (26).

In a different approach, two new salts of propionylerythromycin (*N*-acetylcysteinate and mercaptosuccinate) which combine antibiotic and mucolytic activities in a single agent have been prepared (21, 27). In all of these cases involving different esters, salts, and formulations of erythromycin, the active antibiotic ingredient is always erythromycin base (75), and these agents are not covered in the present review. Instead, this review focuses only upon those new agents whose antibiotic activities are the result of a derivative of erythromycin rather than erythromycin itself.

New derivatives of 14-membered macrolides (erythromycin A). A number of research groups in recent years have synthesized new derivatives of erythromycin A which retain potent antimicrobial activity while offering improved pharmacokinetic properties. All of these new entities can be regarded as ways to inhibit the relatively facile decomposition illustrated in Fig. 1. This objective has been accomplished by modification of the functional groups which participate in the degradation reaction, namely, the ketone at C-9, the hydroxyl group at C-6, the proton at C-8, and the diol moiety at C-11 and C-12 (Fig. 2).

The ketone at C-9 has been modified in several ways. The earliest of these modifications was roxithromycin, selected as the candidate with the best therapeutic index from a new series of oxime derivatives synthesized at Roussel-Uclaf (J. F. Chantot, J. C. Gasc, S. Gouin d'Ambrieres, and A. Lutz, Program Abstr. 23rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 447, 1983). The desired stabilization of erythromycin was achieved, since its oxime derivatives are less prone to intramolecular cyclization. Originally known as RU 28965, roxithromycin is the 9-[*O*-(2-methoxyethoxy)methyl]oxime of erythromycin.

Erythromycylamine is an older derivative of erythromycin, formally the result of reductive amination of the C-9 ketone; however, both it and its *N*-benzylidene derivative gave extremely low levels in blood when administered orally to humans (53). Dirithromycin, a new oxazine formed from erythromycylamine and (2-methoxyethoxy)acetaldehyde, was selected by Boehringer-Ingelheim on the basis of high levels in tissues (52). Formerly designated AS-E 136, it is being developed jointly with Eli Lilly & Co. (formerly LY237216).

A third modification of the ketone of erythromycin utilized a Beckmann rearrangement of its 9-oxime derivative, followed by reduction and N-methylation (12, 28). This transformation yielded a novel 15-membered ring containing a tertiary amino group. This ring-expanded derivative has been named azithromycin, formerly known as either XZ-450 or CP-62,933. It is being developed jointly by Pliva Pharmaceuticals and Pfizer Inc.

Prevention of intramolecular cyclization other than by modification of the ketone has also proven fruitful. Alkylation of the hydroxyl group at C-6, which is involved in the initial cyclization step, has been thoroughly investigated, resulting in the synthesis of 6-*O*-methylerythromycin by Taisho Pharmaceutical Co. (56). Previously described as

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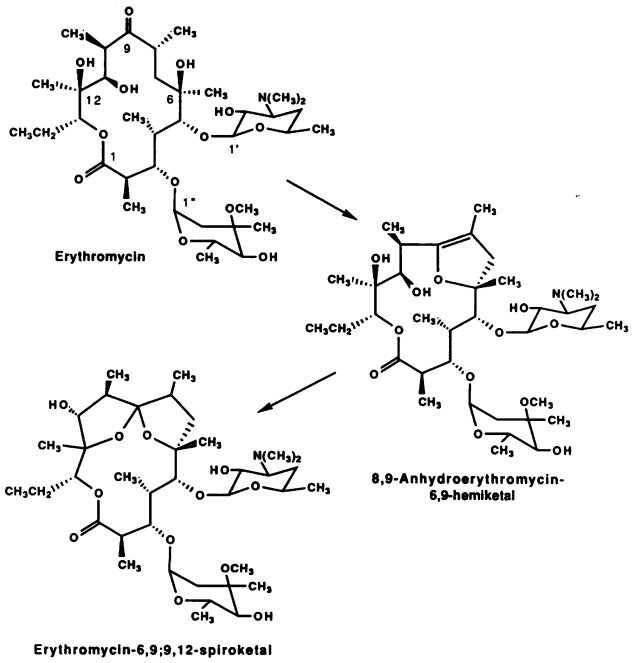


FIG. 1. Acid-catalyzed degradation of erythromycin.

TE-031 and A-56268 and now named clarithromycin, it is being developed in a joint venture with Abbott Laboratories.

Another approach to preventing the decomposition of erythromycin involved inhibition of the dehydration step that leads to the anhydrohemiketal. To accomplish this objective, 8-fluoroerythromycin was prepared at Pierrel S.p.A. by using both chemical and bioconversion methods for its synthesis (76). This compound has been named flurithromycin.

Additional derivatives of erythromycin have been mentioned in the recent literature, but it is unknown whether any will reach clinical evaluation. A new series of derivatives of erythromycylamine, produced by its reductive amination with aliphatic aldehydes, possessed oral efficacy against model infections in mice (H. A. Kirst, J. P. Leeds, and J. A. Wind, EUCHEM Symp. Chem. Synth. Antibiot., abstr. no. P-30, 1988). Expanding from the previously known stabilization of erythromycin against spiroketalization by its 11,12-carbonate derivative (74), an interesting series of cyclic 11,12-carbamate derivatives has been described (5). Modification of the 11-hydroxyl group has very recently been shown to decrease hydrolysis of the lactone ring by an erythromycin esterase isolated from *Escherichia coli* (80). A variety of additional chemical modifications of the 11,12-diol moiety have also been reported (42, 44).

4″-*O*-Carbamoyl-6-*O*-methylerythromycin (A-63075) has demonstrated fewer gastrointestinal effects in animal models (L. A. Freiberg, L. Klein, S. Hannick, H. N. Nellans, P. B. Fernandes, and A. G. Pernet, 27th ICAAC, abstr. no. 224, 1987). Certain derivatives of erythromycin and clarithromycin with activity against inducibly and/or constitutively resistant bacteria have recently been reported (33). Modification of the 4″ position has been reported to eliminate induction of macrolide-lincosamide-streptogramin B resistance (2; S. Kadam, C. C. Doran, and R. C. Goldman, Abstr. Annu. Meet. Am. Soc. Microbiol. 1988, A-11, p. 2).

New derivatives of 16-membered macrolides. Although the number of fermentation-derived 16-membered macrolide antibiotics is somewhat larger than that of 14-membered macrolides, none of the former has achieved the worldwide prominence of erythromycin (62). Substantial effort has been expended in the chemical and biochemical modification of 16-membered macrolides, especially directed toward acylation of the hydroxyl groups on the lactone ring and the neutral sugar, since such modifications improved activity against some resistant organisms and oral bioavailability (70). More recently, acylation of the 3″-hydroxyl group was shown to further increase antibacterial potency and antibiotic levels in serum (68). Rokitamycin (formerly TMS-19-Q), being developed by Toyo Jozo Company, is the 3″-*O*-propionyl derivative of leucomycin A_5 (69) (Fig. 3). A second member of this group is miokamycin, being developed by Meiji Seika Kaisha; also known as MOM, it is the 9,3″-di-*O*-acetyl derivative of midecamycin (48). A new derivative of spiramycin, 3,3″,4″-tri-*O*-propionylspiramycin, has been reported in an early stage of development by Kyowa Hakko Kogyo Company (71). A review of spiramycin itself has recently appeared (25).

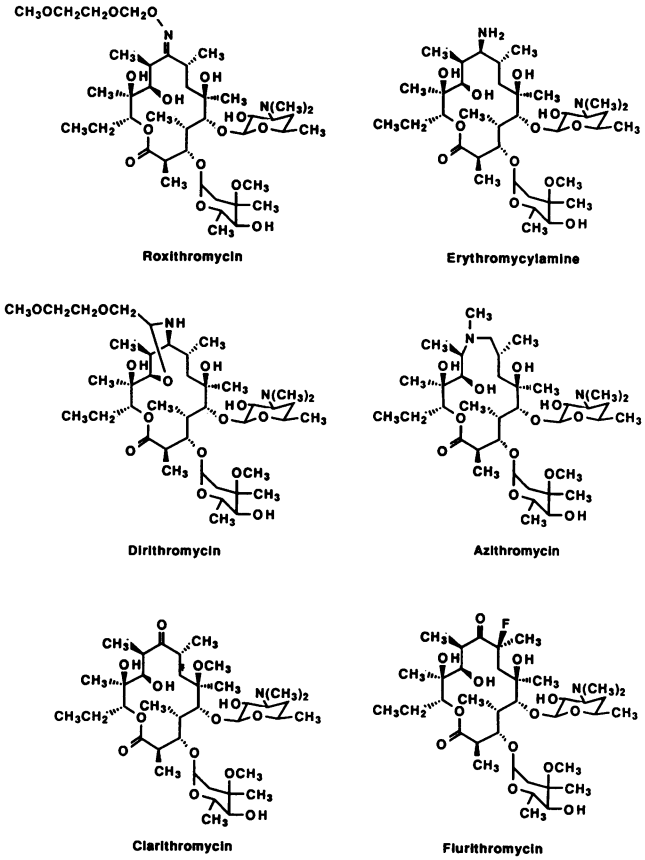
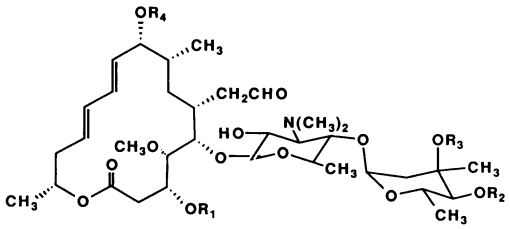


FIG. 2. Derivatives of erythromycin.

MICROBIOLOGY OF NEWER MACROLIDES

Spectrum of antimicrobial activity. In vitro susceptibility studies of new macrolides are too numerous to reference completely in this review. Consequently, only conclusions and general trends from selected representative references are discussed. Since the first studies comparing all of the new macrolides have just appeared (40, 41), this review compares the macrolides with erythromycin.

Erythromycin has an in vitro spectrum which covers principally gram-positive microorganisms and gram-negative



	R_1	R_2	R_3	R_4
Rokitamycin	H	Bu	Pr	H
Leucomycin A_5	H	Bu	H	H
Josamycin	Ac	iVal	H	H
Miocamycin	Pr	Pr	Ac	Ac
Midecamycin	Pr	Pr	H	H
Triacetylspiramycin	Ac	Ac	Ac	Forosaminyl
Spiramycin I	H	H	H	Forosaminyl

Ac = Acetyl, Pr = Propionyl, Bu = Butyryl, iVal = isoValeryl

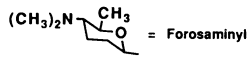


FIG. 3. Derivatives of 16-membered macrolides.

cocci. Macrolide antibiotics are used clinically against susceptible organisms that infect the respiratory, genital, and gastrointestinal tracts and skin and soft tissues; and they are especially useful when potential allergic reactions prevent the use of β-lactam antibiotics or when tetracycline is contraindicated (55). With only a few exceptions, the new macrolide derivatives are similar to their parent compounds with regard to spectrum of antimicrobial activity; bacteriostatic versus bactericidal activity; profile of antibiotic cross-resistance; and effects on MICs of such variables as pH, presence of serum, amount of bacterial inoculum, and bacterial growth medium, etc.

Roxithromycin. Comprehensive reviews of roxithromycin, in which its in vitro activity against a wide variety of pathogens was approximately equivalent to that of erythromycin, have been published (14, 60, 64). In other publications, roxithromycin was approximately half as potent as erythromycin against most susceptible staphylococci and streptococci (6, 19, 46). Against other respiratory pathogens, roxithromycin was equivalent to erythromycin against species of *Legionella* (6, 45) but two- to fourfold less active than erythromycin against *Haemophilus influenzae* and *Branhamella catarrhalis* (4, 47). Activity against the genital pathogens *Chlamydia trachomatis* (11), *Neisseria gonorrhoeae* (6, 46), and *Haemophilus ducreyi* (72) was approximately equivalent to that of erythromycin; against species of *Campylobacter*, it was two- to fourfold lower than that of erythromycin (8, 22). Against other aerobic and anaerobic bacteria, roxithromycin was less active than erythromycin (38). These studies generally concluded that roxithromycin had no distinct advantage over erythromycin in vitro but that favorable differences in pharmacokinetic properties might afford clinical advantages over erythromycin.

Dirithromycin. Only one major study of the antimicrobial activity of dirithromycin has been published (41). Dirithromycin was two- to fourfold less active than erythromycin in vitro against gram-positive bacteria (U. Lechner, K. R. Appel, R. Maier, and E. Woitun, 8th Int. Symp. Future Trends Chemother., p. 31, 1988). Although less active than erythromycin against a variety of clinical isolates, dirithromycin was fourfold more active against *Bordetella pertussis* (K. R. Appel, U. Lechner, H. Meier-Ewert, and G. Ruckdeschel, 28th ICAAC, abstr. no. 921, 1988). Against both *Campylobacter jejuni* and *C. coli*, activity was equal to that of erythromycin (30). As with roxithromycin, the potential advantage of dirithromycin is in its pharmacokinetic properties rather than its in vitro activity.

Azithromycin. Although approximately two- to fourfold less active than erythromycin against most staphylococci and streptococci (29, 65), azithromycin was more potent against other organisms, including a number of gram-negative bacteria which are considered to be resistant to erythromycin (12, 65). Regarding other pathogens of the respiratory tract and auditory canal, azithromycin was 2- to 8-fold more active against *H. influenzae*, *Haemophilus parainfluenzae*, *B. catarrhalis*, and *Legionella pneumophila* (4, 29, 65) and more than 10-fold more active against *Pasteurella multocida* (65) and *Mycoplasma pneumoniae* and *M. hominis* (67). It was more potent against *N. gonorrhoeae* (65) and *Ureaplasma urealyticum* (67) while comparable to erythromycin against *C. trachomatis* (78). Activity against *Campylobacter* species and a variety of anaerobic bacteria varied from slightly higher to slightly lower than that of erythromycin (22, 65). Based on its in vitro spectrum, azithromycin may expand the range of therapeutic utility traditionally assigned to macrolides.

Clarithromycin. Clarithromycin exhibited the same spectrum of in vitro activity as erythromycin (32). It ranged from equally potent to fourfold more potent than erythromycin against susceptible staphylococci and streptococci (20, 31, 35). Activity of clarithromycin was increased two- to fourfold against *Legionella* species (35, 45), *B. catarrhalis* (20), and *P. multocida* (31); in contrast, activity against *H. influenzae* and *H. parainfluenzae* was approximately half that of erythromycin (7, 9, 34, 51). Clarithromycin was more than 10-fold more active against *C. trachomatis* (11, 73) while comparable to erythromycin against *N. gonorrhoeae* (11, 31) and *H. ducreyi* (24). Activity was equivalent to that of erythromycin against various species of *Campylobacter* (8, 9). In vitro activity was increased against *Bacteroides fragilis*, *Clostridium* species, and some other anaerobic bacteria (20, 31, 32). Clarithromycin appears to have significantly increased potency against organisms traditionally considered to be susceptible to macrolides.

Flurithromycin. Although few publications have reported the antibacterial activity of flurithromycin, it appears to be very similar to erythromycin in vitro (41); activity against staphylococci, streptococci, *H. influenzae*, and *B. catarrhalis* was approximately the same as that of erythromycin (37, 61, 76). One study reported some improvement in activity against anaerobic bacteria (37).

Rokitamycin. A large volume of data on rokitamycin has been published in Japanese journals, but much less has appeared in English. Rokitamycin has an antimicrobial spectrum similar to those of erythromycin and josamycin, a related 16-membered macrolide (41, 57, 77). Rokitamycin is especially potent against *L. pneumophila* and *M. pneumoniae*, two important respiratory tract pathogens (39, 54). Like other 16-membered macrolides, it is active against bacteria which are inducibly resistant to erythromycin but inactive against strains which are constitutively resistant to macrolide-lincosamide-streptogramin B antibiotics (41).

Miokamycin. A significant amount of information about miokamycin has been published in Japanese and Italian journals. Miokamycin was generally less potent in vitro than rokitamycin (41, 77). It was less active than erythromycin

against many aerobic bacteria but was more active against *Legionella* species and several anaerobic bacteria (41, 50, 81). Its activity was comparable to that of erythromycin against *Chlamydia* and *Ureaplasma* spp. but superior to that of erythromycin against *M. hominis* (66). It also inhibited strains of *Staphylococcus aureus* which were inducibly resistant to erythromycin (48).

Emerging pathogens. The earlier resurgence of macrolide antibiotics was largely the result of the clinical efficacy of erythromycin against pathogens such as *Legionella* spp. As other microorganisms now emerge as clinical problems, particularly in immunocompromised patients, it is encouraging that new macrolide derivatives have shown some activity against such pathogens. Further developments may lead to a therapeutic role for macrolides against some of these increasingly problematic pathogens.

Macrolides are not generally used as antituberculous agents. However, synergistic effects have recently been reported for roxithromycin with either rifampin (15) or tumor necrosis factor and amikacin (10) against *Mycobacterium avium*; the activity of azithromycin against *M. avium* was also enhanced by tumor necrosis factor (10). In other studies, flurithromycin showed an additive effect with some other antibiotics against *Mycobacterium* species (37) and clarithromycin inhibited the growth of *M. leprae* in a mouse footpad infection model of leprosy (36).

Another problem organism is *Toxoplasma gondii*, against which the macrolide spiramycin has been used (23). Recent studies have shown that roxithromycin, clarithromycin, and azithromycin all inhibited intracellular growth of *T. gondii* (17) and were effective at high doses against murine acute toxoplasmosis (3, 16, 18); the last compound was also effective at high doses against murine toxoplasmic encephalitis, suggesting its accumulation in the cerebrospinal fluid of the mice (3). Synergism with interferon enhanced the in vivo efficacy of roxithromycin (43).

Finally, azithromycin was more effective than erythromycin against infections in hamsters caused by *Borrelia burgdorferi*, the causative agent of Lyme disease (R. C. Johnson, C. Kodner, and M. Russell, 27th ICAAC, abstr. no. 235, 1987).

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