Ketolides – a novel form of macrolide: the way forward?

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The newest group of macrolides are semisynthetic compounds known as ketolides. These compounds are the focus of considerable interest, particularly for activity against several erythromycin-resistant species, including *Streptococcus pyogenes, Streptococcus pneumoniae, Staphylococcus aureus* and some Enterococci. Two ketolides are in Phase II clinical trials. The author discusses the potential for this new class of compounds in an environment of growing microbial resistance to existing antibacterial agents.

The macrolide antibiotics were first discovered in the 1950s, the most well-known compound being erythromycin. This report highlights the prospects for the newest group of macrolides – ketolides – in the light of recent presentations at the last *Interscience Congress of Antimicrobial Agents and Chemotherapy (ICAAC)* in Toronto (October 1997) and at the recent *International Conference on Macrolides, Azalides, Streptogramins and Ketolides (ICMASK)* held in Barcelona in February 1998.

Macrolides

Macrolides are antibiotics produced by *Streptomyces* species and were first discovered in the 1950s. The most widely used macrolide, erythromycin, discovered in 1952, has a 14-membered lactone ring with two sugar groups, a desosamine and a neutral α-L-cladinose ring (Figure 1). The compound has been in clinical use in many countries since the late 1950s for urinogenital tract infections, skin and soft tissue infections, but most especially for respiratory infections. There were many other macrolides isolated as natural products in the 1950s, including several with a larger 16-membered ring, such as spiramycin, carbamycin and leucomycin, and other 14-ring compounds like oleandomycin. Frequently, like erythromycin, a family of compounds were co-produced by the microorganism, differing only in the sugars present on the lactone ring. More 16-ring-membered, naturally occurring compounds were discovered in later decades, illustrating the continued interest in macrolides. These include josamycin (1967) and midecamycin (1973), but although some of these compounds have been, and still are, used in a limited way, none has rivalled erythromycin in the clinic. However, the growth of resistance to erythromycin, particularly over the past decade, has led to a re-evaluation of many of the earlier compounds.

The activity of erythromycin is predominantly against Gram-positive bacteria (*Staphylococci*, *Streptococci*) and against Gram-negative cocci (*Haemophilus*, *Gonococci*), and also includes several atypical pathogens such as *Legionella, Mycoplasma* and *Chlamydia*, species lacking sensitivity to β-lactams. This spectrum of activity combined with the ability to dose orally and the availability of paediatric preparations, has led to the compound being used widely as a second-line drug to β-lactams for respiratory tract infections.

Although absorbed orally, erythromycin is not very stable to acid, its absorption is erratic, and gastric tolerance to the compound is poor. Some improvement has been seen by the use of esters and salts, but bioavailability is still not ideal. There has also been a marked increase in the number of strains of many species with resistance to erythromycin, including *Streptococcus pyogenes* Group A, *Streptococcus pneumoniae*, *Staphylococcus aureus* and

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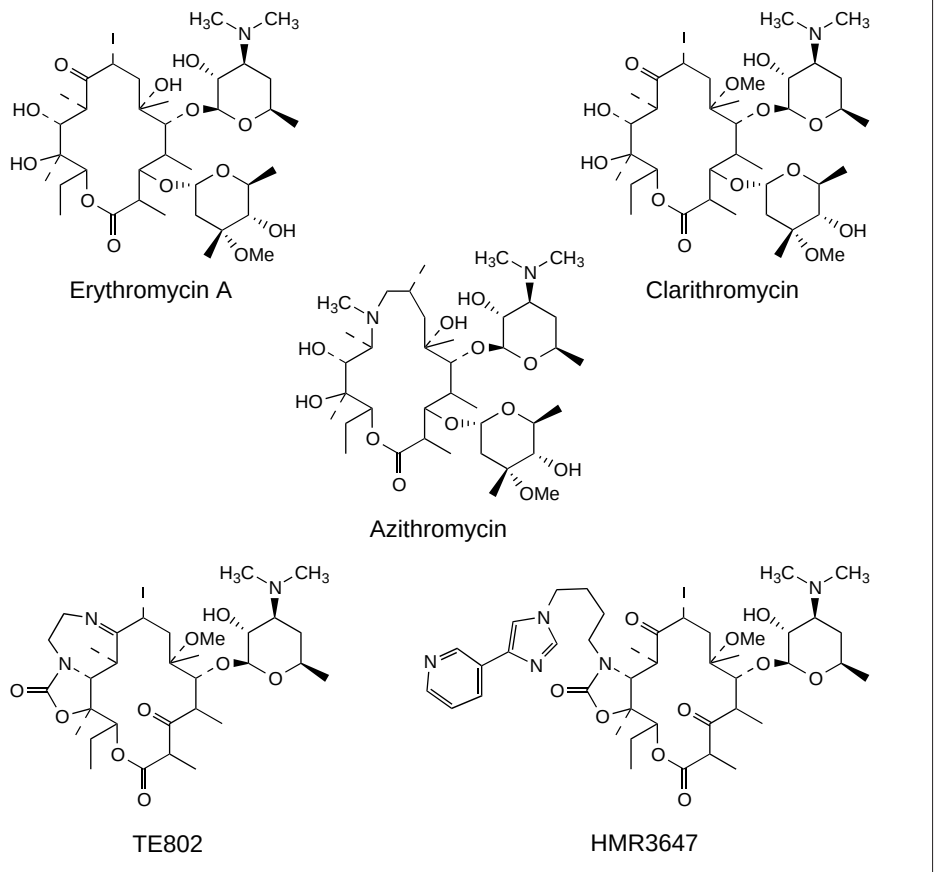

Figure 1. *Macrolides are a group of antibacterial agents produced by* Streptomyces *species. Erythromycin has been the most widely used of the naturally occuring macrolide antibiotics. Clarithromycin is an example of a semisynthetic macrolide. Improvement of bioavailability and the spectrum of activity has been achieved with the semisynthetic azalide, azithromycin (Pfizer), and with the ketolides, TE802 (Abbot) and HMR3647 (Hoechst Marion Roussel). These ketolides are currently in Phase II clinical trials.*

Haemophilus influenzae. Activity against *H. influenzae* is, at best, only barely adequate, so any decrease in sensitivity impacts adversely on the clinical value of the compound. Many have linked this rise in resistance with the widespread use of the compound over the past two decades.

There have been several approaches to the dual problems of resistance and poor tolerance/absorption. Modifications to the basic macrolide molecule have led to improvements in acid stability, oral absorption, bioavailability and in some cases, activity. A variety of semisynthetic 14-membered ring compounds have been developed and marketed, the leading ones being roxithromycin (Hoechst Marion Roussel) and clarithromycin (Abbot; Figure 1). These compounds have an extended spectrum of activity relative to erythromycin, with improved activity against microorganisms such as *Bordetella*, *Mycobacterium avium*, *Helicobacter pylori*, *Campylobacter*, *Toxoplasma gondii* and some anaerobes. In addition, some degree of improvement in activity against resistant strains is seen, but this is still not sufficient, as minimal inhibitory concentration (MIC) values can still be unacceptably high against some methicillin-resistant staphylococci (MRSA), multiresistant pneumococci and enterococci.

Azalides

A further modification was in the ring expansion to C_{15} by the insertion of a nitrogen at the 9-keto position. Azithromycin (Pfizer; Figure 1) is such a compound and has been termed an azalide to distinguish it from other macrolides. Oral absorption, pharmacokinetics, tolerance and activity against *H. influenzae* are all markedly improved, and activity against a significant number of strains resistant to erythromycin is better than that of erythromycin. Azithromycin has such good bioavailability that the compound is only dosed once daily. Like the newer semisynthetic 14-ring compounds, azithromycin also has an extended spectrum of activity; however, many erythromycin-resistant strains are still not susceptible to either azithromycin or to the improved 14-ring compounds, and the search has continued for compounds to combat this resistance.

Ketolides

The newest group of macrolides are semisynthetic compounds known as ketolides, where the α-L-cladinose ring of erythromycin or of clarithromycin is replaced by a 3-keto group. Numerous presentations at the *ICAAC* and *ICMASK* showed that ketolides have substantial improvements in activity against a wide range of microorganisms

resistant to other macrolides. Many modifications have been made to the basic ketolide, most with an emphasis on substitutions at the 11–12 ring position, and numerous SAR papers have been published. There are indications that the side-chain at C11–12 has a major influence on the pharmacokinetic properties of the compound, while the des-cladinose contributes to the activity.

Several companies have an interest in the field; but currently the leaders are Abbot who have a tricyclic compound, TE802 (A161948; Figure 1), and Hoechst Marion Roussel who have a hydrozono derivative, HMR3647 (RU66647; Figure 1). The latter compound replaces an earlier one, RU64004. Both compounds are in Phase II studies, and although no detailed results have been published yet, both are reported to produce prolonged serum levels and to be well absorbed orally.

Much of the interest in ketolides centres around their improved activity against several erythromycin-resistant species, including *S. pyogenes*, *S. pneumoniae*, *S. aureus* and some enterococci. Multiresistant staphylococci and enterococci are becoming increasingly prevalent, causing great problems in seriously ill hospitalized patients. Also, there is a rapidly declining number of effective agents available to clinicians. The rise in the occurrence of enterococci resistant to vancomycin poses a distinct threat as these strains are generally resistant to almost all other commonly used anti-infective agents. The fear of vancomycin-resistance being transferred to staphylococci, especially to multiresistant MRSA, is driving the search for new compounds with good activity against these resistant microorganisms; such activity being regarded by many as the Holy Grail in the anti-infective field.

Macrolide resistance

It has been suggested by some that ketolides differ in a major way from other macrolides, and have a different mode of action. This was a topic of discussion at the recent *ICMASK* meeting. Resistance mechanisms to macrolides are now numerous and complex, and although great advances have been made in recent years, the epidemiology and clinical significance of some of these more recently recognized types of resistance are not as yet clearly established. Professor Acar (University Pierre and Marie Curie, Paris, France) gave an excellent overview of the current state of knowledge of macrolide resistance at the meeting in Barcelona, emphasizing that many of these newer mechanisms were species-specific and possibly, as yet, rare.

One of the earliest to develop, most widely recognized and most common mechanism of macrolide resistance is alteration of the target site; this is frequently accompanied by cross-resistance to lincosamides and streptogramin B compounds (termed MLS_B resistance). Although the macrolides, lincosamides and streptogramin B are structurally diverse compounds, they have a similar target – the 50S ribosomal subunit – and their individual binding sites overlap. This resistance is caused by methylation of the ribosome, which prevents access of the antibacterial to the binding site. This MLS_B resistance is inducible in both staphylococci and pneumococci, and it can be induced by 14- and 15-ring macrolides in both species. However, 16-ring macrolides can induce this target-site change only in pneumococci, not in staphylococci. The ketolides show a major difference from other macrolides, in that they do not induce MLS_B resistance in either species and retain good activity against strains showing such resistance.

In staphylococci, this type of resistance can also be constitutive, which usually confers a far greater degree of resistance. Unfortunately, the ketolides do not have activity against this constitutive MLS_B resistance in staphylococci, and transfer experiments indicate that this type of resistance can develop *in vitro* albeit with exposure to high levels of ketolide. Ribosomal methylation leading to MLS_B resistance is also found in streptococci, enterococci and *Bacteroides fragilis*.

The second most common mode of resistance is a rapid efflux of compound by a microorganism. This imparts resistance to 14- and 15-ring macrolides and to streptogramins B, but not to lincosamide or ketolides. It is a common form of resistance to macrolides in pneumococci, but also occurs with increasing frequency in *Staphylococcus epidermidis*, *S. aureus* and *S. pyogenes*. From the limited studies reported to date, ketolides appear not to induce this mode of resistance.

Resistance to ketolides

As illustrated above, the ketolides do have good activity against many macrolide-resistant and multiresistant strains of *S. pyogenes*, *S. pneumoniae*, *S. aureus*, *S. epidermidis* and Enterococci, but this activity is not universal. Microorganisms displaying constitutive MLS_B resistance, such as staphylococci, are still resistant to these compounds, and this mode of resistance is not rare. Similarly, several enterococci strains, particularly Van B *E. faecium*, are not susceptible to low levels of ketolides; MIC values being as high as 8–16 mg l^{-1} or more. Although ketolides do have greater activity than many other agents, the susceptibility

of enterococci to these compounds is clearly related to their susceptibility to erythromycin. Resistance to ketolides among the atypical pathogens has not yet been reported, but resistance to erythromycin, although reported, is still relatively uncommon in these microorganisms.

Some strains of *M. avium* and *H. pylori* with resistance to erythromycin caused by mutation in the 23S ribosomal RNA (one of the more recently recognized modes of resistance) do retain some degree of susceptibility to ketolides, but this varies with the compound. It is not yet clear how important or widespread this mode of resistance may be. Most strains of *H. influenzae* are highly susceptible to ketolides, but against some erythromycin-resistant strains, the MIC values are somewhat higher. Whether this should be regarded as resistance depends on whether such levels are achievable at the site of infection, which in turn depends upon the bioavailability and tolerance of the compounds in man. The mechanism of resistance of *H. influenzae* to macrolides is not yet known, so it is difficult to predict the likelihood of true resistance to ketolides developing in this species.

Potential of ketolides

It is clear from the extensive studies with these compounds that they do have very promising activity both *in vitro* and in experimental *in vivo* models. However, although they retain activity against microorganisms resistant by virtue of an efflux mechanism, and also against induced MLS_B resistant strains, they do not have activity against constitutive MLS_B resistance. The relative importance of this is difficult to judge because epidemiological studies indicate differences between species and between different parts of the world in the prevalence of the various types of resistance. New modes of resistance (including 23S ribosomal mutations and inactivation of the antibiotic) have been recognized recently, and although they are as yet rare and possibly may not be of major clinical significance, the ability of microorganisms to find new ways of coping with new drugs means that these cannot be disregarded.

In terms of respiratory tract infections, the ketolides could well rival the therapeutic agents currently available, provided that oral bioavailability proves to be as good as the current information indicates and that paediatric preparations are possible. However, in terms of treating serious hospital infections, the Holy Grail of Gram-positive activity, including all MRSA, vancomycin-resistant enterococci and multiresistant staphylococci, still seems elusive.

In short…

A report issued by **Datamonitor** forecasts that product launches, based on new technologies or therapeutics, will play a key role in the expansion of the global cancer market. *Benchmarking the New Cancer Therapeutics* claims that gene therapy 'has the edge over other new cancer therapeutics', although the present hype that surrounds the reported benefits of gene therapy may be unjustified.

Therapeutics, developed largely during the current growth period in cancer treatment studies, are leading to the expansion of the oncology market and, in a recent Datamonitor survey, leaders in this market were asked to benchmark and quantitatively assess the new cancer therapeutics. The survey found that none of the therapeutics currently in development were significantly more competitive than any of the other new therapeutics or any of the more conventional treatments. Indeed, in terms of efficacy, cost, side-effect profile and ease of administration, new therapeutics are closely matched.

Gene therapy was found to have a slight competitive advantage over the new therapeutics, including antibody-based therapy and anti-angiogenic therapy. However, according to respondents, conventional treatments, such as hormonal therapy and surgery, have the edge over gene therapy.

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