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Macrolides Antibiotics in Odontostomatological Practice: Past, Present and Future

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Abstract: Macrolides are considered the second choice in the odontostomatological practice especially in case of allergic reactions to the most important and well-known group of â-lactams. This group of antibiotics are more diffused in the daily practice of dentistry but during the time macrolides have shown a big potential in constant increasing. In this study, we report a review of the major features of these antibiotics which have become in the time farmacological choice effective and reliable versus bacterial infections supported by â-hemolytic streptococci, pneumococci, staphylococci, enterococci, mycoplasma, mycobacteria, some rickettsia and chlamydia. Furthermore, we refer about the recent researches that show the anti-inflammatory potentiality of the macrolides and the recent discoveries on the new pharmacological targets to exceed the problem of the bacterial resistance: the efflux pumps. Finally, we expose about a new class of antibiotic derived directly by the macrolides: Ketolides. They represent the future of the macrolides.

Key words: Antibiotics, macrolides, efflux pumps, bacterial resistance, multidrug resistance, ketolides, telithromycin

INTRODUCTION

Since the discovery in 1952 of the first macrolid, the erythromycin, they have been considered second choice drugs respect penicillins and used in case of allergy to the most important and well-known group of b-lactams. But during the time macrolides have shown a big potential in constant increasing. This study represents a analysis of the literature to underline the macrolides features, their use and future potential. In fact, many studies have shown that the macrolides are not only antibiotics. Moreover, it's purpose of our research to refer about the recent research that show the anti-inflammatory potentiality of the macrolides and the recent discoveries on the new pharmacological targets to exceed the problem of the bacterial resistance: The efflux pumps. Finally, we expose about a new class of antibiotic derived directly by the macrolides: Ketolides. They represent the future of the macrolides.

Macrolides: Macrolides are a group of antibiotics with a basic nature chemically characterized by a macrocyclic lactonic ring (aglycone) which contains 14, 15 or 16 atoms of carbon and one or more molecules of deoxysugar and deoxyaminosugar. A prototype of this class of drug is the erythromycin, obtained by the Streptomyces erithreus in 1952 (Fig. 1).

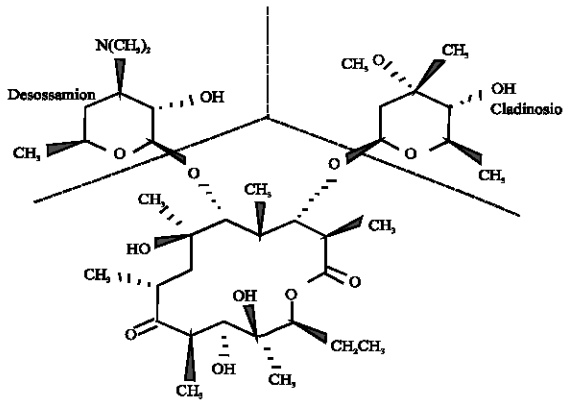

Fig. 1: Structural formula of erythromycin

Macrolides are classified according to the number of atoms in the lactonic ring:

- 14 C atoms Macrolides (Erythromycin, Clarithromycin)
- 15 C atoms Macrolides (Azithromycin)
- 16 C atoms Macrolides (Myocamicin, Spiramicin)

Macrolides are bacterio-statical agents which fulfil their main activity in alkaline PH. Their range action is very similar and it includes several strains of Gram+, Gram-

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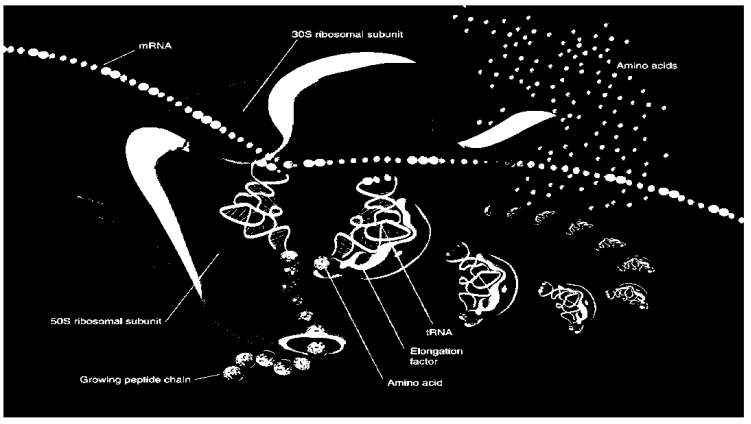

Fig. 2: Mechanism of inhibition of the protein synthesis

and anaerobia bacteria, rickets, chlamydie, mycoplasma pneumoniae, spirochete, atypical mycobacteria and toxoplasma gondii. They do not have activity against entherobacter (Cascone *et al*., 2005; Mabe *et al*., 2004). Therapeutic indications particularly regard air tract infections, but they are also used in treating syphilis, tetanus, gonorrhoea and diphtheria. Macrolides inhibit protein synthesis at bacterial level, binding 50S ribosomal subunit and blocking tRNA molecules in transferring from the acceptor site (A) to the donor one (P) (Hansen *et al*., 2002).

A: View of binding between macrolides (red) and ribosome (white)
B: A site (pink) and P site (yellow)
C: Closure of A site after the carbomycin link (red)

Green atoms are the basis, which interact with macrolides.

In the 50s we had some bacterial strains resistant not only to erythromycin, but also to other macrolides, so their clinical utility has decreased. Modalities of bacteria resistance include the decreasing of drug permeability. As macrolides action site is intracellular, their enzymatic inactivation is mediated by esterasic proteins that idrolize making them inactive, or more often for a target modification (Garza-Ramos, 2001; Poulsen *et al*., 2000).

From a pharmacokinetic point of view, macrolides are characterized by:

- Good tissue diffusion
- Average hepatic metabolism with biliar excretion
- Low kidney elimination
- Low toxicity (Amico-Roxas *et al*., 2003; Maur Neuman, 2000).

Macrolides are used to treat infections such as respiratory tract infections (Takashi Nomura *et al*., 2005) and soft tissue infections. The antimicrobial spectrum of macrolides is slightly wider than that of penicillin and therefore macrolides are a common substitute for patients with a penicillin allergy. Beta-hemolytic streptococci, pneumococci, staphylococci and enterococci are usually susceptible to macrolides. Unlike penicillin, macrolides have been shown to be effective against mycoplasma, mycobacteria, some rickettsia and chlamydia (Hisanaga *et al*., 2005; Li and Nikaido, 2004). Research on the anti-inflammatory properties of the macrolides ring is ongoing. A recent study about the chronic sinusitis has reported the effect of the macrolides on the neutrophils.

The inhibitory effect of macrolides on neutrophil infiltration in inflammatory sites has been well documented in these diseases. Several lines of evidence indicate that macrolides do not function simply as a bactericide. *In vitro* studies have demonstrated various effects of macrolides on immunocompetent cells, inflammatory cells and airway epithelial cells. It has been shown that macrolides inhibit the production of IL-8 and IL-1beta and the expression of ICAM-1, suggesting that macrolides block the aforementioned dual positive feedback system of neutrophil recruitment and thereby exert their clinical efficacy in the treatment of chronic sinusitis (Fig. 2 and 3).

The inhibitory effects of macrolides on multiple steps in the process of neutrophil recruitment are presumably mediated by the inhibition of transcription factors such as nuclear factor-kB and activator protein-1 (Suzuki and Ikeda, 2002).

The primary means of bacterial resistance to macrolides occur by post-transcriptional methylation of the 23S bacterial ribosomal RNA. This acquired resistance can be either plasmid-mediated or chromosomal, i.e.,

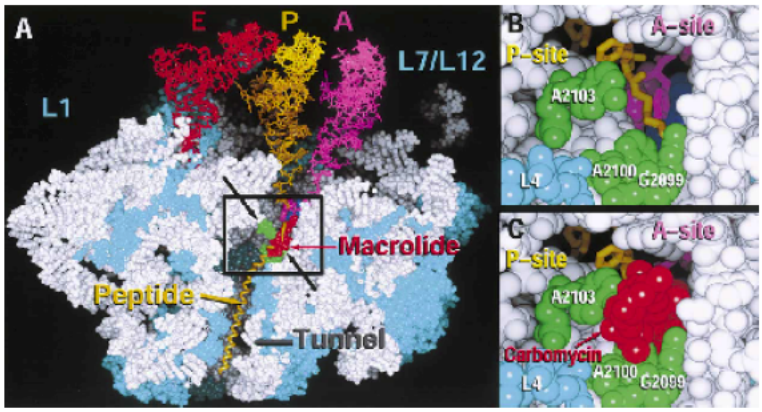

Fig. 3: Scheme of interaction between Macrolides and Ribosome

through mutation and results in cross-resistance to macrolides, lincosamides and streptogramins (an MLS-resistant phenotype). Two other types of acquired resistance rarely seen include the production of drug-inactivating enzymes (esterases or kinases) as well as the production of active ATP-dependent efflux proteins that transport the drug outside of the cell. A study of the University of Wurzburg has referred about the aminopenicillin-induced exanthema as problem in the management of infectious diseases. Due to theoretically possible immunological cross-reactivity, all beta-lactam drugs, i.e., penicillins, penicillin derivatives and cephalosporins, are usually avoided. The available alternative antibiotics (macrolides, quinolones and glycopeptides) may be less effective, have more side effects and their use increases medical costs. Moreover, their use contributes to the increasing bacterial resistance to antibiotics (Trcka *et al*., 2007).

Resistance of microorganisms to many classes of antibiotics can be mediated by various mechanisms such as enzymatic inactivation of the drug, alteration of the target and decreased intracellular concentration of the antimicrobial. The latter mechanism is mediated by either decreased influx or increased efflux or a combination of both. Recently, efflux has become increasingly recognized as a major component of resistance. Some efflux pumps selectively extrude specific antibiotics such as macrolides, lincosamides and/or streptogramins and tetracyclines, whereas others, referred to as multiple drug resistance pumps, expel a variety of structurally diverse anti-infectives with different modes of action. We can consider efflux pumps as potentially effective antibacterial targets. Inhibition of efflux pumps by an efflux pump inhibitor would restore the activity of an agent subject to efflux. An alternative approach is to develop antibacterials that would bypass the action of efflux pumps (Li, 2004; Rouveix, 2007).

- Within the class of secondary active transporters (symports, antiports, uniports) 4 superfamilies (comprising at least 10 families of gene products) including the SMR (Small Multidrug Resistance), the RND (Resistance Nodulation Division) and the MFS (Major Facilitator Superfamily).
- Within the class of primary active transporters (energized by ATP): At last 6 families of gene products including the PgP (in the MDR1 [Multiple Drug Resistance] group) and the MRP (Multiple Resistance Protein).

Schematic representation of the main transporters potentially involved in antibiotic movement at the level of epithelial cells in the main organs (liver, bronchial tree, intestine, kidney), the blood-brain barrier and in leucocytes (polymorphonuclear leucocytes are not considered here since the role of drug transporters in these cells is unclear). Black arrows denote transport towards extracorporeal compartments such as urine, bile, intestine and airways (i.e., transporters involved in drug elimination from the body). Grey arrows indicate uptake processes from extracorporeal fluids into cells (i.e., allowing drugs to accumulate in tissues), or from cells to body fluids [i.e., causing the drug to be transported from one body fluid to another (for example from blood to CSF)]. The level of expression of each transporter may differ between species (arrows with a chequerboard background indicate transporters evidenced, so far, in animals only). The direction of transport of bidirectional transporters may differ according to the cell type (Van Bembeke *et al*., 2003).

We have illustrated the mechanisms of resistance of the bacterial microorganisms to the macrolides. Particularly we have underlined in the Fig. 4 and 5 the mechanism of the efflux pumps. Now, we refer about the

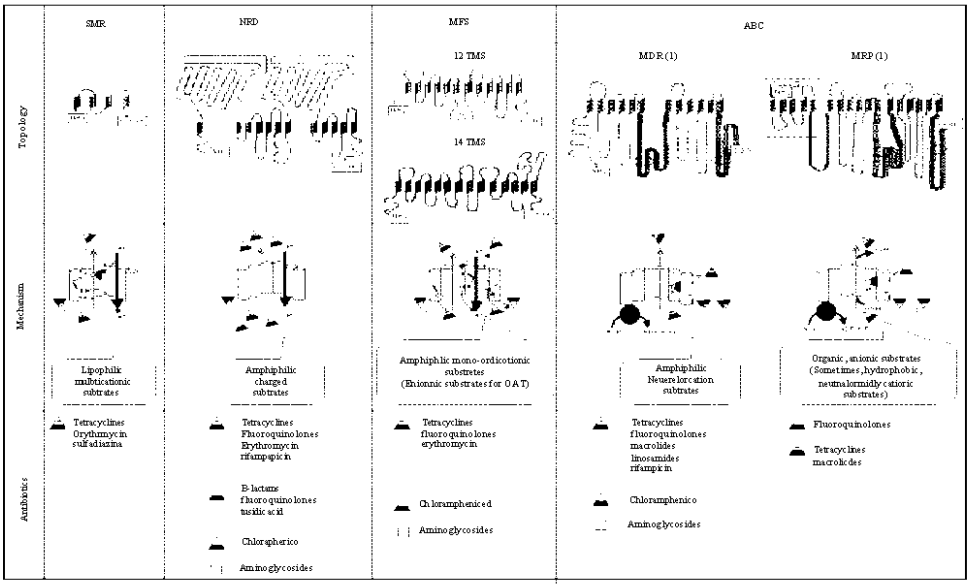

Fig. 4: Main classes of efflux pumps acting on antibiotics (Van Bambeke *et al.*, 2000)

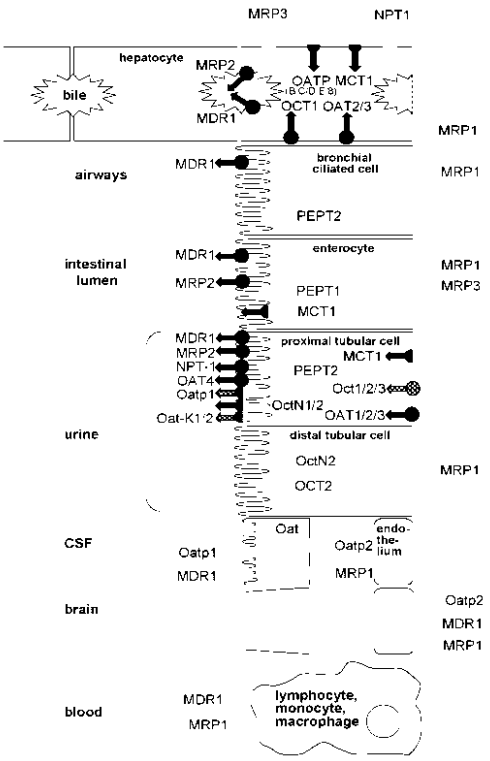

Fig. 5: Active transport of antibiotics in eucaryotes

new mechanisms of drugs that derived from the macrolides able to overcome these mechanisms of resistance: The Ketolides.

Ketolides are antibiotics belonging to the macrolide group that overcome the macrolide resistance mechanisms. Ketolides are derived from erythromycin by substituting the cladinose sugar with a keto-group and attaching a cyclic carbamate group in the lactone ring. These modifications give ketolides much broader spectrum than other macrolides. Moreover, ketolides are effective against macrolide-resistant bacteria, due to their ability to bind at two sites at the bacterial ribosome. They also have improved potency and longer post-antibiotic effects, while maintaining the antibacterial spectrum of the macrolide class. The ketolides exhibit good activity against Gram-positive aerobes and some Gram-negative aerobes and have excellent activity against drug-resistant Streptococcus pneumoniae. Ketolides such as telithromycin display excellent pharmacokinetics allowing once daily dose administration and extensive tissue distribution relative to serum. Evidence suggests the ketolides are primarily metabolised in the liver and that elimination is by a combination of biliary, hepatic and urinary excretion. Pharmacodynamically, ketolides display an element of concentration dependent killing unlike macrolides which are considered time dependent killers. The only ketolide on the market at this moment is telithromycin, which is sold under the brand name of Ketek. Another promising ketolide is cethromycin (Nilius *et al.*, 2002).

Telithromycin: Telithromycin prevents bacteria from growing, by interfering with their protein synthesis. Telithromycin binds to the subunit 50S of the bacterial

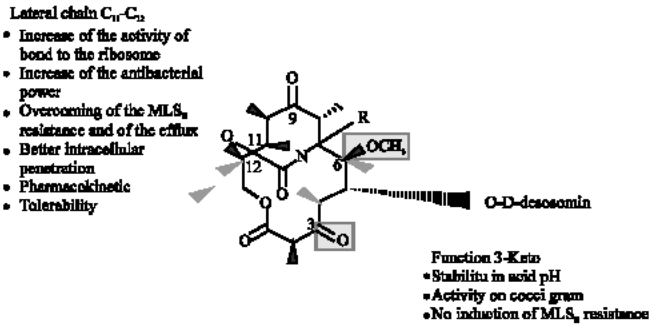

Fig. 6: Characteristics of Telithromycin de`rived by the molecular structures

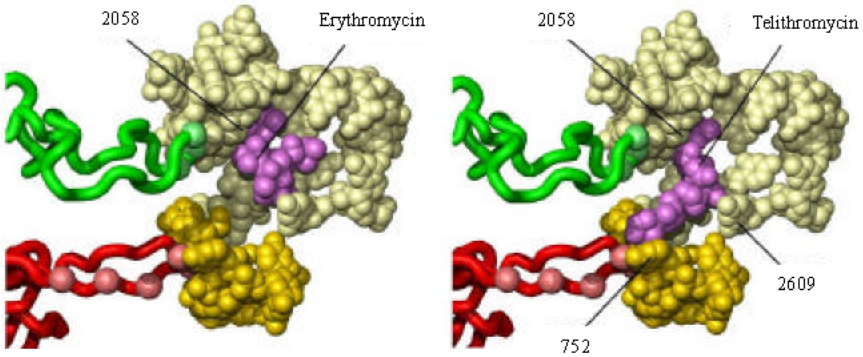

Fig. 7: Double Mechanism of action of the Telithromycin.Telithromycin presences respect the Erytromycin two sites of attack to the ribosome

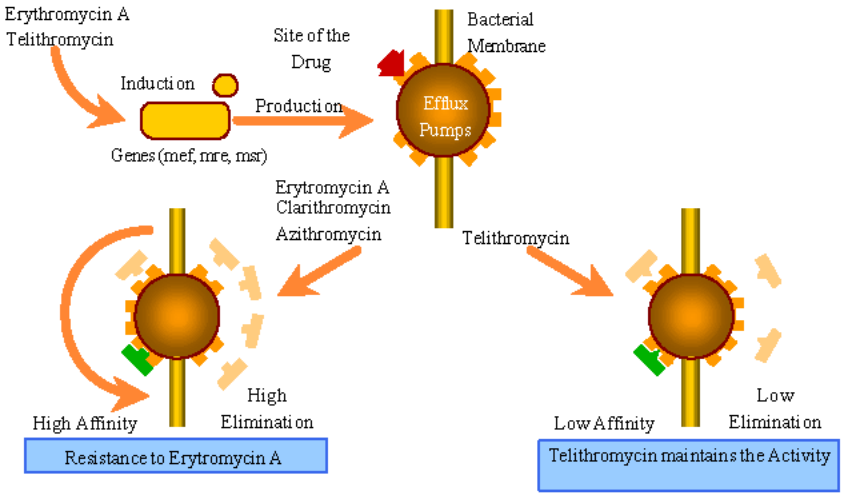

Fig. 8: Comparative scheme between the activity of the Telithromycin and the Macrolides

ribosome and blocks the progression of the growing polypeptide chain. Telithromycin has over 10 times higher affinity to the subunit 50S than erythromycin. In addition, telithromycin binds simultaneously to two domains of 23S RNA of the 50 S ribosomal subunit, where older macrolides bind only to one. Telithromycin can also inhibit the formation of ribosomal subunits 50S and 30S (Fig. 6).

Unlike erythromycin, telithromycin is acid-stable and can therefore be taken orally while being protected from

gastric acids. It is fairly rapidly absorbed and diffused into most tissues and phagocytes. Due to the high concentration in phagocytes, telithromycin is actively transported to the site of infection. During active phagocytosis, large concentrations of telithromycin is released. The concentration of telithromycin in the tissues much higher than in plasma. Unlike erythromycin, telithromycin is acid-stable and can therefore be taken orally while being protected from gastric acids. It is fairly rapidly absorbed and diffused into most tissues and phagocytes. Due to the high concentration in phagocytes, telithromycin is actively transported to the site of infection. During active phagocytosis, large concentrations of telithromycin is released. The concentration of telithromycin in the tissues much higher than in plasma. Most common side-effects are gastrointestinal; diarrhea, nausea, abdominal pain and vomiting. Headache and disturbances in taste also occur. Less common side-effects include palpitations, blurred vision and rashe. Rare, but severe side effects reported in January 2006 involve damage to the liver. Three different incidents have been reported: One ending in death, one in a liver transplant and one case of drug-induced hepatitis. (Clay *et al*., 2006) (Fig. 7 and 8).

CONCLUSION

Several clinical trials demonstrate the useful value of macrolides in odontostomatological field, such as:

- Good activity on oral pathogenic flora
- Absence of gut dismicrobism
- Well tolerate
- Alternative to β-lactamic use in intolerant patients.

Macrolides have a good local diffusion with high salivary concentration and in oral mucosa and also in maxillary bone reaching efficient therapeutic concentration. For these reasons macrolides can be considered useful tool in antibiotical therapy in odontostomatological field.

Moreover, it is object of study, as demonstrated, the anti-inflammatory potentiality of the macrolides that can becomes important in the treatment of many oral disease with an inflammatory base. The study about efflux pumps as new pharmacological target represents a hope to exceed the heavy problem of the bacterial resistance. Problem that could be resolved by the evolution of the new class of macrolides derived: The Ketolides. They represents the future of the pharmacological therapy based on antibiotics of this class. Finally, in literature are reported studies about macrolides that are used as immunosuppressor (sirolimus) but the studies about the potentiality of the new classes of macrolides as anticancer drug are ongoing.

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