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Antibiotics – Macrolides : A Review

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Abstract

Antibiotics are drugs that fight against bacterial infections in humans and animals. They work by killing the bacteria or by making it hard for the bacteria to grow and multiply.

Macrolides are a class of drugs used to manage and treat various bacterial infections. Azithromycin, clarithromycin, and erthromycin are commonly used to treat infections like pneumonia, sinusitis, pharyngitis, and tonsillitis. They are also used in uncomplicated skin infections and otitis media in pediatric patients.

Macrolides are a class of antibiotic that includes erythromycin, roxithromycin, azithromycin and clarithromycin. First-line indications for macrolides include the treatment of atypical community acquired pneumonia, H. Pylori (as part of triple therapy), chlamydia and acute non-specific urethritis.

Key words: antibiotics, macrolide, Azithromycin, clarithromycin, and erthromycin.

Introduction

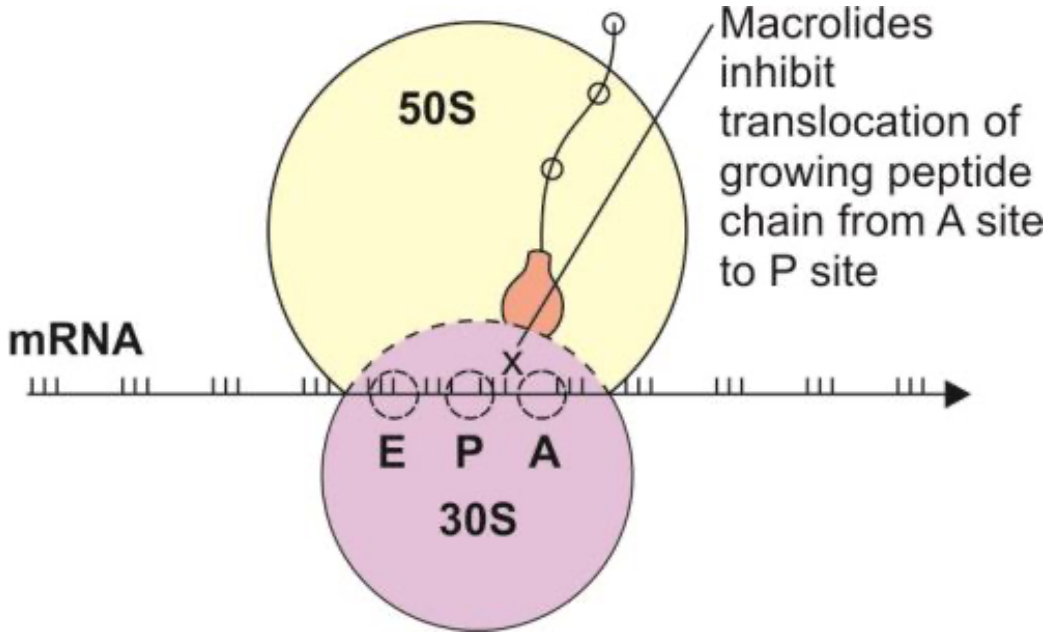
Antibiotics have provided protection against life-threatening bacterial infections for over a century. However, the indiscriminate use of antibiotics and the evolution of organisms have led to the emergence of multi-drug-resistant organisms (MDRO), sometimes resistant to most or even all currently available antibiotic classes, extensively drug-resistant or pan-resistant organisms (XDRO, PDRO). Antibiotic resistance poses a serious and escalating global health threat (1), and certain geographic areas may be disproportionately affected due to patterns of antibiotic usage(2). Consequently, there is a pressing need to discover novel antibiotics that are both effective and safe. Antibiotic development has faced numerous scientific and economic challenges over the years. A significant obstacle to industrial support for new antimicrobial development is the low return on investment (3). Nevertheless, antibiotics remain essential for global health. This paper reviews the antibacterial agents launched worldwide since 2017, detailing their development status, mode of action, spectra of activity, and the indications for which these antibiotics have been approved

MACROLIDE ANTIBIOTICS:

The examination of macrolides over recent decades has unveiled a diverse array of molecules exhibiting a spectrum of structures and functions. Macrolides, characterized by a hydrophobic nature, feature a macrocyclic lactone ring typically comprising at least 12 elements, with significant structural variation among different classes of compounds. (4,5) Numerous macrolides with pharmaceutical potential have been identified, showing promise as antibiotics, antivirals, antiparasitics, antimycotics, or immunosuppressants (5,6). Although naturally occurring macrolides may have limited utility as drugs due to issues such as instability in stomach acid, poor pharmacokinetics, and adverse side effects,

synthetic derivatives have been engineered to address these shortcomings (4). Moreover, many macrolides exhibit toxic bioactivity, contributing to observed adverse effects upon administration. Notably, a substantial proportion of macrolides fall under the category of toxins, with numerous examples sourced from marine organisms.(7) Conversely, certain macrolide mechanisms of toxicity have been harnessed for therapeutic purposes. This review aims to juxtapose five primary functional classes of macrolides sourced from various natural reservoirs: toxins, antibiotics, antivirals/antiparasitics, antifungals, and immunosuppressants. Each subclass is evaluated for structural similarities, mechanisms of action, pharmacological profiles, and human side effects. For a comprehensive examination of macrolides sourced from marine origins, readers are directed to the 2021 review by Zhang et al.(7)

MECHANISM OF ACTION: Macrolide antibiotics exhibit a broad spectrum of activity, effectively targeting both Gram-positive and Gram-negative bacteria. While there may be slight variations in their specific spectrum of action, overall, this range remains similar. These variances stem from differences in the chemical structure of the drugs, which influence their pharmacokinetic parameters.(8) Traditionally, the mechanism of action of macrolides has been linked to the inhibition of translation, thereby disrupting protein synthesis . Typically, protein synthesis is halted at the oligopeptide stage, comprising 5–11 amino acids, in the presence of macrolides. For shorter peptides, there may be a collective expulsion of the antibiotic from the nascent peptide exit tunnel (NPET), leading to the emergence of resistance. Interestingly, it has been observed that the synthesis of certain proteins in bacteria treated with macrolides remains comparable to untreated cells, suggesting that macrolides do not entirely halt translation but rather selectively impede protein synthesis. Additionally, the mechanism of action of macrolides may involve altering the properties of the ribosome's catalytic center, resulting in translation cessation or a shift in the reading frame, leading to abnormal polypeptide chain synthesis.(9)



CLASSIFICATION:

The commonly used macrolides can be classified based on their structure and include:

1. Erythromycin: This macrolide antibiotic is a classic example, consisting of a 14-membered macrocyclic lactone ring with a sugar moiety attached. Erythromycin has been widely used for its antibacterial properties.

2. Clarithromycin: This is a semi-synthetic derivative of erythromycin with a 14-membered ring structure. It has enhanced acid stability and improved pharmacokinetics compared to

erythromycin, making it a preferred choice for various bacterial infections.

3. Azithromycin: Another derivative of erythromycin, azithromycin contains a 15-membered ring structure. It exhibits a longer half-life and improved tissue penetration compared to erythromycin, making it suitable for once-daily dosing in the treatment of respiratory tract infections and other bacterial diseases.

4. Roxithromycin: Roxithromycin is a derivative of erythromycin with a 14-membered ring structure. It has a similar spectrum of activity to erythromycin but with improved tolerability and tissue penetration. These macrolides share a similar core structure characterized by a macrocyclic lactone ring, with variations in side chains and substitutions influencing their pharmacokinetic properties and spectrum of activity. For chemical structures and detailed information, refer to the cited sources [10, 11, 12, 13]

ANTI INFLAMMATORY AND IMMUNOMODULATORY EFFECT:

Macrolides not only possess direct antimicrobial effects but also play a significant role in modulating various components of the immune response. Due to their anti-inflammatory or immune-modulating properties, macrolide antibiotics have found extensive use as maintenance treatments for various chronic inflammatory airway diseases.(14) The interest in the immunomodulatory effects of macrolides sparked when it was observed that in patients with bronchial asthma requiring administration of glucocorticoids, the use of macrolide antibiotics enabled a reduction in the dose of steroids needed(15). This phenomenon is commonly referred to as the 'sparing effect.' Even small doses of macrolides, independently of glucocorticoid action, have been shown to reduce bronchial hyperreactivity in patients with severe asthma. Moreover, studies have demonstrated that macrolide treatment can prolong survival in patients with diffuse panbronchiolitis (DPB). Following the introduction of erythromycin as standard therapy for DPB in 1987, a remarkable increase in 10-year survival rates was observed. Previous research has suggested that the efficacy of such treatment is primarily associated with 14- and 15-membered macrolides(16) Among the commonly used macrolides, namely azithromycin, clarithromycin, and erythromycin, it is believed that they exhibit the most potent immunomodulatory activity.(17) Macrolides demonstrate diverse immunomodulatory actions both in vitro and in vivo. They have the capacity to down-regulate prolonged inflammation, enhance mucus clearance, hinder bacterial biofilm formation, and modulate the activation of the immune system, either augmenting or attenuating it. Additionally, macrolides can impact various functions of phagocytes, such as chemotaxis, phagocytosis, oxidative burst, bacterial killing, and cytokine production. Specifically, macrolides have been found to reduce the production of reactive oxygen species, inhibit the activation and mobilization of neutrophils, accelerate the apoptosis of neutrophils, and impede the activation of nuclear transcription factors involved in inflammatory responses. These actions collectively contribute to the immunomodulatory effects of macrolides.(18)

EPILEPTOGENIC PROPRETY OF MACROLIDES:

Erythromycin, clarithromycin, and azithromycin are commonly prescribed macrolide antibiotics for patients with upper respiratory infections.(19) However, caution is advised when co-administering these antibiotics with antiseizure drugs due to potential drug interactions. Clarithromycin and erythromycin inhibit the enzyme CYP3A4, which can affect the metabolism of antiseizure drugs like carbamazepine, potentially leading to changes in drug levels. Patients should be closely monitored, and dose adjustments may be necessary to reduce the risk of drug toxicity, which could result in seizures or status epilepticus. Clarithromycin has been associated with increased neuronal activity by stimulating CA3 pyramidal neurons through a reduction in GABAergic signaling(20). Cases of clarithromycin-induced delirium due to nonconvulsive status epilepticus (NCSE) have improved significantly after discontinuation of clarithromycin therapy(21). In contrast, azithromycin does not inhibit CYP3A4 and has

not been found to induce seizures. However, the exact mechanisms underlying macrolide-induced neurotoxicity remain unclear and warrant further research. Although evidence regarding the epileptogenic properties of macrolides is limited in the literature, clinicians should be mindful of the potential neurotoxic side effects of clarithromycin. They are encouraged to perform electroencephalograms (EEGs) in patients who develop neurotoxic side effects to differentiate seizures from other neurological or psychiatric diagnoses(22)

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