



REVIEW ARTICLE

Use of macrolides in lung diseases: recent literature controversies[☆]



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KEYWORDS

Pulmonary diseases;
Macrolides;
Inflammation;
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Abstract

Objective: To review the mechanisms of action of macrolides in pediatric respiratory diseases and their clinical indications.

Sources: Review in the PubMed database, comprising the following terms in English: “macrolide and asthma”; “macrolide and cystic fibrosis”; “macrolide bronchiolitis and viral acute”; “macrolide and bronchiolitis obliterans” and “macrolide and non-CF bronchiectasis”.

Summary of the findings: The spectrum of action of macrolides includes production of inflammatory mediators, control of mucus hypersecretion, and modulation of host-defense mechanisms. The potential benefit of macrolide antibiotics has been studied in a variety of lung diseases, such as cystic fibrosis (CF), bronchiectasis, asthma, acute bronchiolitis, and non-CF bronchiectasis. Several studies have evaluated the benefits of macrolides in asthma refractory to therapy, but the results are controversial and indications should be limited to specific phenotypes.

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In viral bronchiolitis, there is no consistent benefit in acute conditions, although recent data have shown an effect in recurrent wheezing prevention. In patients with CF results are also contradictory, but the consensus states there is a small clinical benefit, especially for patients infected with *P. aeruginosa*. There was also no positive action of macrolides in patients with post-infectious bronchiolitis obliterans. Children with non-CF bronchiectasis seem to have clear benefits regarding the use of macrolides, which showed clinical advantages in parenchyma protection and lung function.

Conclusions: The long-term use of macrolides should be limited to highly selected situations, especially in patients with bronchiectasis. Careful evaluation of the benefits and potential damage are tools for their indication in specific groups.

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PALAVRAS-CHAVE

Doenças pulmonares;
Macrolídeos;
Inflamação;
Crianças;
Adolescentes

Uso de macrolídeos em doenças pulmonares: controvérsias da literatura recente

Resumo

Objetivo: revisar os mecanismos de ação de macrolídeos em doenças respiratórias pediátricas e as suas indicações clínicas.

Fonte de dados: revisão na base de dados Pubmed, compreendendo os termos em inglês referente ao tema básico.

Síntese dos dados: O seu espectro de ação estende-se desde a produção de mediadores inflamatórios, o controle da hipersecreção de muco e modulação de mecanismos de defesa do hospedeiro. O potencial benéfico dos antibióticos macrolídeos foi estudado em doenças pulmonares como a fibrose cística, as bronquiectasias, a asma, a bronquiolite aguda e as bronquiectasias não ligadas à fibrose cística. Diversos estudos avaliaram os benefícios dos macrolídeos na asma resistente a terapia, porém, os resultados são controversos e as indicações devem ser limitadas a fenótipos específicos. Na bronquiolite viral não há benefícios consistentes nos quadros agudos, embora dados recentes mostrem um efeito na prevenção de sibilância recorrente. Em pacientes com fibrose cística os resultados também são contraditórios, mas o consenso é de que há um pequeno benefício clínico, especialmente para os pacientes infectados por *P. aeruginosa*. Também não foi observada ação positiva dos macrolídeos em pacientes com bronquiolite obliterante pós-infecciosa. Crianças com bronquiectasias não relacionadas à fibrose cística parecem ter claros benefícios em relação ao uso de macrolídeos, os quais mostraram vantagens clínicas, de proteção ao parênquima e na função pulmonar.

Conclusões: O uso em longo prazo de macrolídeos deve ser limitado a situações altamente selecionadas, especialmente em pacientes com bronquiectasias. Avaliação cuidadosa dos benefícios e potenciais danos são ferramentas para indicação em grupos específicos.

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Introduction

Macrolides are antibiotics belonging to a chemical compound family characterized by the presence of a macrocyclic lactone ring, for which the reference drug is erythromycin.¹ These are drugs that have been used for years to treat respiratory infections, given their excellent tissue penetration and action against many of the common respiratory pathogens, including *Mycoplasma* species, *Chlamydia*, and *Legionella*.^{2,3} Macrolides exert their antimicrobial effect by binding to bacterial ribosome, specifically the 50S subunit, promoting protein synthesis inhibition. The effect may be bacteriostatic or bactericidal, depending on the concentration and susceptibility of microorganisms.⁴

In the early 1980s, positive results of erythromycin use in patients with a disease originally described in Japan and known as acute diffuse panbronchiolitis (DPB)

aroused the interest of physicians and researchers on the immunomodulatory potential of macrolides.⁵ Acute DPB is an idiopathic disease characterized by distal airway obstruction, mucoid impaction, and dilation, with extensive inflammatory infiltration of neutrophils and CD8+ lymphocytes. It can be associated with infection by *Pseudomonas aeruginosa* species in more advanced stages and develop into extensive bronchiectasis.⁶ The use of erythromycin is recommended for patients with this disease, representing one of the main therapeutic resources; it is believed that its action mechanisms include anti-inflammatory and anti-mucus actions.^{6,7}

In an extensive review of action mechanisms of macrolides as immunomodulators in lung diseases, Kanoh and Rubin⁴ described the existing evidence regarding the action of these drugs in several areas of pulmonary and systemic physiology, including modulation of inflammatory

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