EDITORIAL OPEN ACCESS

Non-anti-infective effects of long-term treatment with macrolides in non-cystic fibrosis bronchiectasis

Marco Mosella, Mariasofia Accardo, Mauro Maniscalco

Antibiotic therapy represents a milestone in the treatment of bronchiectasis [1] and long-term therapy with macrolides has increasingly being used in these patients only as an empirical extension of their proven effectiveness in the management of other chronic airway pathologies such as cystic fibrosis [1, 2]. Over the years many therapeutic approaches have been used trying to limit sequences resulting from the natural evolution of bronchiectasis. Bronchiectasis is defined as a structural alteration of the bronchus with dilation of the lumen and impairment of the wall itself as consequence of repeated infections and inflammatory episodes. These conditions establish a persistent morbid state that determines the activation of a 'vicious circle' of infection and inflammation that hesitates in a remodeling of the bronchial wall [3].

We know that, beside the classical antibacterial activity, macrolides have anti-inflammatory and immunomodulatory properties [4, 5]. Available evidences show that these properties are able to determine actual benefits both in terms of reductions in the number of both exacerbations and attenuation of respiratory function decline. One of the major anti-inflammatory activities of macrolides is the inhibition of interleukin 8 (IL-8), a potent chemotactic agent and neutrophil activator, they also limit the production of interleukin-1 beta (IL-1 beta) and TNF-α in macrophages, reducing the expression of adhesion molecules on vascular endothelial cells. Macrolides inhibit the expression of ICAM-1 (Intercellular Adhesion Molecule-1) and VCAM-1 (Vascular Cell Adhesion Molecule-1) on epithelial airways cells and the production of metalloproteins by fibroblasts and neutrophils, inhibiting the activation of NF-kB (Nuclear Factor kappa light-chain enhancer of activated B cells) and AP-1 (Activator Protein 1) [6, 7]. They have anti-elastolytic action by inhibiting cytotoxins such as ROS and elastases and act on certain functions of lymphocytes such as cytokine production by Type 1 (Th1) and Type 2 (Th2) T-helper cells, interfering with intra-cellular and extra-cellular signal mechanisms and therefore, with cellular chemotaxis and apoptosis of T cells [8, 9]. Finally, they suppress the production of nitric oxide at the level of alveolar macrophages [10, 11].

Macrolides also have important actions directly on pathogens. It is known that bacterial adhesion to an epithelium is essential to penetrate and so to determine an infection. Furthermore, in vitro it has been shown that low dose of erythromycin can reduce the adhesion of *Pseudomonas aeruginosa* to the basal membrane by altering its morphology [12] and inhibit its motility by reducing the expression of flagellin in many strains [13].

We know that chronic infection is the main cause of inflammation and tissue destruction in many chronic lung inflammatory diseases. It has been observed that *Pseudomonas aeruginosa* strains involved in this type of alteration develop a mucoid phenotype synthesizing alginate, an important component of bacterial biofilm; bacteria resist within this biofilm both the action of antibiotics and phagocytic cells. Macrolides not only can reduce the formation of this biofilm, but they can also disrupt it by offering the possibility to attack the pathogen with different antibiotic molecules free of its armor [14].

About the immunomodulatory properties it should be stressed that hypersecretion causes inflammation of the airways leading to a functional limitation and altering the clearance mechanism with subsequent recurrent infections. We know that changes in volume and biophysical characteristics of the bronchial mucus play an important role in the mucous ciliary clearance , allowing an effective defence system when approaching the physiological state [15].

Immunohistochemical studies demonstrate that some macrolides modulate gene expression of mucins through both MAPKinase activation factors and various transcription factors, reducing mucosal hypersecretion without altering the normal drainage mechanisms, important factors for immunomodulatory activity [16, 17].

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The action of pathogens responsible for recurrent bronchial infections or colonization in patients with non-cystic fibrosis bronchiectasis and their role in the chronicization of this pathology is well known. Therefore, it is useful to evaluate the possibility of adopting low-dose and long-term drug therapy with molecules that offer actions that can reinforce the achievable therapeutic result [3]. In this regard, macrolides, not considering the wide spectrum of action and their good diffusibility that makes them suitable for treating various bacterial infections of the respiratory tract, represent a family of antibiotics used for various reasons [18]. In particular, the new generation molecules that are provided with a simple posology and a long half-life offer the possibility of daily administration; they also have good tolerability, causing only occasional dose-dependent gastric disorders, arrhythmias, ototoxicity and transient deafness, favored by conditions of kidney or liver failure.

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Keywords: Antibiotics, Bronchiectasis, Macrolides

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Author Contributions

Marco Mosella – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Mariasofia Accardo – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Mauro Maniscalco – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

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