Long-Term Treatment with Macrolides – Light in the Darkness of COPD Therapy?

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Chronic obstructive pulmonary disease (COPD) affects millions of people in the world, constituting the sixth leading cause of death and the only condition in the top 10 causes of death with an increasing prevalence and mortality [1]. The economic burden of COPD is very high and further increases are foreseen. Acute exacerbations are one of the most important characteristics of COPD, because they worsen the patient's quality of life and health status [2]. When exacerbations recur frequently, they are associated with loss of pulmonary function [3]. The only interventions known to influence the natural history of COPD are smoking cessation and oxygen therapy, but efficacious treatments for COPD are not yet available.

Several studies have demonstrated that airway and lung parenchyma inflammation play an important role in COPD [4]. Both neutrophil and eosinophil inflammation have been observed and several inflammatory mediators have been implicated in the inflammatory process [5]. Patients with frequent exacerbations show increased airway inflammation and a more rapid decline in lung function. Due to the growing importance of inflammation in the pathogenesis of COPD, many studies have been focused on the development of methods suitable for studying inflammation in these patients. Several biomarkers are measurable in sputum, bronchoalveolar lavage, bronchial biopsies, exhaled breath and blood [6, 7]. The first and most extensively utilized method for study-

ing airway inflammation is the analysis of induced sputum. Neutrophils are the most represented cells in sputum samples from COPD patients and their number relates with the degree of airway obstruction and rate of FEV₁ decline. Inflammatory mediators involved in neutrophil recruitment are elevated in sputum from COPD patients and increase further during exacerbations [6, 7].

In this issue of *Respiration*, He et al. [8] present the results of a study aimed at assessing the effects of a 6-month treatment with erythromycin on airway inflammation and health outcomes in COPD patients. The ability of macrolides to influence airway inflammation has been known for many years. Antibiotics were initially utilized with the belief that infection played a prominent role in the pathogenesis of COPD, an assumption that has not been confirmed [9]. However, it has been observed that treatment of panbronchiolitis and cystic fibrosis patients with macrolides is accompanied by improved lung function and a reduced number of exacerbations [10], an effect that is not mediated by the antibacterial effects of these drugs [11]. More recently, it has been shown that similar effects occur also in COPD patients [12]. These results are of interest, since they open new perspectives on the treatment of COPD. Despite the growing evidence of the important role of inflammation in the genesis and progression of COPD, a small effect of classical anti-inflammatory drugs, such as glucocorticosteroids, has been seen.

Results obtained with drugs such as macrolides and roflumilast [13] suggest that substances other than steroids might be able to influence the inflammatory process in COPD patients. Macrolides exert anti-inflammatory activity through different mechanisms, such as inhibition of inflammatory cell chemotaxis, cytokine synthesis, adhesion molecule expression and reactive oxygen species production [14]. The study by He et al. [8] confirms the anti-inflammatory action of macrolides, as shown by the reduction of neutrophils and neutrophil elastase in sputum, and suggests the possibility of monitoring the effects of these drugs in the clinical setting by a simple technique such as induced sputum. However, these indications should still be taken with some caution, because other studies reported no effects of macrolides in COPD

[15], probably due to the too short duration of treatment. There are also some discrepancies between the studies of He et al. [8] and Seemungal et al. [12]: both authors reported positive results in the number of exacerbations, but Seemungal et al. [12] did not observe any change in inflammatory markers in sputum, unlike He et al. [8].

In conclusion, more studies are needed to confirm the clinical efficacy of macrolides in the treatment in COPD. Moreover, as suggested by Kunisaki and Niewoehner [16] in their recent editorial on this topic, the possible side effects of long-term therapy with antibiotics need to be accurately assessed. However, considering the disappointing results obtained with the standard anti-inflammatory therapy, this line of research merits further investigation.

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