Are statins a treatment option for COPD?

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Chronic obstructive pulmonary disease (COPD) is expected to become the third most common cause of death worldwide by the year 2020.[1] It is generally accepted that, in addition to its respiratory effects, COPD may be accompanied by systemic manifestations, such as cardiovascular disease (ischaemic heart disease, heart failure, hypertension), osteoporosis, anaemia, diabetes mellitus (DM), lung cancer, and depression. These conditions, that affect in multiple ways the complex outcome of COPD, are associated with increased risk of hospitalization, which is one of the strongest predictors of disease severity. Patients with COPD usually die from non-respiratory causes.[2]

Although the mechanisms leading to systemic manifestations are not fully understood, they are believed to be related to the presence of increased systemic inflammation and oxidative stress.[3] Cigarette smoking, considered to be responsible for about 85% of diagnosed cases of COPD, has been shown to induce an inflammatory process in the lungs characterized by the recruitment and activation of inflammatory cells,[4] inflammatory cytokines and matrix metalloproteases.[5,6] All of the above responses, with or without the coexistence of other risk factors such as hyperlipidaemia, obesity, sedentary lifestyle and hypertension, can, in combination with exposure to tobacco smoke, contribute to the development of cardiovascular disease. It has been shown that cardiovascular diseases are more common in smokers who develop COPD, that COPD is an independent risk factor for cardiovascular disease, and that reduced FEV1 is an indicator for cardiovascular mortality. Finally, chronic low grade systemic inflammation in COPD is thought to play a central role in the formation of atherosclerotic plaque, as the endothelium overexpresses adhesion molecules that allow circulating leukocytes to adhere to it and trigger inflammatory reactions, which are among the pathogenetic mechanisms of cardiovascular disease.[7]

Despite the application of current forms of treatment, mortality from COPD continues to increase, in spite of decreases in cardiovascular disease. One possible explanation for this decline is the widespread use of prophylactic cardiovascular therapy. Based on this reasoning, it is attractive to assume that the application of such forms of treatment could achieve a similar reduction in COPD. The statins, which in addition to lowering cholesterol, appear to have both local and systemic anti-inflammatory and antioxidant effects, constitute a type of treatment that attracts attention because of its pleiotropic potential in COPD.[8] It is known that statins inhibit endogenous cholesterol synthesis in hepatocytes by blocking the synthesis of cholesterol in the mevalonate pathway, which is a precursor molecule, reducing the

synthesis of several non-steroidal isoprenoeidon molecules, which play an important role in various cellular functions, such as breakdown of some proteins, synthesis of glycoproteins, and electron transfer. These mechanisms are though to underlie most of the pleiotropic effects of statins, including their anti-inflammatory, antioxidant and immune-modulatory characteristics. Statin therapy has been shown to decrease coronary and cerebrovascular events and mortality from coronary artery disease.

Human and animal studies have shown that statins have strong immune-modulating, anti-inflammatory effects in systemic and pulmonary circulation which may have useful actions in COPD pathways through the following mechanisms: 1) Inhibition of production of cytokines, including tumour necrosis factor-a (TNF-a), interleukins (IL) IL-6 and IL-8 and C-reactive protein (CRP), and neutrophil infiltration into the lungs; 2) Inhibition of the fibrotic activity in the lung that leads to small airway fibrosis and irreversible airflow limitation; 3) Enhancement of clearance of apoptotic cells by the alveolar macrophages; 4) Inhibition of the metalloproteinases which are responsible for significant structural deterioration of lung; 5) Exertion of a strong anti-oxidant effect by reduction of IL-8 release from neutrophils and neutrophil derived oxidant species; 6) reduction of lipopolysaccharide-induced goblet cell hyperplasia in bronchial epithelium, which induces mucus hypersecretion.[9]

Given the increasing evidence that COPD is a systemic inflammatory disease, it has been postulated that the pleiotropic effects of statins may have a beneficial effect on the progression and sequelae of COPD.

In support of this hypothesis, several studies document a benefit of statin treatment on various clinically-relevant COPD endpoints. Specifically, with statin therapy, a reduction has been shown in the frequency of COPD exacerbation, hospitalization, need for intubation, and mortality from chest infections and all-cause mortality. In addition, statin therapy is associated with slower decline in FEV1 and FVC, with or without smoking history, and significant improvement in exercise capacity. A recent Greek prospective study showed that patients with COPD receiving statins after hospitalization for COPD exacerbation have a lower incidence of exacerbations and improved quality of life at 1 year follow-up.[10]

What is not clear from the literature is whether statins exert beneficial effects in COPD indirectly, by influencing cardiovascular comorbidities, or directly, by contributing to the treatment of COPD with their pleiotropic impact, or both.

Since there is synergy between cardiovascular events and pulmonary inflammation, statins improve mortality in COPD indirectly, by contributing to the prevention of non-ischaemic heart disease due to various risk factors (e.g., smoking, obesity, DM). This is confirmed by studies showing that inflammation associated with atherosclerosis may be worsened by the systemic inflammatory component of COPD. Other literature reports, however, support the direct disease-modifying effect of statins in COPD, as their use was associated with an attenuated decline in lung function and reduction in the frequency of respiratory-related emergency department visits and hospitalizations for exacerbations.[7,11]

Further support of this hypothesis has been provided by animal studies that showed that statins inhibit the progression of emphysema in murine models. The first study showed that simvastatin inhibits the development of elastase induced emphysema, with a decrease in inflammatory markers in the lungs and promotion of alveolar epithelial cell proliferation. Another study found that simvastatin inhibited both the destruction of lung parenchyma and the development of pulmonary hypertension.[12]

The lack of information in most of the reviewed studies on the effects of specific statins and the doses required-precludes detailed analysis here, as different types of statin may have different modes of action. It appears that the lipophilicity of statins may be associated with the range of their effects. For example, studies have shown that lipophilic statins such as simvastatin, atorvastatin have the strongest anti-inflammatory potential.[13]

In conclusion, more and more authors highlight the need for forms of treatment for patients with COPD not limited to relieving symptoms or reducing hospital admissions, but extending beyond the lungs and aimed at changing the natural course of disease. Given the increasing evidence that COPD is a systemic inflammatory disease, the pleiotropic effects of statins could explain their positive effects in patients with COPD. The available data are derived mainly from retrospective studies and it has not been entirely clear whether these beneficial effects are due to indirect actions, such as improvement of cardiovascular risk or immediate, from the effects of the pleiotropic properties of statins on inflammatory processes. For this reason more randomized prospective trials are needed to be put in place to confirm the positive effect of statin on the outcome of patients with COPD and to determine its mechanisms, the dosage required and the risk of side effects.

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