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The Anti-Inflammatory Benefit of Statins for *Chronic Obstructive Pulmonary Disease* (COPD): Review Article

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A B S T R A K

Chronic Obstructive Pulmonary Disease (COPD) is characterized by progressive, minimally reversible airflow limitation and systemic inflammation. Over the last 5 years, there have been abundant studies proving the benefit of statin in COPD as an anti-inflammatory agent. So far, statin is mostly utilized in cardiology due to its effects of cholesterol reduction, immune system modulation, and anti oxidant. In point of fact, the effects of statin have proven to be advantageous when administered to COPD patients. The aim of this review is to examine the pharmacological mechanism of statins as anti-inflammatory drugs so that they can be considered as therapy in COPD.

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1. Introduction

WHO defines *Chronic Obstructive Pulmonary Disease* (COPD) as a pulmonary disease characterized by chronical obstruction of airways in the lungs inhibiting normal breathing and it is not totally reversible.[1] COPD affects more than 5% of population and is related to high morbidity and mortality.[2] COPD is the second-highest rank of pulmonary diseases in the world in 2015, coming after asthma.[3] Mortality due to COPD is 8 times greater than the one because of asthma. Globally, COPD is the fourth rank of mortality causes in the world. Furthermore WHO predicts that it is going to be the third rank by 2030.[6] COPD is often related to smoking history and is the most primary contributor of mortality. In Korea, 15.5/1,000 people are diagnosed wtih COPD each year. The rate of occurrence accelerates along with increasing age, heavy smoking history, and lower income associated with sosioeconomic status, with faster acceleration to males compared to females.[5] COPD is the third rank disease in the USA, killing more than 120,000 people each year. [7]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD), a project initiated by the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO) defines COPD as follows,
"COPD is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases".

Limitation of airways which characterizes COPD is caused by a mixture of small airways disease (e.g. obstructive bronchiolitis) and parenchymal destruction (emphysema). However, this contribution varies among people. Chronic inflammation causes structural change, airways constriction, and lung parenchymal desctruction. A little lost of airways contributes to limited airways and mucociliary dysfunction.[8]

Currently COPD covers 3 main pathopysiological characteristics, including emphysema, chronic bronchitis, and airways constriction. Chronic bronchitis is defined as productive chronic cough lasting for 3 months in each of 2 consecutive years. In patients with other causes of chronic cough, e.g. bronchiectasis, it is excluded.[8] Emphysema is pathologically defined as an abnormal permanent enlargement of air spaces distal to the terminal bronchioles, accompanied by the destruction of alveolar walls and without obvious fibrosis.[9] The Global Initiative for Asthma (GINA) gives the following definition of asthma: "Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.[10]

The aim of COPD therapy is to reduce the symptoms, frequency, and exacerbation severity, and to increase exercise tolerance as well as health status. One of therapeutical managements in COPD is anti inflammation, i.e. inhaled corticosteroid, oral glucocorticoid, PDE4 inhibitor, antibiotics, and mucolytic/ antioxidants, as well as the use of statins and leukotrienes.[13]

Many studies mention that besides the use of statins in cardiovascular diseases and coronary heart disease, statins have pleiotropic effects which significantly contribute to other conditions, e.g. inflammation and neuropathology or even tumor.[19] Statins belong to 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors known for their effects to decrease cholesterol and to modulate immune system which can be used as anti-inflammatory agents.[14]

In COPD, anti-inflammatory effects of statins influence pulmonary and respiratory system and prevent early mortality due to infection or pulmonary exacerbation, lung cancer, and heart disease. This evidence was obtained from an observation study in the laboratorium based on mouse models or cell cultures. The research showed that statins decreased airways inflammation, level of systemic inflammation marker such as C-reactive protein (CRP). [15,16] Statins were also reported to fight pulmonary emphysema progression and inhibit hyperreactive airways in mouse models.[17,18]

The benefit of using statins in COPD can rationally be explained by understanding the pharmacological effects of statins in lungs. The aim of this review is to examine the pharmacological mechanism of statins as anti-inflammatory drugs so they can be considered as therapy in COPD.

2. Pathophysiology Inflammation in COPD

The inflammation in COPD patients involves both innate immunity (neutrophils, macrophages, eosinophils, mast cells, natural killer cells, T cells, innate lymphoid cells, and dendritic cells) as well as adaptive immunity (T and B lymphocytes). Moreover, there is activation of structural cells, including airways and alveolar epithelial cells, endothelial cells, and fibroblasts.[11] Those cells and structural cells, including epithelial cells, endothelial cells, and fibroblasts, secrete different kinds of pro-inflammatory mediators such as cytokines, chemokines, growth factors, and lipid mediators. Most COPD patients undergo neutrophils increase, while some have eosinophils increase. The existence of sputum induction indicates characteristics due to neutrophils increase.[12]

Smoking has direct stimulating effects on granulocytes production and their release from bone marrow and they survive in airways, mediated by hematopoietic growth factor (GM-CSF) and granulocytes-colony stimulating factors released from lung cell macrophages.[11]

There are granulocytes markers from neutrophil inflammation named as myeloperoxidase and human neutrophil leptin which actively degranulate.[12] The marker release causes neutrophils in airways to be activated. Neutrophils secrete serine proteases, i.e. neutrophil elastase, cathepsin G, and proteinase 3 which contribute to alveolar destruction. The secretion is also related to mucus hypersecretion because it is a potent stimulant of submucosal glands and goblet cells. In patients with exacerbation, there is purulent sputum increase. There is an

increase of chemotactic factors, including LTB4 and CXCL8. Neutrophills in COPD patients show marked abnormality in chemotactic responses with migration increase but accuracy decrease.[11]

Oxidative stress also holds an important role in the inflammation process, resulting in transcription factor activation, disturbing antiprotease defense, DNA damage, cell aging, autoantibody regeneration, and corticosteroid resistence through histone deacetylase inactivation.[11] Inflammation and structural cells, including neuthropils, macrophages, and epithelial cells are activated in patients with COPD, producing ROS. Oxidative stress leads to oxidation of arachidonic acid and prostanoid mediator formation, called isoprostane which gives significant effects including bronchoconstriction and plasma exudation. The level of peroxynitrite is also increasing in patients' breath. NO elevates in peripheral lung cells. Oxidant production in human airways is affected by several factors, i.e. catalase, SOD, and glutathione formed by the enzyme g-glutamyl cysteine ligase and glutathione synthetase. ROS-induced antioxidants are mostly extracellulars. The extracellulars antioxidants, particularly glutathione peroxidase is formed in response of cigarette smoke and oxidative stress.[11]

Oxidative stress forms activation of histone acetyltransferase activity opening chromatin structure and relates to the increase of multiple inflammatory gene transcription. Oxidative stress also disturbs antiprotease function such as a1-antitrypsin and secretory leukoprotease inhibitors so they accelerate elastin breakage in lung parenchyma. Oxidative stress decreases HDAC2 activity and expression through activation of phosphoinositide 3-kinase d and peroxynitrite-induced nitration of tyrosine resides. The inflammation prevents therapy such as corticosteroid form inactivation effects of inflammation gene's activity.[11] Oxidative stress reduces sirtuin-1 activity, a key of molecular regeneration implicating in aging. The decrease of sirtuin-1 results in aging acceleration.[11] Oxidative stress activates growth factors and DNA damage, also leading to formation of carbonylated proteins which are antigenic and stimulate autoantibody development in patients with COPD causing persistent inflammation. [11]

Systemic inflammation is also found in COPD patients and can be worsening in patients with different complications i.e. DM, osteoporosis, and cardiovascular diseases. Acceleration of lung cell aging in patients with COPD can cause inflammation protein release from the lung cells ~~in the cells~~.[11]

3. Statins: Chemical Structures and Mechanisms

The chemical structures of statins consist of 2 components, i.e. pharmacophore called dihydroxyheptanoic acid segment and the part of ring system with different substituents. The pharmacophore function is to competitively inhibit HMG-CoA reductase and depends on dosage. The stereoselectivity of statins has 2 chiral carbon atoms, i.e. C3 and C5 in the pharmacophore. In the ring, the structure is a complex hydrophobics structure, covalently bond with pharmacophore. Substituents sticking to the ring decide statin solubility with different pharmacological activities.[19]

Statins are commony divided as 2 types, i.e. type 1 which derives from fungi, e.g. lovastatin, simvastatin and pravastatin. Type 1 is identified as secondary metabolite of fungi while type 2 is synthetically constituted. The functional difference of type 1 and 2 is on the ability to interact and inhibit HMG-CoA reductase and its lipofilicity. Type 2 statins are known to have more interaction with HMG-CoA reductase due to its structural characteristics. For example, atorvastatin and rosuvastatin have hydrogen bond. Lovastatin, simvastatin, atorvastatin, fluvastatin are lipophilics while pravastatin and rosuvastatin are more hydrophilics.[19]

Statins are the most efficient 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase agent in decreasing cholesterol. The beneficial effect of HMG-CoA reductase is its capacity in decreasing endogen cholesterol synthesis by competing to inhibit enzyme development. Mevalonate, a product of HMG-CoA reductase reaction, is a precursor not only for cholesterol but also inhibition of non-steroid isoprenoidic components, where the inhibition results in pleiotropic effects. They are grouped as 2 categories, i.e. directly on lipids or via intrasel signaling pathways. The first category is cholesterol biosynthesis inhibition, uptake increase and LDL degradation, lipoprotein secretion inhibition, LDL oxydase inhibition, and inhibition of scavenger receptor expression. Statins accumulate a series of process leading to esterified cholesterol accumulation into macrophages, increase of endothelial synthetase, decrease of inflammation process, increase of artherosclerosis plaque stability, regenerating platelet activity, and in coagulation process. Additionally, statins inhibit tumor cell development and increase intracel calcium mobilization. It was observed that HMG-CoA reductase also induces osteoclast formation in mouse model ~~animals~~.[20]

4. Pharmacological Mechanism of Statins in COPD

In pulmonary inflammation, statins entering neutrophils have strong effects in reducing inflammation occurence, e.g. the entrance of macrophages, lymphocyte activation, and inhibition of cytokine release, particularly in IL-8 which appears when there is inflammation due to neutrophils in lungs. Inhibition of IL-6, IL-8, and GM-CSF expression due to statins is proven in a research using human cell cultures.[25,26] It is also shown that statins have modification effects of airways inflammation so there is an inhibited emphysema formation.[27] The effect of statins in IL-6 is in systemic circulation and an antioxidant effect in muscle athropy.[28] Statins also inhibit apoptosis which is linked to lung cancer.[29] Statins own such property because intracellular prenylation inhibition and inhibition of GTP-binding protein which become the foundation of the inflammation occurence.[30]

Statins have two mechanisms related to their effects

in reducing inflammation. First, they modulate the amount of cholesterol so that they decrease fat formation stability within large amount which next continues to activation and regulation of immune cells. Second, they prevent prenylation from signaling molecules which later regulate decreasing gene expression. Both result in the decreasing expression of cytokine, chemokines and molecule adhesion with apoptosis cell effect or proliferation.[31] Statins also have antioxidant effects because of their ability to scavenge oxygen from free radicals.[32] Atorvastastatin metabolite is proven to provide potent antioxidant potential and to protect VLDL, LDL, and HDL from oxidation.[37]

Some fats rich of cholesterol and glycosphingolipid are the location of intracell enzymes, particularly kinase. This lipid can translocate due to existence of actin cytoskeleton controlling redistribution, grouping, and stabilization of cell membrane. This set of lipid forms a critical place for processes such as cell transfer, intracell transportation or signal transduction. The layers of lipid do not only serve as a bridge to carry essential molecules to activate immune cells but also to separate molecules when the condition is not appropriate for activation. Cholesterol synthesis inhibition by statins distracts the layers of lipid so that it affects lymphocyte function.[33] Interaction between lymphocytes and antigen presenting cells result in T cell activation, next IFN-c induces regulation improvement and a set of major histocompatibility complex class II. Statins decrease IFN-c production via Th1 34 cells so that they act as repressors of T cell activation mediating MHC-II.[36,38]

Disruption in cytokine synthesis is a consequence of lipid raft disruption. Regardless, there is cytokine synthesis alternative which is affected by statins. Mevalonate synthesis pathway mediated by HMG-CoA reductase is important for isoprenoid biosynthesis which is essential for proliferation and activity of normal cells. Farnesyl pyrophosphate is the mediator of this pathway and it provides a precursor for synthesis of different isoprenoids which are prenylated proteins through covalent bond. Many of prenylated proteins have important roles in regulating cell growth, cell secretion, and signal transduction. By inhibiting cell prenylation, statins affect many processes involved in inflammation.[33]

5. Evidence of Statins's Benefit in COPD

There was a study in emphycema mouse model induced by cigarettes, and it indicated that simvastatine inhibited lung parenchymal destruction and peribronchial infiltration and perivascular inflammation. Induction of MMP-9, major inflammation mediators decreased in the same models when the experiment was repeated using in vitro microvascular endothelial cells of human lungs. Pulmonary vascular remodelling was also inhibited and it was also reduced in NO endothelial synthase induced from smoking.[21]

In another research in an emphysema mouse model, the result showed that simvastatin decreased expressions of mRNA from IFN-c, TNF-a and MMP-12 in rinse wipe of bronchoalveolar indicating the reduction of inflammation and remodeling.[22]

A cohort-based population study was conducted in New Zealand. 1,687 patients aged 50-80 years old diagnosed with COPD were included in the inclusion criteria. Next, they were categorized into two groups, the first one was statin-user group consisting of 596 people while the second group was non-statin users consisting of 1,091 people. 91% was included as simvastatin users whereas 9% was the users of atorvastatin. The mortality proportion of both group was almost similar, which was 242 mortalities (40.6%) in the statin group and 429 mortalities (39.3%) in non-statin group (HR 0.69; 95% CI, 0.58 to 0.84). The conclusion was the use of statins was related to 30% decrease of all mortality causes in the first 3-4 years after admission of COPD, regardless the history of cardiovascular and diabetes diseases.[35]

A retrospective control case study used data of an insurance in Taiwan. 14,316 patients were 45 years old with COPD and 2 or more patient with the history of COPD and 2 or more patients with COPD-related medication for 1 year; 1,584 inpatient cases with COPD were compared with 5,950 controls. The used statins (atorvastatin, simvastatin, lovastatin, fluvastatin) were prescribed in 9% cases and 12.3% control. After multivariate logistic regression analysis, COPD exacerbation risk was 30% less in patients using statins, 95% CI, 0.44-0.81 and the history of using statins was connected to the amount of risk decrease, OR 0.60; 95% CI, 0.44-0.81). The COPD risk decrease related to dosage was also observed with the result of medium average daily dose, OR 0.60; 95% CI, 0.41-0.89; high daily dose, OR 0.33; 95% CI, 0.14-0.73). The conclusion was that the use of statins had a relationship with the decrease of COPD exacerbation risk, with further risk reduction for statins prescribed more recently or at high doses.[36]

There was a case control research investigating the use of statins in COPD. It consisted of 5,794 people; During the 3 year follow up, 530 were patients with COPD exacerbation and 1,016 patients as control group. After 3 years, the exacerbation occurrence and inpatients were recorded or with the existence of corticosteroid therapy. The outcome of the research was to estimate the relationship of statin use and its exacerbation. The result was that the use of statin linked to the decrease of exacerbation occurrence number, OR=0.68 (95% CI 0.51 to 0.91, p=0.01). This number was the same as the result of multivariable conditional logistic regression analysis, OR=1.1 (0.5 to 2.1, p=0.83). In subgroup with heavy COPD level, and without comorbid cardiovascular, it was observed the relationship between the use of statin and exacerbation, OR=1.1 (0.5 to 2.1, p=0.83). Furthermore, the use of statin was linked to the chance decrease of high CRP, OR=0.69 (0.56 to 0.85, p<0.001) and the high CRP was related to the risk increase of exacerbation, HR=1.62 (1.35 to 1.94, p<0.001). It was concluded that the use of statins was related to the decrease of exacerbation number of COPD patients with cardiovascular diseases, although based on this study, the event did not appear in heavy

COPD without comorbid cardiovascular.[37]

There was an observational study reviewing all systematic review and meta analysis which were related to COPD, mortality occurrence, exacerbation, and side effects of cardiovascular. HR with 95% confidence interval was estimated. 15 studies with a total number of 23,459 patients were included in the inclusion criteria. 9 articles provided all data causing mortality (124,543 participants) with HR 0.62 (95% Confidence Interval 0.52 to 0.73). 3 studies provided data about cardiovascular mortality (90,041 participants), HR 0.93 (0.50 to 1.72). 6 articles provided data about COPD exacerbation with or without inpatients (129,796 participants), HR 0.64 (0.55 to 0.75). The conclusion was that the use of statins was related to the decreasing risk of myocardial infarction but not stroke. Systematic review displayed the benefits of statins in patients with COPD.[38]

A meta analysis from Randomized Controlled Trials covered 10 studies with 1,471 patients included in the inclusion criteria. The research results indicated that the use of statins was linked to the increase of exercise capacity and lung function. The score of St George's Respiratory Questionnaire (SGRQ) was compared to the placebo's. The analysis of subgroup indicated that statins were able to increase clinical outcome in the subjects from trials enrolling patients with overt cardiovascular disease (CVD), as well as to increase baseline C-reactive protein level or the high level of cholesterol level.[39]

6. Conclusion

Inflammation in COPD is caused by the release of inflammation mediators, the increase of inflammatory cells, e.g. neutrophils as well as the occurrence of oxidative stress induction. Statins have pleothropic effects which are able to modulate the amount of cholesterol so that they decrease fat formation stability within large amount which next continues to activation and regulation of immune cells. Besides, statins prevent prenylation from signaling molecules which later result in the decreasing expression of cytokine, chemokines and molecule adhesion with apoptosis cell effect or proliferation. Statins also have antioxidant effects because of their ability to scavenge oxygen from free radicals. The use of statins can be considered as an anti-inflammatory therapy in patients with COPD.

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