Journal of
Cardio - Thoracic Medicine

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Statins and pulmonary hypertension in chronic obstructive lung disease: A narrative review

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ARTICLE INFO

Article type:
Narrative Review

Article history:
Received: 2 August 2019
Revised: 24 Nov 2019
Accepted: 9 Feb 2020

Keywords:
Chronic Obstructive Lung Disease
Pulmonary Artery Hypertension
Statins

ABSTRACT

Chronic obstructive lung disease (COPD) is a chronic multisystem disease with a considerable burden. One of its most common complications is pulmonary artery hypertension (PAH). It has been demonstrated that the development of PAH is correlated with decreased quality of life and survival. Different medications have been proposed for the treatment of PAH, among which one can name statins. However, the same as other medications for the treatment of PAH, statins are still providing controversial results across different study settings. Moreover, the effect of statins on PAH in COPD patients has not been widely investigated so far. According to the present review, most of the available clinical trials demonstrated that the utilization of statins, including pravastatin, atorvastatin, and rosuvastatin may have beneficial effects on PAH in COPD patients. Nonetheless, it is necessary to conduct clinical trials with longer follow-up duration.

►*Please cite this paper as:*
Hejazi S. Mozdourian M. Statins and pulmonary hypertension in chronic obstructive lung disease: A narrative review. J Cardiothoracic Med. 2020; 8(1):565-570

Introduction

Chronic obstructive lung disease (COPD) is a multisystem disease that is mainly characterized by diminished pulmonary function and reduced forced expiratory volume in pulmonary function tests. Since the main presentation of COPD is historically summarized on pulmonary manifestations and lung tissue pathologies, the major therapeutic options available for this disease were restricted to inhalers (1). As the pathophysiology of COPD is becoming more clear, the importance of using systemic drugs are becoming more evident (1). The role of systemic and local inflammation has been recently elucidated in COPD resulting in the disruption of lung epithelial cell function (2, 3).

The COPD may have various complications which can affect its course. Pulmonary artery hypertension (PAH) is one of the common COPD complications which can worsen the

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prognosis of disease course (2). The development of PAH is based on various underlying pathologies happening during COPD. Furthermore, hypoxic pulmonary vasoconstriction alongside the vascular remodeling and disruption of lung epithelium lead to PAH (2).

Moreover, systemic and local inflammation have additive effects on the development of PAH in COPD settings (2, 3). As the underlying causes of PAH in COPD are uncovered, the novel therapeutic agents become more evident. Researchers have recently put their efforts in to investigating novel therapeutic approaches, including 5-HT receptor antagonists, stem cell therapy, and statins (4). Statins are among these medications which resulted in conflicting findings on the treatment of COPD complications, including PH. The present review aimed to evaluate the available clinical trials using statins as a therapeutic regimen for controlling PAH in COPD patients.

Statins: Common medications with a novel usage

Statins or hydroxymethylglutaryl coenzyme A reductase inhibitors are a group of drugs that are widely known due to their leading role in controlling low-density lipoprotein cholesterol (LDL-C) and triglycerides level as well as increasing high-density lipoprotein cholesterol (5). While LDL-C promotes inflammation, the lipid-lowering effect of statins may reduce inflammation. In addition, statins can reduce interferon-gamma and tumor necrosis factor-alpha production which inhibit the immunologic response (6). Moreover, it has been demonstrated that statins may have a beneficial effect on reducing mortality.

Taylor et al. reviewed early clinical trials on statins and demonstrated that these drugs could decrease both fatal and non-fatal cardiovascular events as well as reduce all-cause mortality (7). Since the introduction of statins in clinical trials, there are different types of this drug developed with different therapeutic potentials (8). The most noticeable difference among statins can be observed in their lipid-lowering potentials. For instance, pravastatin and simvastatin have fewerlipid-lowering potentials than newer statins, including rosuvastatin and atorvastatin (8).

The same as any other medications, statins have their unique side effects which can limit their use. The musculoskeletal complications include the development of muscle weakness and myopathy, diabetes, hepatic dysfunction, and diabetes mellitus(5). Even after more than two decades of introducing statins, many different clinical trials and systematic reviews are still providing controversial results regarding the effects of statin on the development or treatment of different chronic diseases (i.e., from psychiatric diseases to even cancers)(9-11). The PAH as a complication of COPD is an example of such topics that have conflicting results.

Pathophysiology of pulmonary artery hypertension and the possible role of statins

The PAH is defined as an increase in mean pulmonary artery pressure (PAP). Additionally, PAP depends on pulmonary vascular resistance, cardiac output, and pulmonary artery wedge pressure. Patients with COPD face hypoxia, and therefore, their lung becomes remodeled to overcome this hypoxic environment. The development of destructive changes in lung tissue and emphysema will be the highlight of these changes, which further result in increased pulmonary vascular resistance and PH(2, 4).

There are many different factors thatcan predispose a healthy lung epithelium into dysfunctional and damaged tissue resulting in the disturbance of pulmonary circulation (2). Although COPD patients tend to have lower nitric oxide production which will further result in increased proliferation and vasoconstriction, they have also elevated levels of inflammatory markers and cytokines resulting in increased inflammation in their lung tissue (2, 4). Statins may have beneficial effects on both COPD course and PAH in different ways. Improvements in HDL level and decreases in LDL level have beneficial effects on the cardiovascular system, thereby reducing adverse cardiac events (12).

The effects of statins on pulmonary artery pressure were first proposed in late 2010 (13). Since then, many studies havebeen investigated the efficacy of statin therapy on reducing pulmonary artery pressure in

various clinical settings, including COPD. Statins can provide anti-inflammatory and anti-oxidative effects which can be helpful in improving overall endothelial function in COPD patients developing polycyclic aromatic hydrocarbons (PAH)(2). Moreover, statins affect inflammatory pathways, including the NF-kB and STAT3 pro-inflammatory pathways which are thought to be important in the development of systemic and pulmonary inflammation (3).

Additionally, early animal studies demonstrated that statin therapy could reverse the pulmonary effects of smoking and PAH preventing the development of emphysema; however, it may have no effects on small airway remodeling (14). Lee et al. demonstrated that simvastatin could ameliorate both functional and structural changes in the lungs damaged by cigarette smoke. They revealed that simvastatin exerted its effect by suppressing the inflammation pathways and matrix metalloproteinase-9 induction (15). Another potential effect of statins can be made by modulation of endothelia. The endothelin-1 (ET-1) is a pulmonary vasoconstrictor thatis increased in COPD patients who develop PH. The patients who have increased levels of ET-1 are tended to develop vascular abnormalities in PAH (16). It should be noted that statins can reduce synthesis of ET-1 (16).

The final yet important potential therapeutic effects of statins are on lung stem cells in COPD patients. Endothelial progenitor cells even show reduced adhesion and migration capacities among these patients, which means a reduced repair capacity in the lungs. It has been shown that atorvastatin treatment can improve adhesion and migration capacities (17). Moreover, statins can reduce pulmonary artery pressure and improve endothelial function in chronic pulmonary heart disease (17).

Despite these mechanisms, there are still controversial results obtained from studies investigating the effects of statins on COPD patients. However, Shahmiri et al. demonstrated that statins could decrease systolic pulmonary artery pressure by their anti-inflammatory and anti-proliferative effects (18). On the other hand, some other studies revealed that statins might not have beneficial effects on non-COPD patients (13, 19, 20).

In the same line, Zeng et al. demonstrated that the consumption of atorvastatin10 mg once a day might not have beneficial effects on the natural history of PAH or even chronic thromboembolic pulmonary hypertension (19). According to a study conducted by Kawut et al., it was shown that the routine use of simvastatin might not have beneficial effects on controlling PAH. Furthermore, patients who received simvastatin 40 mg daily for 6 months tended to have a lower 6-minute walk test (20). In line with the results of the two aforementioned studies, Wilkins et al. also reported that simvastatin might only provide a transient beneficial effect on the right ventricle and N-terminal pro–B-type natriuretic peptide which would be vanished after a 12-month follow up (13).

Clinical trials on statins use in COPD patients with PH

The PAH has adverse effects on COPD and will decrease the patient's survival and functional capacity. The goal of every clinical study includes the reduction of exacerbations and the increase in exercise tolerance and survival. A recent large cohort study demonstrated that the utilization of statins might reduce the mortality of COPD patients (21).

Holzhauser et al. conducted a long term study on COPD patients with PAH. They demonstrated that the consumption of statins might not improve pulmonary artery hypertension though it could reduce mortality risk in those with severe PAH independent of COPD severity (21).

In contrast to other studies, this study used 60 mmHg as a cut-off point for PAH which was higher than that in other studies. Moreover, they did not mention the reason for using statins in their cohort study (21). Another small retrospective cohort study demonstrated that in severe COPD, statins could significantly reduce mean pulmonary artery pressure and pulmonary artery wedge pressure (22).

Table 1. Summary of clinical trials evaluating the effect of statins on COPD patients with pulmonary artery hypertension

Author	Year	COPD + PAH population/controls	Mean age (year) cases/controls	Intervention	Treatment duration (months)	Daily dose	Outcomes
Lee et al.	2009	27/26	71/72	Pravastatin	6	40 mg	Improved PH
Moosavi et al.	2013	24/21	65/68	Atorvastatin	6	40 mg	No significant effects on PH
Liu et al.	2013	33/35	66/64	Atorvastatin	6	20 mg	Improved PH
Chogtu et al.	2016	32/30	61/65	Rosuvastatin	3	10 mg	Direct PAP was not measured
Arian et al.	2017	21/21	65/63	Atorvastatin	6	40 mg	Improved PH

PAH: Pulmonary artery hypertension
PAP: Pulmonary artery pressure

Despite the presence of such cohort studies, when it comes to clinical trials, there would not be many studies evaluating the effect of statins on COPD patients with PH. The trials listed in Table 1 used statins as the therapeutic regimen among COPD patients with PH. Most of these studies did not mention their COPD treatment regimens and the duration of previous COPD or PAH therapies; however, they still provide valuable insights about the effect of statins in patients with PAH. Among 5 available clinical trials evaluating the effect of statins on PAH in COPD patients, only 3 studies demonstrated that statins could improve pulmonary artery pressure. On the other hand, one study revealed that statins might not affect PAH.

The first study was conducted by Lee et al. in 2009 (16). They showed that the consumption of pravastatin 40 mg once daily would ameliorate exercise limitation, PH, and dyspnea, thereby increasing the quality of life (16). Moreover, this study showed that pravastatin could reduce the urinary ET-1 level and improve patient's symptoms regardless of changes in blood pressure or lipid profile (16). In the same line, Liu et al. conducted a study with greater sample size, younger age, and the same duration used in a study performed by Lee et al. (17, 16).

Liu et al. demonstrated that pulmonary artery pressure would reduce significantly after 6 months of receiving 20mg atorvastatin, compared to control patients(17). Moreover, this study demonstrated that aggression and migration of endothelial progenitor cells would improve significantly after treatment with atorvastatin (17). The third study was performed by Arian et al. who showed the positive effect of atorvastatin on the PAH (21). This study was conducted within the same setting as the one carried out by Liu et al.; however, the atorvastatin dose was doubled in this study(21).

Despite the abundance of these studies, others have shown contradictory findings. According to the results of a study conducted by Moosavi et al., atorvastatin was well tolerated; however, no significant improvements were observed after taking 40 mg atorvastatin once daily among the COPD patients who developed secondary PH(23). On the other hand, different results were obtained from a similar study to the one conducted by Moosavi et al. in the same country with approximately the same population (23). The results of a study carried out by Arian et al. demonstrated that the same dose of atorvastatin in the same duration could improve pulmonary artery pressure (24).

The first difference between these studies can be attributed to the age of the control groups (23, 24). Moosavi et al. conducted their study on patients who were 3 years older than those who participated in a study

carried out by Arian et al. Moreover, the severity and duration of COPD werenot clearly stated in these studies which could be the other explanation for the presence of different results (23, 24). The last study was conducted by Chogtu B et al. without evaluating the pulmonary artery pressure (25). However, Chogtu B et al. demonstrated that their patients experienced improvements only in the peak expiratory flow rate not the other pulmonary function test parameters (25). Moreover, their exercise capacity, as well as COPD exacerbations improved along with no severe adverse drug reactions (25).

Limitations of the available clinical trials and future remarks

The effect of statins on COPD patients who developed PAH was not widely investigated in this study. Moreover, the effective dose and time interval of statin therapy were not clearly determined in the available clinical trials though they demonstrated that this therapy was well tolerated in COPD patients with PAH (23). All the available clinical trials had a small sample size and the longest follow-up period was6 months in these studies. Furthermore, some studies demonstrated that statins might only have transient beneficial effects that might disappear after 6 months (13). Additionally, regarding the statin groups, pravastatin, atorvastatin, and rosuvastatin were only investigated in this study. It has been demonstrated that every different statin from this family may have a specific effect that could be beneficial or even ineffective in PAH patients (8). Another specific issue that should be addressed in future studies is the potential differences among study population. Moreover, COPD duration and treatment, as well as the duration and severity of PAH were not clearly addressed in the studies. Therefore, they should be considered in further studies to obtain reliable results regarding the effectiveness of statins on COPD patients who developed PH. It is noteworthy to mention that some studies stated that the long-term safety of using statins is still under debt (5).

Conclusion

The present review demonstrated that the majority of the studies evaluating the effectiveness of statins in COPD patients who developed PAH provided favorable results interim of improving PH. Pravastatin, atorvastatin, and rosuvastatin are the medications evaluated for up to 6 months. It is recommended that further studies be conducted with greater sample size and longer follow-up duration.

Conflict of interest:

The authors declare that they have no competing interest.

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