Are statins beneficial for the treatment of pulmonary hypertension?

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Abstract

Pulmonary hypertension (PH) is a condition characterized by vasoconstriction and vascular remodeling with a poor prognosis. The current medical treatments available are supportive care therapy and pulmonary vascular-targeted therapy. Targeted treatments for PH include prostacyclin analogs, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors; however, these treatments cannot reverse pulmonary vascular remodeling. Recently, many novel treatment options involving drugs such as statins have been emerging. In this review, we attempt to summarize the current knowledge of the role of statins in PH treatment and their potential clinical effects. Many basic researches have proved that statins can be helpful for the treatment of PH both in vitro and in experimental models. The main mechanisms underlying the effects of statins are restoration of endothelial function, attenuation of pulmonary vascular remodeling, regulation of gene expression, regulation of intracellular signaling processes involved in PH, anti-inflammatory responses, and synergy with other targeted drugs. Nevertheless, clinical researches, especially randomized controlled trials for PH are rare. The current clinical researches show contrasting results on the clinical effects of statins in patients with PH. Carefully designed randomized, controlled trials are needed to test the safety and efficacy of statins for PH treatment.

Keywords: Pulmonary hypertension; Statins; Mechanism; Clinical effect

Introduction

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest by right-sided heart catheterization, and is characterized by vasoconstriction and vascular remodeling. Increased pulmonary vascular resistance and pulmonary artery pressures can lead to right ventricular hypertrophy and subsequently to death due to right-sided heart failure. According to the most recent classification, PH can be divided into five categories:
pulmonary arterial hypertension (Group 1); PH due to left heart disease (Group 2); PH due to lung diseases/hypoxemia (Group 3); chronic thromboembolic PH (CTEPH) (Group 4); and miscellaneous (Group 5). The pathogenesis of PH remains poorly understood to date, and it has a poor prognosis.

Being an orphan disease, pulmonary arterial hypertension is a therapeutic challenge. Although the available treatments are diverse, no therapy alone can reverse the disease process. The standard treatment options include oral anticoagulants, diuretics, oxygen supplementation, and calcium channel blockers. Targeted treatments such as prostacyclin analogs, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors, which mainly address the increased vascular tone, lack the ability to reverse pulmonary vascular remodeling. As the impact of targeted therapies on the secondary forms of PH is uncertain, the search for new therapeutic drugs is an urgent need. Researchers have turned to existing drugs, such as statins, to investigate their effects on PH.

Statins are often used to prevent cardiovascular disease and mortality in high-risk patients by lowering cholesterol levels via inhibition of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase). In addition, statins exhibit other effects such as improvement of endothelial function, modulation of inflammatory responses, prevention of thrombus formation, and antioxidant activity. It is known that inflammatory processes, oxidative stress, in situ thrombosis, and impaired endothelial function are involved in the pathogenesis of PH. Recently, many studies have focused on statins as important therapeutic agents for PH; therefore, in this review, we will focus on the pharmacological mechanism of statins and their clinical effects in the treatment of PH.

Possible mechanisms of statins in the treatment of PH

Previous experimental studies have concluded that statins are beneficial for the treatment of PH. The main underlying mechanisms are as follows.

Restoration of endothelial function

Endothelium can synthesize/release vasorelaxant and vasoconstrictor substances. The production of vasorelaxant substances are often decreased, while that of vasoconstrictor substances are increased in PH. Endothelial-derived nitric oxide (eNO) is an important vasorelaxant. It has been reported that statins can increase endothelial cell nitric oxide synthase (eNOS) activity, indicating that statins may have beneficial effects in PH treatment. Besides, statins induce pulmonary microvascular endothelial cell apoptosis via caspase-3 activation.

Attenuation of pulmonary vascular remodeling

PH is characterized by hypertrophy/hyperplasia and anti-apoptosis of the cells comprising the pulmonary vasculature (fibroblasts, smooth muscle cells, and endothelial cells). Smooth muscle cells are the principal cell constituents of the pulmonary vasculature. Simvastatin inhibits the proliferation of vascular endothelial and smooth muscle cells and attenuates pulmonary vascular remodeling in a PH model. In addition, simvastatin can induce the apoptosis of neo-intimal smooth muscle cells. Researchers have also proved that simvastatin inhibits the proliferation of pulmonary artery smooth muscle cells (PASMCs) via activating hemeoxygenase 1 (HO-1) and cyclin-dependent kinase inhibitor 1 (p21Waf1), and can therefore be beneficial in the treatment of PH. Mevastatin can arrest cell cycle and induce apoptosis of PASMCs via p27Kip1-independent pathway. Besides proliferation, migration is involved in vascular remodeling. Atorvastatin inhibits 5-hydroxytryptamine (5-HT)-induced PASMC migration via inhibition of Rho signaling. Pulmonary adventitial fibroblasts (PAF) also play an important role in the vascular remodeling process. It has been reported that fluvastatin selectively inhibits chronic hypoxia-induced PAF proliferation and reverses a proproliferative phenotype switch in PAF. Atorvastatin, fluvastatin, and simvastatin inhibit adventitial fibroblast proliferation in hypoxia-induced PH by offsetting p38 mitogen-activated protein kinase (MAPK) activity.

Regulation of gene expression

Simvastatin inhibits the expression of genes involved in the pathogenesis of PH, which was identified by genome array. Bone morphogenetic protein receptor type 2 (BMPR2) mutation is a risk factor for the development of familial primary PH. Simvastatin attenuated PH by upregulating BMPR2 expression. The expression of 5-hydroxytryptamine transporter (5-HTT) is upregulated in PH. Atorvastatin can downregulate 5-HTT expression, thereby preventing monocrotaline (MCT)-induced PH. Simvastatin prevents
MCT-induced PH via upregulating GATA-6 expression, which plays an important role in cell proliferation resulting in vascular remodeling.27

Regulation of intracellular signaling processes involved in PH

Statins can regulate several known signaling pathways involved in PH. Statins inhibit RhoA/Rho-kinase signaling pathway, which plays a key role in various models of PH.28,29 In MCT-induced PH and chronic hypoxia-induced PH, simvastatin activates HO-1 pathway to prevent PH.30,31 Pravastatin suppresses stromal cell-derived factor-1 (SDF-1)/CXCR chemokine receptor 4 (CXCR4) and intercellular cell adhesion molecule-1 (ICAM-1)/CD18 pathways to ameliorate hypoxia-induced PH.32 Bone morphogenetic protein (BMP) signaling also plays an important role in maintaining the normal structure of pulmonary vasculature through the pro-apoptotic and anti-proliferative effects of BMP. Simvastatin induces BMPR-II signal transduction to prevent MCT-induced PH.33 The upregulation of NF-κB signaling is crucial in the development of PH, and statins can inhibit NF-κB activity.34,35 Akt/eNOS cellular signal transduction pathway plays a role in the pathogenesis of PH. Rosuvastatin attenuates MCT-induced PH by regulating Akt/eNOS signaling pathway and asymmetric dimethylarginine (ADMA)/dimethylarginine dimethylaminohydrolase 2 (DDAH-2) metabolism, which is an endogenous inhibitor of NOS.36 In aortic-banded rat PH model, simvastatin decreased the levels of plasma brain natriuretic peptide, endothelin-1, reactive oxygen species (ROS), and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 regulatory subunits, and upregulated the pulmonary expression of phospho-eNOS, NOx, and cyclic guanosine monophosphate (cGMP), resulting in decreased mPAP.37 In carotid artery-jugular vein shunt model of PH in rats, shunt induced the expression of matrix metalloproteinases, which was reversed by simvastatin.38

Anti-inflammatory responses

Inflammation has been demonstrated to play a significant role in PH.39,40 Statins can modulate inflammatory responses. A previous study showed that simvastatin prevented MCT-induced PH by down-regulating inflammatory factors such as interleukin (IL)-6, tumor necrosis factor (TNF)-alpha, and monocyte chemotactic protein (MCP)-1.41 In vitro experiments have shown that atorvastatin inhibits C-reactive protein (CRP)-induced IL-6 and MCP-1 production.42

Synergy with other targeted drugs

PH management requires targeted medical treatment. The most commonly used drugs are prostacyclin analogs, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors. Sildenafil is a phosphodiesterase type 5 inhibitor, whose treatment effect can be enhanced by combining with simvastatin.43,44 The effect of another phosphodiesterase type 5 inhibitor tadalafl can be strengthened by combining with simvastatin in a rat model of MCT-induced PH.45 The combined use of beraprost sodium (prostacyclin analogs) and simvastatin show beneficial effects in the treatment of MCT-induced PH, and the efficacy of this combination therapy is superior to that of the monotherapy.46 Simvastatin when used in combination with pinacidil, a potassium channel opener often used to lower systemic blood pressure, noticeably reverses MCT-induced PH.47 In 2003, a randomized controlled trial (RCT) demonstrated that imatinib improves exercise capacity and hemodynamics in patients with advanced PH by inhibiting platelet-derived growth factor signaling; however, serious adverse events and study drug discontinuation were observed.48 A recent research confirmed that combination of statins with imatinib showed an enhanced effect in PH treatment, and statins can improve imatinib safety.49 Combining drugs of different mechanisms to achieve greater therapeutic effects is beneficial for PH treatment. Therefore, combining statins with prostacyclin analogs, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors should be considered a possible therapeutic strategy. Another study showed no additive effects when statins were used in combination with sildenafil;50 thus, further studies are needed to assess the effects of combination therapy on PH.

Effects of statins in PH animal models

The safety and efficacy of statins for PH have been recently verified in vivo. Overall, the results are promising because of the pleiotropic effects of statins. Almost all in vivo experiments showed that statins were effective against PH. In a smoking-induced chronic obstructive pulmonary disease (COPD)-related PH rat model, simvastatin significantly inhibited smoking-induced increase in mPAP via up-regulation of eNOS expression.51 In addition, it has been reported that simvastatin reversed the pulmonary vascular effects of cigarette smoke and prevented smoke-induced emphysema.52 A significant elevation in mPAP, right ventricular hypertrophy index (RVHI), and percentage
of wall thickness (WT%) and wall area (WA%), a significant reduction in animal body weight, and an increase in circulating 5-HT and 5-HTT expression in the lung were observed in a cigarette smoke-induced PH rat model. Simvastatin reversed the above effects induced by cigarette smoke.\(^{53}\)

Several studies reported that statins prevented PH in MCT-induced PH rat models.\(^{30,34–59}\) Rosuvastatin can ameliorate remodeling of pulmonary arteries in MCT-induced PH rats.\(^{60}\) Rho-kinase inhibitors improved PH in experimental and clinical studies. In MCT-induced PH rats, rosuvastatin intensified the beneficial effects of Rho-kinase inhibitor on the Rho/Rho-kinase pathway, which reversed the MCT-induced increase in right ventricle pressure, thereby leading to a more prominent reduction in right ventricular hypertrophy.\(^{61}\) A previous study reported that statins could not improve MCT-induced PH. The study showed that rapamycin (2.5 mg·kg\(^{-1}\)·d\(^{-1}\), gavage), an anti-proliferative agent, or rapamycin (2.5 mg·kg\(^{-1}\)·d\(^{-1}\), gavage) plus atorvastatin (10 mg·kg\(^{-1}\)·d\(^{-1}\), gavage) therapy for 12 days could not significantly reduce the mPAP and cardiac index. However, simvastatin (2 mg·kg\(^{-1}\)·d\(^{-1}\), gavage) treatment for 2–4 weeks significantly improved pulmonary hemodynamics and right ventricular hypertrophy.\(^{62}\) The negative results of atorvastatin treatment may be due to the relatively short duration of the therapy.

In pulmonary hypertensive transgenic (mRen2)\(^{27}\) rats, rosuvastatin attenuated the elevated right ventricular systolic pressure.\(^{63}\)

In chronic hypoxia-induced PH rats, simvastatin reduced PH and right ventricular hypertrophy by activating the HO-1 pathway.\(^{30}\) Simvastatin was effective against chronic PH in newborn rats. Newborn Sprague–Dawley rats were exposed to either normoxia (room air) or normobaric hypoxia (13% O\(_2\)) for 3 weeks. The rats received simvastatin [2 mg·kg\(^{-1}\)·d\(^{-1}\), intraperitoneal (i.p.)] or vehicle from postnatal days 1–14 (prevention protocol) or from days 14–21 (rescue protocol). The results showed that preventive or rescue treatment with simvastatin decreased pulmonary vascular resistance, right ventricular hypertrophy, and pulmonary arterial remodeling via inhibition of RhoA/Rho-kinase activity.\(^{64}\)

Statins are also effective in Group 2 PH animal models. In aortic-banded rats with PH, simvastatin attenuated mPAP and pulmonary arteriolar remodeling through Rho-kinase pathway and NADPH oxidase.\(^{37}\)

Following simvastatin treatment, Rho kinase, Rho-associated protein kinase (ROCK) I, ROCK II, and endothelin-1 were downregulated in the lung, while the expression of cGMP, NOx, and phosphorylated -eNOS were upregulated. In addition, simvastatin attenuated the upregulation of ROS. In a carotid artery-jugular vein shunt PH rat model, administration of simvastatin (4 mg·kg\(^{-1}\)·d\(^{-1}\)) for 12 weeks reduced shunt-induced right ventricular systolic pressure and medial area/total area in pulmonary arteries.\(^{38}\)

**Clinical efficacy of statins for PH patients**

PH animal models do not completely display the severity of PH observed in humans with respect to both histological and hemodynamic parameters;\(^{65}\) therefore, mixed results have been reported on the efficacy of statins in patients with PH (Table 1).

| References | Study type | Number of patients (statins + vs. −) | PH category | Statin type | Statin dose | Clinical efficacy |
|------------|------------|-----------------------------------|-------------|-------------|-------------|------------------|
| 66         | Observational study | 16\(^{a}\) | Group 1 | Simvastatin | 20 to 80 mg/d | Valid |
| 67         | Cross-sectional analysis | 34 vs. 78 | Group 3 | N/A | N/A | Valid |
| 68         | Retrospective, observational study | 12\(^{a}\) | Group 1 & 3 | Simvastatin | 0.09–0.28 mg·kg\(^{-1}\)·d\(^{-1}\) | Valid for 3–36 m |
| 69         | Retrospective study (propensity score matching) | 138 vs. 624 | Group 3 | N/A | N/A | Valid |
| 70         | Randomized controlled trial | 30 vs. 30 | Group 1 | Rosuvastatin | 10 mg/d for 6 m | Valid |
| 71         | Randomized controlled trial | 32 vs. 30 | Group 3 | Rosuvastatin | 10 mg/d for 6 m | Valid |
| 72         | Randomized controlled trial | 27 vs. 26 | Group 3 | Pravastatin | 40 mg/d for 6 m | Valid |
| 73         | Randomized controlled trial | 19 vs. 23 | Group 1 | Simvastatin | 80 mg/d for 6 m | Valid for NT-proBNP |
| 74         | Randomized controlled trial | 32 vs. 33 | Group 1 | Simvastatin | 40 mg/d for 6 m | Invalid |
| 75         | Randomized controlled trial | 112 vs. 108 | Group 1 & 4 | Atorvastatin | 10 mg/d for 6 m | Invalid |
| 76         | Randomized controlled trial | 24 vs. 21 | Group 3 | Atorvastatin | 40 mg/d for 6 m | Invalid |
| 77         | Randomized controlled trial | 33 vs. 35 | Group 3 | Atorvastatin | 20 mg/d for 6 m | Valid |

PH: pulmonary hypertension; N/A: not applicable; NT-proBNP: N-terminal pro-brain natriuretic peptide.

\(^{a}\) Number of patients treated with statins.
An open-label observational study conducted in 2005 evaluated the effect of simvastatin on PH and showed that simvastatin was safe and effective in patients with PH. Sixteen patients with primary and secondary causes of PH were included in the study. Simvastatin treatment (20–80 mg/d) improved exercise tolerance and cardiac output, decreased the right ventricular systolic pressures, and showed no evidence of toxicity. Combination treatment of simvastatin and epoprostenol showed additive effects. A cross-sectional study analyzed 112 patients with severe COPD for lung transplantation using hemodynamics data from 1995 to 2009. Thirty percent of patients receiving statin therapy (the drug regimen was not introduced in the paper) showed that statin use was associated with a decrease of 5.2 mmHg in mPAP. Statin non-use was the only significant determinant of mPAP in the univariate analysis. An observational study reviewing 12 children with PH treated with simvastatin (0.09–0.28 mg·kg\(^{-1}\)·d\(^{-1}\)) demonstrated that simvastatin may decrease pulmonary arterial pressure in patients with alveolar hypoxia-induced PH. In 2017, a retrospective study analyzed the effect of statin therapy for 12 consecutive months after the diagnosis of PH in 138 patients and found that all-cause mortality was significantly lower in the statin group than in patients who were not on statin therapy.

There are few RCTs, especially carefully designed randomized, controlled trials, of statin therapy in patients with PH available, and the clinical effect of statins is still unclear. Barreto et al designed a placebo-controlled study to investigate the effects of rosuvastatin (10 mg/day, orally, 6 months) vs. placebo on vascular dysfunction markers in 60 patients with idiopathic PH and congenital heart disease-associated PH. The plasma levels of vascular dysfunction markers, such as and tissue-plasminogen activator, decreased in the rosuvastatin group. Postexertional peripheral oxygen saturation improved, but no increase in the 6-min walking distance (6MWD) was observed. Another RCT study evaluated the effect of rosuvastatin in patients with COPD-related PH. Patients in the rosuvastatin group received rosuvastatin 10 mg once a day for 12 weeks, and a significant increase in 6MWD was observed. In a double-blind parallel design study, 53 COPD patients with PH were randomly assigned to receive either placebo or pravastatin (40 mg/day) for over 6 months. The results showed that exercise time increased significantly, systolic pulmonary artery pressure decreased, and the Borg dyspnea score improved significantly in the pravastatin-treated group. Wilkins et al designed a RCT study to verify the effect of simvastatin on PH. They recruited 42 patients (23 received placebo and 19 received simvastatin, 80 mg/d). After 12 months, a transient early reduction of right ventricular mass index and N-terminal pro-brain natriuretic peptide (NT-proBNP), which did not last for 12 months, was observed in the simvastatin-treated group. However, there were no significant changes in the 6MWD, cardiac index, and circulating cytokines. A phase II clinical trial was conducted to test whether simvastatin shows beneficial clinical effects in patients with PH. The results of the clinical trial showed that simvastatin (40 mg/d) had no significant effect on 6MWD at 6 months. Recently, some studies showed that atorvastatin (10 or 40 mg/d) administered over a 6-month period had no beneficial effects on PH or CTEPH or COPD-related PH. Another RCT study showed that atorvastatin (20 mg/d, 6 months) improved the migration and adhesion of endothelial progenitor cells and reduced pulmonary artery pressure in patients with chronic pulmonary heart disease.

The published meta-analysis of clinical trials showed that statins have no effect on PH. The RCT studies included in the following three meta-analysis studies have been mentioned above. Anand et al analyzed four high quality RCTs and found that statins were not beneficial in the treatment of PH. When PH patients were treated with statins, no improvement in mortality, 6MWD, and cardiac index was observed. The other meta-analysis, which included eight studies, comprising 665 patients, showed no improvement in many clinical indices, such as 6MWD, pulmonary arterial pressure, right atrial pressure, cardiac index, and pulmonary vascular resistance, in patients treated with statins. In 2017, Zhang et al reviewed six RCT studies comprising 249 patients (Group 1, Group 3, and Group 4) who received statin treatment and 247 patients who received placebo. The exercise capacity and hemodynamic parameters of the patients did not improve.

The mixed results of clinical studies and the invalid results of meta-analysis may be due to the following possible reasons. First, the dosage, course and type of statins were different in the included studies. Second, most patients recruited to the studies were in a stable condition or in early-stage, and they did not belong to the same category. Third, negative results may be due to inadequate sample size because most of the studies included very few patients. Fourth, as PH is a chronic disease, the follow-up time in the studies may be short; therefore, a valid result cannot be obtained in a limited time.
Conclusions

Because of the pleiotropic effects of statins and the complicated pathogenesis of PH, statins have recently been evaluated for their effects in the treatment of pulmonary arterial hypertension. Overall, statins have been shown to both prevent and attenuate PH in vitro and in animal models; however, its potential therapeutic benefits for PH patients remain to be assessed. Therefore, well-designed RCTs are required to assess the long-term clinical impact of statin therapy.

Conflicts of interest

No conflicts of interest, financial or otherwise, are declared by the authors.

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