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Perspective

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) $\geq$ 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.[1] According to the most recent classification, PH can be divided into five categories:

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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).[2] The pathogenesis of PH remains poorly understood to date, and it has a poor prognosis.[3]

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,[4,5] 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,[6–8] 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.[9]

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.[10] 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.[11] Besides, statins induce pulmonary microvascular endothelial cell apoptosis via caspase-3 activation.[12]

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).[13,14] 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.[15,16] In addition, simvastatin can induce the apoptosis of neointimal smooth muscle cells.[17] 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 ($p21^{Waf1}$), and can therefore be beneficial in the treatment of PH.[18] Mevastatin can arrest cell cycle and induce apoptosis of PASMCs via p27Kip1-independent pathway.[19] Besides proliferation, migration is involved in vascular remodeling. Atorvastatin inhibits 5-hydroxytryptamine (5-HT)-induced