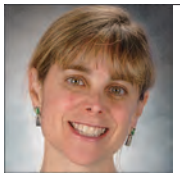
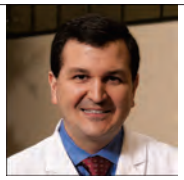
Simvastatin as a Treatment for PAH



Section Editor
Deborah Jo Levine, MD



Section Editor
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The Clinical Trials Update highlights new and ongoing research trials that are evaluating therapies for pulmonary arterial hypertension. In this issue, Deborah Jo Levine, MD, describes a recent trial of simvastatin.

Both researchers and clinicians have shown a significant amount of interest in the potential benefit of HMG-CoA reductase inhibitors (statins) for the treatment of patients with pulmonary arterial hypertension (PAH). The statins, in addition to having cholesterol-lowering benefits, have been shown to possess potent antiproliferative, antithrombotic, and antiinflammatory cardiovascular properties. Statins have been reported to suppress endothelial and vascular smooth muscle cell responses to injury in animal models. Over the last several years, a series of investigations in animal models of pulmonary hypertension (both the hypoxic-and monocrotaline-rat models) have provided data suggesting possible potential therapeutic benefit for patients with PAH.

In this issue of the Clinical Trials Update, we review the multicenter trial by Wilkins et al,[1] which looks into the addition of simvastatin as a treatment for PAH in patients with class II and III symptoms who are already stable on oral therapy. The authors conducted a double-blind, randomized, placebo-controlled trial evaluating the effects of simvastatin added on to optimized therapy in patients with idiopathic PAH (IPAH), associated PAH (APAH) with connective tissue disease, or atrial septal defects (ASDs). Patients were either on a stable dose of phosphodiesterase type-5 (PDE-5) inhibitors or endothelin receptor antagonist or both, plus background therapy. Patients were randomized to receive either simvastatin or placebo for 24 weeks and after that were offered open label simvastatin (40 mg po QD and then titrated up to 80 mg po every day).

The primary outcome measure studied was the change in right ventricular (RV) mass and function, assessed by cardiac MRI. Secondary end points included change in 6-minute walk distance; plasma NO metabolites and cytokines levels as well as biomarkers (NT-proBNP and growth factor-15 [GDF-15]). Quality of life was documented using the Cambridge Pulmonary Hypertension Outcome Review. BORG dyspnea scale was used post 6-minute walk.

At 6 months, the RV mass was shown to decrease in the statin group by 5.2 +/- 11 g ($P=0.045$) while the RV mass increased in the placebo group by 3.9 g +/- 14 g. The NT-proBNP significantly decreased during the initial 6 months in the statin group but not in the placebo group. There were no significant changes in other outcome measures (including the 6-minute walk, cardiac index, and cytokines).

From 6 to 12 months, both the RV mass and the NT-proBNP increased back toward baseline in the patients who had been started on the statin and continued on the statin so that there was no longer a difference from baseline. Patients who were started on the statin after placebo showed a stable RV mass and NT-proBNP. As in the first 6 months, there were no significant differences in the secondary outcomes between the 2 groups. There was not a significant reduction in the quality of life score between the patients on the statin and those on the placebo.

In this study, the addition of simvastatin to the treatment of patients with IPAH/hereditary PAH (HPAH) and PAH associated with ASD or connective tissue disease was associated with this reduction in RV mass and NT-proBNP in the first 6 months, but these improvements were not sustained over 12 months.

This study had some limitations. It was a relatively small study. The fact that the statin was added to stable patients who were already on 1 or 2 different classes of treatment (PDE-5 inhibitors and endothelin receptor antagonists) made this small group difficult to interpret. These drugs may all interact with each other as they are all substrates for CYP3A4, which would make this even more difficult to evaluate. A larger study looking at each one individually to evaluate the effects they have on each other would be of interest.

This study's primary outcome was RV mass. The question arises on how this relates clinically to patients with PAH and the outcomes to which it relates. Even with the decrease in the RV mass, there were no significant changes in the clinical secondary outcomes. Also, as the authors point out, there were no data on the changes in pulmonary vascular resistance and therefore no way to evaluate whether the reduction in RV mass was secondary to a reduction in the resistance.

This study brings up many questions on how the statins may be used in patients with pulmonary hypertension in the future. It provides a launching pad to begin considering how best to study this class of drug in larger and possibly longer studies.

1. Wilkins MR, Ali O, Bradlow W, et al; Simvastatin Pulmonary Hypertension Trial (SiPHT) Study Group. Simvastatin as a treatment for pulmonary hypertension trial. *Am J Respir Crit Care Med*. 2010;181(10):1106-1113.

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