

IRB Protocol: Simvastatin Therapy for WHO Group III Pulmonary Hypertension

A. Study Purpose and Rationale:

Pulmonary hypertension is a disease associated with heterogeneous underlying etiologies. The most recent clinical classification by the World Health Organization (WHO) classifies pulmonary hypertension (PH) into 5 groups (1). Many clinical trials have been conducted for Group I PH, but the purpose of this study is to evaluate subjects with WHO Group III PH, which includes pulmonary hypertension associated with lung disease and/or hypoxia, as seen in chronic obstructive pulmonary disease (COPD), interstitial lung disease, alveolar-hypoventilation disorders, sleep disorders, and chronic exposure to high altitude. Of note, the prevalence of PH in COPD may range from 30-70% and we anticipate many of our study participants will have COPD (2). Although there have been recent breakthroughs in advanced therapy for PH, those therapies are most appropriate for WHO Group I PH unresponsive to standard therapy which may involve diuretics, calcium channel blockers, and anticoagulation. Advanced therapy is not currently recommended as first line therapy for WHO Group III PH. However, Group III PH, especially COPD associated PH remains an important health problem because of the increased risk of hospitalization and the decreased 5-year survival associated with the development of PH (3). Currently, the cornerstone of therapy for PH associated with COPD remains long term oxygen therapy to slow the progression of disease, though PH does not completely reverse (2, 3).

Previously, COPD associated PH was thought to be primarily a consequence of hypoxic pulmonary vasoconstriction. More recently, investigators have made compelling arguments for the pathogenic roles of pulmonary vascular remodeling and airway remodeling exacerbated by cigarette smoke, oxidative damage, endothelial dysfunction, and inflammatory changes (3). With these new insights, investigators are searching for agents, including statins, with potential to interact with the pathways speculated to be involved in the inflammatory cascade and vascular remodeling seen in-vitro and in animal models.

Statins have been documented in-vitro to have effects on endothelial nitric oxide synthase, which may effect pulmonary vasculature (4). Moreover, statins used in animal models of hypoxia and cigarette smoke induced PH have been shown to improve pulmonary hypertension (5) (6). With respect to human subjects, statins have been involved in many cardiovascular clinical trials and remain a commonly prescribed class of medication for lowering cholesterol. The most important recent clinical trials involving statins include a RCT examining simvastatin in PAH, with reduction in RV mass as the primary outcome (7). Although the study did not achieve statistical significance in any outcomes, this study did not evaluate pulmonary hypertension associated with lung disease or hypoxia. Another recent trial in Taiwan evaluated pravastatin's effect on functional capacity in subjects with COPD and PH. This trial hypothesized that endothelin-1 (ET-1), a potent pulmonary vasoconstrictor and vascular cell proliferator, could be attenuated with pravastatin, and would result in improved functional capacity as measured by improvement in exercise time on a treadmill at 6 months (8). The study was notable for showing improvements in exercise treadmill time (Naughton protocol) and Borg dyspnea scores. The findings are impressive, but the prognostic value of exercise treadmill time may be more difficult to interpret and to compare with the previous important trials which used 6MWT as the primary outcome. Nonetheless, it is conceivable that statin therapy may be an effective treatment for Group III PH based on cell culture, animal models, and recent clinical trials.

Hypothesis: In patients with WHO Group III pulmonary hypertension, simvastatin treatment will improve exercise capacity compared with placebo.

B. Study Design and Statistical Analysis

This study will be a double-blind, randomized, placebo controlled trial involving patients classified with WHO Group III Pulmonary Hypertension, conducted at Columbia University Medical Center. They will be randomly assigned either to the statin treatment group (40mg Simvastatin daily) or to placebo. Double blinding of patients and physicians will be used to minimize bias. The pills that both groups receive will appear the same in color, size, shape, and taste.

Each group will contain 110 subjects. The primary outcome will be improvement in the 6 minute walk test (without encouragement) from baseline, measured in meters at 12 months. Several previous clinical trials have used the 6MWT as the primary outcome because it has prognostic implications. The current, accepted, clinically significant change in 6MWT is 54m. However, there is ongoing debate whether a lower number, such as 35m is a clinically significant difference, especially in COPD (9). Our secondary outcomes will assess for changes in pulmonary artery pressure and Borg dyspnea score.

A two-sample t-test will be used to compare the mean change from baseline in 6MWT in the two groups at various time points. The analysis will be based on intention to treat. We determined that 98 subjects were needed in each group for 90% power to detect a mean difference of 35 meters from baseline, assuming a standard deviation of 75m (previous PAH trials have used a standard deviation of 75m), with type I error 0.05 (two-sided) (10, 11). However, 220 total subjects will be enrolled to account for possible attrition.

Similarly, the two-sample t-test will also be used to calculate the mean change in baseline pulmonary artery pressure and Borg dyspnea score.

C. Study Procedure

The likely duration of the entire study, including recruitment, will require 2-3 years. The study subjects will participate over a course of 12 months. A physician evaluation followed by the 6-minute walk test (6MWT) will be performed prior to randomization, at week 12, 6 months, and 12 months. The 6MWT is an assessment of functional exercise capacity in COPD and pulmonary hypertension. The participant attempts to walk as far as possible along a corridor (of at least 30 meters) in 6 minutes on a flat, hard surface. Participants are allowed to stop and rest during the 6MWT if they experience discomfort. In addition, pts will also receive a transthoracic echo (TTE) prior to randomization and at the conclusion of the study. The TTE is a noninvasive test and can be useful for estimating pulmonary artery pressure. The timing of the 6MWT prior to randomization, 12 weeks, 6 months, and 12 months do not violate any standard clinical care. Patients will also have their lipid panel obtained prior to randomization and at the conclusion of the study. A hepatic function panel will also be collected prior to randomization and potential statin therapy.

D. Study Drugs*

Simvastatin (Zocor) will be administered in the treatment group. It is an FDA approved drug for hypercholesterolemia, dyslipidemia, and reductions in risk for CHD mortality and cardiovascular events. Statins have been used in many clinical trials, with over 20,000 people who have been tested with this class of medication (12). Although generally regarded as a safe medication, there is a risk of myopathy that can progress to rhabdomyolysis. According to the manufacturer, approximately 0.9% may develop myopathy and 0.2% may develop rhabdomyolysis when simvastatin is taken at a dose of 80mg. Another risk is liver toxicity, though that has occurred in less than 2% of clinical trials involving statins(12).

This study aims to investigate the potential therapeutic effect of simvastatin, separate from the cholesterol lowering properties. Simvastatin has been shown to improve pulmonary hypertension in animal models and has been the subject of several clinical studies(6, 7, 13-15). In our proposed clinical trial, study subjects will receive 40mg of simvastatin daily by mouth. The dose, oral route of administration, and frequency do not differ from standard use. The duration of treatment over 12 months is not beyond the limits of standard use.

E. Medical Device

Not applicable

F. Study Questionnaires

The Modified Borg Scale will be used during each 6MWT to assess baseline dyspnea and fatigue prior to walking and at the conclusion of the 6MWT. Research assistants trained to follow the American Thoracic Society guidelines for performing a 6MWT will administer the Modified Borg Scale (16). Below is a sample of the questionnaire.

“Please grade your level of fatigue using this scale. Please grade your level of shortness of breath using this scale.”

The Modified Borg Scale

- 0 Nothing at all
- 0.5 Very, very slight (just noticeable)
- 1 Very Slight
- 2 Slight (light)
- 3 Moderate
- 4 Somewhat severe
- 5 Severe (heavy)
- 6
- 7 Very Severe
- 8
- 9
- 10 Very, very severe (maximal)

G. Study Subjects

Inclusion Criteria:

WHO Group III pulmonary hypertension
Mean Pulmonary Artery Pressure \geq 25mm Hg at rest or \geq 30mm Hg during exercise, confirmed with prior cardiac catheterization
WHO functional class II-IV
Baseline 6MWT \geq 100m

Exclusion Criteria:

Idiopathic PAH
Familial PAH
PAH associated with collagen vascular disease, HIV, drugs, or toxins
Age $<$ 18
Unable to perform 6 minute walk test
Clinical instability or recent hospitalization within past 30 days
Baseline 6MWT $>$ 600m
Use of a statin within the past year prior to study enrollment
Use of advanced therapy including sildenafil, bosentan, iloprost, or any experimental medication within the past 30 days of study enrollment
Scheduled by primary physician to start advanced therapy
Active hepatitis with transaminitis $>$ 3 times the upper limit of normal.
Allergy to statins

H. Recruitment of Subjects

Study subjects will be identified and recruited by their primary physician, who will be affiliated with Columbia University Medical Center. Other patients will be recruited via flyers, but their primary physician will be informed of possible enrollment and must approve prior to participation.

I. Confidentiality of Study Data

All study data will be coded. A unique code number will be used for all study subjects. Data will be stored at the Columbia University Medical Center, accessible only to the investigators.

J. Potential Conflict of Interest

No conflicts of interest.

K. Location of the Study

Department of Medicine, Columbia University Medical Center

L. Potential Risks

The risk of myopathy and rhabdomyolysis exists with statin treatment. Hepatotoxicity and transaminitis are additional risks. The study treatment will not preclude current standard treatment, which consists of long term supplemental oxygen therapy.

M. Potential Benefits

Study subjects may or may not benefit from the participation in this study. It is conceivable that study subjects in the statin treatment group will experience improved exercise function and decreased dyspnea. The potential benefits to society include validating a new treatment for Group III PH that is relatively inexpensive, well tolerated, and will impact functional activity.

N. Alternative Therapies

Alternative therapies include use of the advanced therapy medications that are used for WHO Group I Pulmonary Hypertension. These therapies are not indicated for Group III PH, and generally not considered unless current standard of care fails and patient continues to deteriorate.

O. Compensation to Subjects: Not applicable.

P. Costs to Subjects: None

Q. Minors as Research Subjects: Not applicable

R. Radiation or Radioactive Substances: Not applicable

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