Clinical Trial Proposal Form

Study Title:
Pulmonary Rehabilitation in COPD: response to inhaled Treprostinil (Tyvaso)

Investigator/s:
Principal Investigators
Steven Nathan, MD
Christopher King, MD

Co-Investigators
Gerilynn Connors
James Lamberti, MD
Shahzad Ahmad, MD
Oksana Shlobin, MD
Whitney Brown, MD

Coordinators
Edwinia Battle, RN
Lori Schlegel, RN
Renee Brenner, BS
Merte Lemma, BS
Stephanie Garofalo, RN

Name/Address of Institution:
Inova Fairfax Hospital
3300 Gallows Rd
Fall Church, VA 22042

Date of First Request for Support:
2013

Study Hypothesis:
Our hypothesis is that pretreating patients with COPD with inhaled treprostinil prior to pulmonary rehabilitation sessions will result in improved exercise tolerance during sessions. This in turn will lead to an increased response to pulmonary rehabilitation, resulting in improved exercise tolerance and quality of life.

Study Background:
Pulmonary rehabilitation (PR) is a widely accepted intervention in patients with advanced COPD. This has consistently been shown to improve patients' quality of life and functional ability. Indeed, enrollment and completion of a course of PR is a prerequisite prior to major interventions such as lung volume reduction surgery or transplantation. A typical course of PR includes 20 sessions of supervised exercise and educational activity over an 8 week period. Sessions are usually held three times per week and last between 2-3 hours each. Most patients with COPD will have a ventilatory limitation to exercise and

while many are oxygen dependent, a minority of patients will have a true hypoxic limitation to exercise. Nonetheless, when patients with COPD are ambulated on oxygen they feel better and walk further. Indeed, supplemental oxygen remains one of the few interventions that have been demonstrated to be associated with improved survival in patients with COPD.

There have been a few studies and case reports utilizing inhaled pulmonary vasodilators in patients with COPD, although none to date have used treprostinil. One study of 10 patients with COPD and pulmonary hypertension found improved gas exchange and exercise tolerance following using of inhaled iloprost an alternative inhaled pulmonary vasodilator. No adverse effects were observed. [Dernaika TA, Beavin M, Kinasewitz GT. Iloprost improves gas exchange and exercise tolerance in patients with pulmonary hypertension and chronic obstructive pulmonary disease. Respiration; 2010: 79(5): 377-382.)] A case report of a patient with pulmonary hypertension and COPD found sustained improvements in exercise tolerance with regular use of inhaled iloprost. [Hegewald MJ, Elliott CG. Sustained improvement with iloprost in a COPD patient with severe pulmonary hypertension. Chest 2009; 135(2): 536-537.]

While these limited trials support the concept of physiologic improvement with use of inhaled pulmonary vasodilators in COPD, our study differs from these in several important ways. This study is unique in that there has never been a prior similar study of medication pretreatment prior to PR to enhance exercise performance in any patient subgroup. Furthermore, treprostinil has not yet been evaluated for use on an as needed basis.

Indication Studied:
COPD/Pulmonary rehabilitation

Study Objectives:

- Primary Objective: To determine the effect of inhaled treprostinil, administered prior to pulmonary rehabilitation sessions, on the six minute walk test distance (6MWT) in COPD patients after completing an 8 week course of pulmonary rehabilitation
- Secondary Objectives: To assess the effect inhaled treprostinil, administered prior to pulmonary rehabilitation in COPD patients, on secondary outcomes including quality of life (as measured by the St. George's respiratory questionnaire, Clinical COPD Questionaire), BODE index, lowest nadir of oxygen saturation on 6 minute walk test, number of exacerbations, ER visits, hospitalizations, and change in measures of strength training.

Trial Design:

An adaptive, prospective, randomized, double-blind, placebo-controlled study of 34 patients with advanced COPD who have been referred for pulmonary rehabilitation. All patients will have a six-minute walk test (6MWT). They will then receive 3 puffs of tyvaso and repeat the 6MWT on the same amount of oxygen as the initial test was performed on. Patients who have a worsened desaturation on 6MWT following the test dose will be screened out. Patients will be randomized to receive one dose (3 puffs) of inhaled treprostinil or placebo prior to each of their exercise sessions. All patients will be pretreated with albuterol prior to the dose of inhaled treprostinil (or placebo).

Patient Population:

We plan to screen 50 patients with a goal of enrolling 34 patients. Patients referred for pulmonary rehabilitation at Inova Fairfax Hospital with moderate to severe COPD as a primary diagnosis will be screened for inclusion in the trial. Inclusion and exclusion criteria are listed below.

Inclusion:

Step 1: Initial Screening

1. Willing to sign informed consent prior to initiation of any study mandated procedure
2. Male or female ≥ 40 years of age
3. Women of childbearing potential must use a reliable method of contraception from screening until 1 month after end of study medication
4. Clinical diagnosis of moderate to severe COPD, with an obstructive pattern on pulmonary function tests showing both:
    1. $FEV_1/FVC < 0.7$ and
    2. $FEV_1 \leq 60\%$ of predicted value, on standard COPD therapy
5. Current or past smokers of ≥ 10 pack years
6. If taking oral (≤ 20 mg/day of prednisone equivalent) or inhaled corticosteroids, inhaled beta-agonists (short and long acting), or inhaled muscarinic antagonists (short and long acting), or statins the dose must be stable for at least 30 days prior to initial PR visit.
7. Ability to adequately participate in exercise testing/pulmonary rehabilitation program with supplemental oxygen use over the period of the study (in the best opinion of the investigator)

Exclusion

1. Patients fulfilling one or more of the following criteria of documented COPD exacerbation within 1 months prior to screening:
    - Use of antibiotics for COPD exacerbation
    - Initiation or dose increase of steroids (inhaled, oral or intravenous) for COPD exacerbation
    - Hospitalization for COPD exacerbation

2. BMI > 40 kg/m^2
3. Unstable coronary artery disease, unstable angina, or myocardial infarction within 3 months prior to screening
4. History of pulmonary edema, or uncontrolled heart failure
5. Uncontrolled systemic hypertension with a blood pressure >180/105 mmHg at rest
6. Systemic hypotension with systolic blood pressure < 85 mmHg
7. Uncontrolled arrhythmias
8. History of syncope
9. Planned surgical intervention during the study period
10. Any known factor or disease that might interfere with treatment compliance, study conduct or interpretation of the results including musculo-skeletal limitations, peripheral arterial disease, drug or alcohol dependence or psychiatric disease
11. Severe hepatic impairment (Child-Pugh Class C)
12. Chronic renal insufficiency, as defined by serum creatinine of > 2.5 mg/dL or estimated creatinine clearance < 30 mL/min or the requirement for dialysis
13. Pregnant or nursing
14. Currently (within 30 days prior to enrollment) taking specific pulmonary arterial hypertension therapy (e.g., bosentan, ambrisentan, tadalafil, sildenafil, epoprostenol, treprostinil, iloprost, beraprost), sildenafil and tadalafil for erectile dysfunction is permitted
15. Initiation of a pulmonary rehabilitation program within 3 months prior to screening or initiation or changes during the study
16. Participation in any other clinical trial, except observational, or receipt of an investigational medicinal product within 30 days prior to RHC visit
17. Known concomitant life-threatening disease with a life expectancy < 6 months
18. Known hypersensitivity to treprostinil or any of the excipients of the drug formulations.
19. Known hypersensitivity to inhaled nitric oxide

Trial Methods

1) All patients with COPD referred to the Inova Fairfax Pulmonary Rehabilitation program will be screened for inclusion in the study.

2) Informed consent will be obtained from eligible patients based on the above inclusion/exclusion criteria.

3) Baseline visit

    a. Medication list, past medical history, co-morbidities and allergies will be recorded.

    b. Full pulmonary function data to include spirometry, lung volumes and diffusing capacity.

c. 6MWT on room air or usual amount of supplemental oxygen.

d. 6MWT repeated test dose of three puffs of tyvaso. Patients with worsened oxygena saturation will be deemed "non-responders" and not qualify for the next phase of the trial. Patients with a stable or improved oxygen saturation will be deemed "responders."

4) Eligible patients categorized as "responders" will then be randomized in a double-blinded fashion to active drug or placebo. Ingredients for the placebo are: Sodium Citrate; Sodium Chloride; Sodium Hydroxide Pellets; 1N HCL; 1N NaOH; Water for Injection

5) Randomized patients will undergo baseline 6MWT on room air on their usual amount of supplemental oxygen.

6) Baseline BODE index will be calculated in randomized patients. [Celli BR, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. New Engl J Med. 2004; 350: 1004-1012.]

7) Randomized patients will be given Quality of life questionnaires including;

   a. Saint George's questionnaire

   b. Clinical COPD Questionaire

8) If any significant medical or psychological issues are identified during the screening process or treatment phase of the study, these will be reported to both the primary investigator and the safety monitor, Dr. Lamberti. A full assessment of the issue will be performed and arrangements made for appropriate evaluation and treatment of the problem by the patient's primary care provider(s).

9) Strength testing will performed prior to pulmonary rehabilitation in randomized patients.

10) A dose of active drug/placebo will be administered to all study participants prior to each of their PR sessions. A dose of inhaled albuterol will be administered prior to each inhaled agent. Vitals signs will be taken prior to administering the dose and no medication will be given if the systolic blood pressure in < 85 mm Hg. Three puffs (18mcg) of inhaled trepostinil dose will be administered each time to all patients .

11) Patients will be required to take currently prescribed long acting inhalers 1 hour or more prior to start of their exercise session. Enrolled subjects will not be permitted to change long-acting inhaler therapies while enrolled in the trial.

12) At the end of the pulmonary rehabilitation course, the following will be obtained

    a. QOL measures (St. George's respiratory questionnaire and clinical COPD Questionaire)

    b. 6MWT on room air or usual amount of oxygen (same as at start of study).

    c. Any hospitalizations or exacerbations requiring either oral steroid or antibiotic treatment.

    d. Strength testing

We plan to maintain enrollment for 1 year or until the desired number of enrollees are obtained, whichever occurs first.

Statistical Plan

Patient demographics and co-morbidities will be obtained during the initial history and physical exam. Data to be collected includes age, race, sex, body mass index, smoking history (active, former, never), smoking history in pack years, current COPD medications, mean pulmonary pressure (if available), co-morbid medical conditions (coronary artery disease, peripheral vascular disease, congestive heart failure, interstitial lung disease, obstructive sleep apnea, gastroesophageal reflux disease), and use of supplemental oxygen and liter flow. Data extracted from baseline pulmonary function testing will percent predicted values based on NHANES reference equation for total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and diffusing capacity of the lung for carbon monoxide (DLCO). The absolute values of the FEV1/FVC ratio, alveolar-arterial gradient, carbon dioxide partial pressure (pCO2), and arterial oxygen tension (pO2) will be recorded. Distance on 6MWT in meters, lowest O_2 saturation achieved, and Borg dyspnea score will be recorded prior to starting and after completing PR. Quality of life tools (St. George's, UCSD, MMRC) will be recorded prior to and after completing PR. Number of exacerbations, ER visits, hospitalizations and sessions completed will also be assessed. Data collection sheet is attached. The primary endpoint will be change in distance walked on 6MWT. Secondary endpoints include change in Borg dyspnea scale and baseline and transitional dyspnea index, St. George's respiratory questionnaire, number of exacerbations and hospitalizations.

Logistic regression will be utilized to compare baseline characteristics of groups. Data measured prior to and after PR (primary outcome: 6MWT distance secondary: Borg dyspnea, St. George's Respiratory Questionnaire score, Baseline dyspnea index and transitional dyspnea index) will be compared using two sample t-test. Data will be analyzed primarily based on patients completing PR, but a secondary analysis will be performed based on the intention-to-treat principle. A p value of 0.05 will be considered statistically significant. Formal consultation with a statistician will be solicited.

Safety Monitoring/Adverse Drug Reactions:

Definitions of adverse events

An AE is any adverse change from the subject's/patient's baseline condition, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease, that occurs during the course of the study, whether or not considered related to the study drug.

A treatment-emergent AE is any AE temporally associated with the use of a study drug (from study drug initiation until 24h after study drug discontinuation), whether or not considered related to the study drug.

Adverse events include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.
- Lack of efficacy in the acute treatment of a life-threatening disease.
- Events considered by the investigator to be related to study-mandated procedures.
- Abnormal assessments, e.g., change in physical examination, ECG findings, if they represent a clinically significant finding that was not present at baseline or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at baseline or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study drug.

Adverse events do not include:

- Medical or surgical procedure, e.g., surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative.
- Pre-existing disease or medical condition that does not worsen.
- Situations in which an adverse change did not occur, e.g., hospitalizations for cosmetic elective surgery or for social and/or convenience reasons.
- Overdose of either study drug or concomitant medication without any signs or symptoms. However, overdose of study drug must be mentioned in the Study Drug Log.

Intensity of adverse events

The intensity of clinical AEs is graded on a three-point scale – mild, moderate, severe – and is reported on specific AE pages of the CRF.

If the intensity of an AE worsens during study drug administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

If an AE occurs during a washout or placebo run-in phase and afterwards worsens during the treatment phase, a new AE page must be filled out with the intensity observed during study drug administration.

The three categories of intensity are defined as follows:

- **Mild**

The event may be noticeable to the subject/patient. It does not influence daily activities, and usually does not require intervention.

- **Moderate**

The event may make the subject/patient uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

- **Severe**

The event may cause noticeable discomfort, and usually interferes with daily activities. The subject/patient may not be able to continue in the study, and treatment or intervention is usually needed.

A mild, moderate, or severe AE may or may not be serious. These terms are used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction). However, a severe event (such as severe headache) may be of relatively minor medical significance and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically serious. Fever of 39 °C that is not considered severe may become serious if it prolongs hospital discharge by a day. Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

These definitions do not apply to clinically significant and asymptomatic laboratory test abnormalities or abnormal assessments (e.g., ECG findings) considered as AEs. The investigator should tick “non-applicable” on the AE page of the CRF to qualify the intensity of the AE.

Relationship to study drug

Each adverse event must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study drug, and reported as either related or unrelated.

- **Related to study drug**

This category applies to any AE (whether serious or not) that appears to have a reasonable possibility of causal relationship to the use of the study drug (i.e., a

relationship cannot be ruled out). Guidelines to determine whether an event might be considered related include (but are not limited to) the following:

- The event occurred in close temporal relationship to study drug administration.
- The event abated (diminished) or disappeared when treatment with the study drug was down-titrated, interrupted, or discontinued.
- The event reoccurred when treatment was reintroduced.
- Environmental factors such as clinical state and other treatments could equally have caused the event.

- **Unrelated to study drug**

This category applies to any AE (whether serious or not) that does not appear to have a reasonable relationship to the use of study drug (see above guidelines).

Reporting of adverse events

All AEs occurring after study medication initiation and up to 24 hours after study medication discontinuation must be recorded on specific AE pages of the CRF.

Follow-up of adverse events

Adverse events still ongoing after study drug discontinuation for a given patient must be followed until 30 days after study drug discontinuation or until resolution or stabilization or until the event is otherwise explained.

Serious adverse events

Definitions

Serious adverse events

An SAE is defined by the International Conference on Harmonisation (ICH) guidelines as any AE fulfilling at least one of the following criteria:

- Fatal
- Life-threatening
- Requiring inpatient hospitalization, or prolongation of existing hospitalization
- Resulting in persistent or significant disability or incapacity
- Congenital anomaly or birth defect
- Medically significant, or requires intervention to prevent at least one of the outcomes listed above

Life-threatening refers to an event in which the subject/patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.

Important medical events that may not immediately result in death, be life-threatening, or require hospitalization may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the subject/patient, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The reference safety document to assess whether or not an SAE should be reported by the sponsor to Health Authorities, ECs/IRBs and investigators in an expedited fashion is the (Investigator's Brochure; Package Insert/SmPC)

Hospitalization – prolongation of existing hospitalization

The following reasons for hospitalizations are not considered AEs, and are therefore also not SAEs:

- Hospitalizations for cosmetic elective surgery, or social and/or convenience reasons.
- Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a patient with stable angina pectoris.
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., elective hip replacement for arthritis. Complications that occur during hospitalization are AEs or SAEs (for example if a complication prolongs hospitalization).

Serious adverse events related to study-mandated procedures

An SAE is defined as related to study-mandated procedures if it appears to have a reasonable possibility of a causal relationship (i.e., a relationship cannot be ruled out) to such a procedures (other than administration of study drug). Examples of study-mandated procedures include discontinuation of a subject/patient's previous treatment during a washout period, complication of a mandated invasive procedure such as blood sampling or heart catheterization, car accident on the way to the hospital for a study visit, etc.

Data Safety Monitoring Process

Dr. James Lamberti will serve as the protocol safety officer for this trial. All serious adverse events (SAE) will be reported to Dr. James Lamberti for adjudication. Statistical analysis will be performed and reported to Michael Sheridan.

An analysis of the first four patients (of 12) will be performed in all reported SAE's. This seeks to enhance safety, and assess the relationship of SAE to study drug. All SAE's will be reported to United Therapeutics within 24 hours of site awareness regardless to relatedness to study drug.