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Materials and Methods

Six minute walk distance (6MWD) and Oxygen Supplementation (OS) protocols:

Patients were seated for 10 minutes on room air and peripheral pulse oximetry (PPO) was recorded. A 10 liter oxygen face-mask (FM) was then applied and PPO was recorded after an additional 10 minutes at rest. 6MW testing was subsequently performed on a 10 liter oxygen FM with recording of the nadir oxygen saturation by PPO and the Borg Dyspnea Index (BDI) at the end of six minutes or at the end of the final ambulatory effort. The 6MW test was not interrupted or terminated for any degree of hypoxemia. No baseline 6MWD minimum was required for study entry. All RHCs and associated measurements were performed on a 10 liter oxygen FM.

Pulmonary function testing (PFT) and Doppler Echocardiogram (DE) protocols:

All measurements were made by 2 experienced echocardiographers (AF, PF) blinded to invasive hemodynamics and clinical data. Standard parameters were measured, including left ventricular ejection fraction, dimensions of the left atrium, left ventricular cavity and wall thickness, transtricuspid flow velocity, valvular regurgitation, transmitral E and A wave velocities, tissue Doppler of the mitral annulus, and inferior vena cava dimensions and collapse. In addition, parameters specific to pulmonary vascular disease and right ventricular size and function were assessed, including systolic eccentricity index, notching of the right ventricular outflow tract (RVOT) Doppler profile, acceleration time of this profile, RV two-dimensional area, and tricuspid annular plane systolic excursion (TAPSE). All measurements were made in accordance with American Society of Echocardiography guidelines and previously published literature,[1-3]

Dyspnea and Quality of Life Assessments:

A higher UCSD SOBQ score indicates more dyspnea with a minimally important difference (MID) of 5 points.[4] The BDI measures perceived breathlessness on a scale of 0 to 10 (maximum) with a MID of 1 point.[4]

The 8 SF-36 scales and the PCS and MCS scores are standardized to a mean of 50 and standard deviation of 10 in the US general population. MID estimates for SF-36 PCS and MCS are 2.5 points.[5]

Parenteral treprostinil titration protocol:

After treprostinil initiation at 2ng/kg/min and at any subsequent dose uptitration, vital signs including PPO were recorded every 15 minutes for 1 hour, then every hour for 3 hours, and subsequently every 4 hours until discharge. Arterial blood gases were not obtained in a standardized fashion. Inpatient treprostinil was increased by a maximum of 1ng/kg/min every 12 hours such that patients were discharged from the hospital at 48 hours on treprostinil doses of 3 to 5 ng/kg/min. After discharge, all attempts were made to uptitrate treprostinil by a maximum of 1ng/kg/min every 48 to 72 hours; however, the frequency and final dose of treprostinil was determined by the individual patient adverse reaction profile.[6]

High Resolution Computed Tomography (HRCT) Lung Parenchymal Scoring:

A likert scoring system was used based on percentage of area affected (0 = absent, 1= 1 to 5%, 2= 6 to 25%, 3= 26 to 50%, 4= 51 to 75% and 5= 76 to 100%) and assessed the extent of parenchymal abnormality involving three categories: groundglass opacity, lung fibrosis, and honeycombing. Each lobe and then both lungs were scored separately. Our scoring system is modified from earlier scoring systems reported by Kazerooni et al. and Kim et al.[7-8] In addition, both lungs were scored for total extent of ground glass opacity, fibrosis and/or honeycombing as being definitively less than 20%, definitively more than 20%, or indeterminate (10-30%).[9] In the few patients with combined pulmonary fibrosis and emphysema (CPFE), the extent of parenchymal abnormality was calculated without taking into account the extent of emphysema.

The following definitions were used for description of each of the radiographic findings: (1) ground-glass opacity; hazy parenchymal opacity with preservation of bronchial and vascular markings in the absence of reticular opacity, (2) architectural distortion/lung fibrosis; reticular opacification,

inter and intralobular septal thickening, traction bronchiectasis, or bronchiolectasis and architectural distortion, and (3) honeycombing; clustered air-filled cysts with well defined walls.[10]

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