PROTOCOL

Title: Improving treatment personalization of pulmonary hypertension associated with diastolic heart failure

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Study Hypothesis and Specific Aims

The objective of this application is to evaluate nebivolol as a potential treatment for patients with pulmonary hypertension (PH) associated with diastolic heart failure, or heart failure with preserved ejection fraction (HFpEF). Our central hypothesis is that nebivolol improves PH severity in patients with HFpEF, as measured by hemodynamic and clinical parameters. The rationale for this research is that once we determine the extent to which nebivolol improves PH, it could be developed as a treatment for PH and HFpEF, especially if patients who respond best can be identified before treatment.

We will test our central hypothesis and accomplish these objectives by pursuing the following specific aim:

Define the clinical role of nebivolol as a potential treatment for PH associated with HFpEF using hemodynamic and functional status measurements.

Our working hypothesis is that nebivolol, via its β_1-antagontistic and β_3-agonistic activities, as well as its anti-inflammatory, anti-proliferative, and endothelial NO-stimulating properties, will decrease pulmonary pressures and improve 6-minute walk distance and dyspnea scores in patients with HFpEF-associated PH.

Background and Significance

Clinically, PH is marked by increased pulmonary vascular resistance leading to right heart failure, and ultimately death.[1] Thus, PH carries a poor prognosis, with a yearly mortality rate of 9%.[2] PH can include either pulmonary arterial hypertension (PAH) or pulmonary venous hypertension (PVH), which is often caused by left-sided heart failure. Increased pulmonary artery pressure (PAP) in patients with PVH develops from backward transmission of increased left atrial pressure, and is the most common cause of PH, with studies estimating its presence in 60-90% of heart failure patients.[3-6] However, approximately half of these patients have PAPs that are disproportionally higher than expected from their left arterial pressure, with greatly increased peripheral vascular resistance.[4] This increase in PAP is associated with significantly worse outcomes, with one study estimating that heart failure patients with very high PAP possess an increased the risk of death by greater than 2-fold compared to heart failure patients with normal PAP.[7] Such poor outcomes are particularly troubling in patients with PH and HFpEF, where no established guidelines for treatment exist.[8] Thus, development of treatments for this category of PH is greatly needed.

Current approved treatment classes for PAH, such as endothelin receptor antagonists and prostacyclins have either been shown ineffective, or have been associated with increased mortality when used in heart failure patients.[9,10] Nebivolol is a third generation β-blocker which has been shown to improve diastolic dysfunction in both rats and humans with HFpEF.[11-13] In addition, this particular β-blocker has a profile that should make it ideal for treatment HFpEF patients with PH. Importantly, nebivolol has been shown in a clinical study to improve mean PAP and PCWP in HFpEF patients without PH.[13] However, to what extent it improves these hemodynamic parameters in HFpEF patients, who also have PH, is unknown.

This project will contribute toward determining whether these potentially beneficial properties of nebivolol, known to improve diastolic dysfunction, will also improve PH severity in patients with HFpEF. This contribution will be important because it could uncover a potential treatment for a disease category that currently has no accepted treatments. If nebivolol significantly improves PH severity in patients with HFpEF, it can be further researched as a probable treatment. Furthermore, this project should also advance knowledge of the hemodynamic effects of chronic nebivolol treatment in HFpEF patients, as very few clinical studies have measured hemodynamics by right heart catheterization both before and after chronic oral treatment.

Methods

This project will be a prospective, open-label four-month clinical pilot study of 40 patients with PH and HFpEF. Patients will be started at 2.5 mg of nebivolol by mouth daily if they were not taking a beta-blocker at enrollment, and titrated up to 10 mg daily, as tolerated. Patients who cannot tolerate a dose increase will continue on the maximum tolerated dose throughout the study. Patients already on a beta-blocker at enrollment will begin on 5 mg and will be titrated to 10 mg daily. DNA and RNA will be collected for genomic studies of disease and drug response. All study procedures will occur at either the UF Clinical Research Center (CRC) or Shands Hospital.

Table 1. Procedures for each interaction with subjects

Test/Procedure	Visit 1/1A (wk 0-1)	Call 1 (wk 1)	Call 2 (wk 2)	Visit 2 (wk 4)	Call 3 (wk 5)	Visit 3 (wk 8)	Call 4 (wk 9)	Visit 4 (wk 18)
right heart catheterization	X*							X
transthoracic echo	X*							X
electrocardiogram	X			X		X		X
6-minute walk distance	X			X		X		X
vital signs	X			X		X		X
dyspnea index	X			X		X		X
complete blood count	X			X		X		X
INR	X					X		X
liver function test	X			X		X		X
basic metabolic panel	X			X		X		X
nt-proBNP	X					X		X
RNA collection	X			X		X		X
DNA collection				X		X		
serum collection	X			X		X		X
change in nebivolol dose	X		X	X				X
adverse effect assessment		X	X		X		X	
medication history	X			X		X		X

* = if not done within previous 3 months as part of clinical care

Visit 1 (week 0):

- Blood sample: 2x 8 mL PAXgene (RNA), 1x 10mL lavender top (plasma and PBMCs), 1x 3mL lavender top (CBC with diff), 2x 4mL Li Heparin (nt-proBNP, CMP), 1x2.7mL blue top (INR)
- Vital signs: blood pressure, pulse, respirations, height, weight, etc.
- Dyspnea index
- 6-minute walk test
- Medication history
- EKG

- Patients will be asked to take oral nebivolol 2.5 mg (or 5 mg) once daily until Visit 2 (**if visit 1A is not needed**). Instruct patient to discontinue previous beta-blocker and begin nebivolol today if they have not taken any beta-blocker today, and tomorrow if they have already taken a beta-blocker today.
- Place note in medical record documenting name of study, responsible physician, procedures, and medication dose.
- If possible, schedule Visit 1A or Visit 2.
- Once complete, provide patient with compensation ($50).

Visit 1A – IF NEEDED (week 0-1):

- If the patient has not received a two-dimensional transthoracic echocardiogram (TTE) within 3 months of enrollment, it will be done for research purposes, possibly on the same day as visit 1.
- If the patient has not received a right heart catheterization (RHC) within 3 months of enrollment, it will be done for research purposes (Appendix 1).
- Patients will be asked to take oral nebivolol 2.5 mg (or 5 mg) once daily until Visit 2. Instruct patient to discontinue previous beta-blocker and begin nebivolol today if they have not taken any beta-blocker today, and tomorrow if they have already taken a beta-blocker today.
- Once complete, provide patient with compensation ($200).

Phone Call 1 (week 1):

- How does patient feel compared to before starting study drug?
- Any perceived side effects?
- If not done already, schedule Phone Call 2

Phone Call 2 – IF NEEDED (week 2):

- How does patient feel compared to before starting study drug?
- Any perceived side effects?
- If tolerated, increase nebivolol dose to 5 mg (after approval by study physician)
- If not done already, schedule Visit 2.

Visit 2 (week 4):

- Blood sample: 1x 6 mL purple top (DNA), 1x 8 mL PAXgene (RNA), 1x 10mL lavender top (plasma and PBMCs), 1x 3mL lavender top (CBC with diff), 1x 4mL Li Heparin (CMP)
- Vital signs: blood pressure, pulse, respirations, height, weight, etc.
- Dyspnea index
- 6-minute walk test
- Medication history
- EKG
- If tolerated, increase nebivolol dose to 10 mg once daily.
- Update medical record to reflect new dose.
- If possible, schedule Visit 3.
- Once complete, provide patient with compensation ($40).

Phone Call 3 (week 5):

- How does patient feel compared to before starting study drug?
- Any perceived side effects?
- Provide results of safety assessment (everything looks similar to baseline OR significant difference in _____; the study physician recommends you _____.)

- If not done already, schedule Visit 3.

Visit 3 (week 8):

- Blood sample: 1x 6 mL purple top (DNA), 1x 8 mL PAXgene (RNA), 1x 10mL lavender top (plasma and PBMCs), 1x 3mL lavender top (CBC with diff), 2x 4mL Li Heparin (nt-proBNP, CMP), 1x2.7mL blue top (INR)
- Vital signs: blood pressure, pulse, respirations, height, weight, etc.
- Dyspnea index
- Medication history
- 6-minute walk test
- EKG
- If possible, schedule Visit 4.
- Once complete, provide patient with compensation ($40).

Phone Call 4 (week 9):

- How does patient feel compared to before starting study drug?
- Any perceived side effects?
- Provide results of safety assessment (everything looks similar to baseline OR significant difference in _____; the study physician recommends you _____.)
- If not done already, schedule Visit 4.

Visit 4 (week 18):

- Blood sample: 2x 8 mL PAXgene (RNA), 1x 10mL lavender top (plasma and PBMCs), 1x 3mL lavender top (CBC with diff), 2x 4mL Li Heparin (nt-proBNP, CMP), 1x2.7mL blue top (INR)
- Vital signs: blood pressure, pulse, respirations, height, weight, etc.
- Dyspnea index
- Medication history
- 6-minute walk test
- EKG
- Two-dimensional transthoracic echocardiogram (TTE) for research purposes
- RHC for research purposes (Appendix 1).
- Based on study physician recommendation, patients will be advised on how to proceed with beta-blocker treatment after the end of the study.
- Update medical records to indicate patient has completed study.
- Once complete, provide patient with final compensation ($250).

Eligibility Criteria

Study Population. This study will include PH patients from Shands Hospital and UF Health pulmonary hypertension and cardiology clinics. Patients must be diagnosed with PH by right heart catheterization (RHC). This procedure is the gold-standard for PH diagnosis and is the most accurate way to measure the hemodynamics necessary to differentiate subtypes of PH. Inclusion criteria for this study include:

1. Adults (≥ 18 years of age) with World Health Organization Group 2 Pulmonary Hypertension:
    a. Mean pulmonary artery pressure (mPAP) ≥ 25 mmHg,
    b. And pulmonary capillary wedge pressure (PCWP) ≥ 15 mmHg or left ventricular end diastolic pressure (LVEDP) ≥ 15 mmHg

2. Evidence of either diastolic dysfunction on echocardiogram OR elevated filling pressures on invasive hemodynamic testing OR BNP>200 (NT-proBNP>220) pg/mL
3. NYHA class II-IV symptoms
4. Left ventricular ejection fraction (LVEF) ≥ 45%

To assure any effect on hemodynamics are not due to other medications, patients must have no changes within one month to their cardiovascular medication regimen, including ACE-inhibitors, angiotensin receptor blockers, diuretics, and nitrates. Exclusion criteria include:

1. Other causes of heart failure other than diastolic dysfunction, such as restrictive cardiomyopathy or infiltrative cardiomyopathy
2. Women who are pregnant or nursing
3. Liver cirrhosis,
4. primary valvular disease
5. Acute coronary syndrome
6. Causes of PH other than that of heart failure, such as: chronic thromboembolic PH, sickle-cell disease, or sarcoidosis
7. Severe bradycardia or greater than 1st degree heart block
8. Decompensated heart failure
9. Current use of a third generation beta-blocker (nebivolol, carvedilol, or labetalol) or high dose of other beta-blockers (greater than 100 mg daily of metoprolol, or equivalent).

Plans for subject selection, recruitment, and documentation of informed consent

This study will include PH patients from Shands Hospital and UF Health pulmonary hypertension and cardiology clinics. Eligibility will be reviewed and if requirements are met, patients will be approached to gauge interest. If interested, patients will be asked to provide informed written consent.

Description of Procedures

Hemodynamic Measurements. To confirm the diagnosis of PH associated with HFpEF and obtain baseline hemodynamic measurements, right heart catheterizations (RHCs) will be performed by UF cardiologists and pulmonologists using standard techniques. Any procedures done during catheterization beyond those mentioned will be at the discretion of the physician performing the for clinical indications.

Transthoracic echocardiograms (TTEs) performed by UF Health technicians will also be used to obtain further hemodynamic parameters, including those that are indicative of diastolic dysfunction. TTEs will be read by a cardiologist as per American Society of Echocardiography guidelines. Diastolic dysfunction will be determined by tissue Doppler imaging. RV measurements including size, lateral tricuspid annular velocity, E wave, A wave, and isovolumic relaxation time will be performed.

Functional Assessments. The 6-minute walk test will be performed in accordance with standard practice both at baseline and at completion of the study. Briefly, subjects will be asked to walk for six minutes along a pre-measured path, with a practice walk being performed first. Distance walked, oxygen saturation, and a Dyspnea Index will be determined.

Statistical Methods

Planned statistical analysis: Student's t-test for paired samples will be used to determine differences between hemodynamic measurements taken before and after six months of nebivolol

treatment. Thus, each patient will serve as their own control. The two primary efficacy phenotypes to be measured are mPAP and PCWP. In secondary analyses, mitral valve Doppler flow velocity pattern, CO, PVR, CI and TPR will also be analyzed in an attempt to better characterize the mechanisms by which nebivolol affects the hemodynamic profile. In addition, Student's t-test for paired samples will be used to determine differences in 6-minute walk time before and after nebivolol treatment. Fisher's Exact Test will be used to compare dyspnea scores before and after six months of nebivolol treatment. In all analyses, $P \leq 0.05$ in a two-tailed distribution will be considered statistically significant. Statistical analyses will be performed using SAS 9.2 (SAS Institute, Cary, NC).

Rationale for selection of subject

Sample Size Calculation. Change in mean pulmonary artery pressure was used to estimate the sample size required to achieve satisfactory statistical power for this study. We calculated our sample size to be well-powered to detect a 15% decrease in mean mPAP (a clinically significant change). This would be approximately 4 mmHg at our minimum mPAP cut-off of 25 mmHg. We assumed a standard deviation of 5.5 derived from previous HFpEF treatment studies.[13] Thus, with a power of 0.95, and a two-sided α of 0.05, we would require a sample size of 27 patients. Because of the length of the study, we estimate an additional 30% will be needed to offset study attrition, thus a total sample size up to 40 patients will be enrolled.

Safety Monitoring and Assessment

Patients will be called 1 week after each dose change. BP and HR will be measured at each visit, as well as BMP, ECG, and LFT will be performed as safety assessments. Accumulated safety data will be reviewed by a study physician every six months to assess overall safety of nebivolol treatment.

Data Management

Patient data will be initially recorded using the patient data collection form and RHC data collection form. Patient data will then be transferred and stored using a custom-built REDCap database. REDCap is a secure, web-based application for building and managing online databases for the collection and entry of research data. Consents and other paper documentation will be kept in a locked cabinet in Dr. Duarte's locked, private office.

Risks and Benefits

Patients may not directly benefit. There is a potential benefit from improvements in progression of their PH. The potential risks include:

- Nebivolol: Risk of side effects such as: large decrease in blood pressure (less likely), headache (less likely), dizziness (less likely), nausea (rare), fatigue (rare), diarrhea (rare), difficulty breathing (very rare), and slow heart rate (very rare).
- Blood draws: discomfort at needle site (less likely), bruising at needle site (less likely), pain at site (less likely), swelling of vein (rare), fainting (rare), and infection (rare).
- Echocardiogram: no risks associated with this procedure
- Right heart catheterization: pain (less likely) or infection at catheterization sight (rare), vascular/valve damage (very rare), edema (rare), bruising (less likely), internal bleeding (very rare), blood clots (very rare), excessive fluid around the heart (very rare), and irregular heart rhythms (very rare).
- 6-minute walk distance: fatigue during walk (less likely)
- Accidental disclosure of PHI (rare)

Relevant Literature

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