Betablocker Therapy in Pulmonary Arterial Hypertension

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON34177

Source
ToetsingOnline

Brief title
*-blocker in iPAH

Condition

- Other condition
- Heart failures

Synonym
high bloodpressure pulmonary vascular system, pulmonary hypertension

Health condition

idiopathische pulmonale hypertensie

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: ZONMW

Intervention

Keyword: Beta adrenergic receptors, Pulmonary hypertension, Remodelling, Right ventricular dysfunction

Outcome measures

Primary outcome

The main question of this study is: *Is selective beta-blocker treatment safe and effective in reducing sympathetic overdrive, thereby improving RV function and remodeling in patients with iPAH?*

Safety of Bisoprolol treatment in iPAH patients is not taken as a primary endpoint but seen as a precondition for this study and will be closely monitored. Dose titration will be guided by possible side effects. Furthermore, although beta-blocker are considered contraindicated in PAH patients, a considerable number of patients frequently receives beta-blocker therapy in an uncontrolled way, without any side effects being reported until now.

Our primary efficacy endpoint is improvement in RV function as reflected by RVEF determined by means of cardiac MRI.

The efficacy of the drug will be determined by means of right ventricular ejection fraction derived from MRI. Additional information on the effects of the drug on sympathetic overdrive, remodeling and perfusion characteristics of the right ventricle, mechanical efficiency and exercise will be obtained by means of various techniques including PET.

Secondary outcome

In addition to the determination of RVEF, we will explore how beta-blocker therapy affects sympathetic overdrive, remodeling of the RV, single beat elastance, exercise capacity and mechanical efficiency. This will provide us with useful information with regards to the mode of action of beta-blocker therapy in iPAH, or alternatively, why beta-blocker may be ineffective in these patients. Therefore we have the following additional study questions:

* Is Bisoprolol treatment effective in reducing sympathetic overdrive?
* Is Bisoprolol effective in reversing maladaptive remodeling of the right ventricular wall, and does Bisoprolol thereby improve the diastolic properties of the right ventricle?
* Is Bisoprolol treatment effective in improving the perfusion and mechanical efficiency (oxygen consumption per joule) of the heart?
* Is Bisoprolol effective in improving exercise capacity?

Study description

Background summary

Idiopathic Pulmonary Arterial Hypertension (iPAH) is a rare disease in young humans with an estimated incidence of 10 per million per year. PAH is characterized by progressive pulmonary vascular remodeling and the associated increased right ventricular (RV) afterload eventually leads to right heart failure and premature death. Even with maximal treatment, prognosis remains poor: 5 year survival is about 50%. Currently available medical treatments aim to reduce RV afterload by dilating small pulmonary arteries, thereby * secondarily* improving RV function. Recognition of the key role of RV function in patient survival has not yet resulted in a treatment to directly improve RV function.
Preclinical and clinical left heart failure studies have shown detrimental effects of a chronically increased adrenergic activity on left ventricular (LV)

function. This is the fundamental basis for beta adrenergic receptor (AR) blockade in current left heart failure management. Beta-AR blockade attenuates maladaptive LV remodeling and reduces mortality by about 30%. Absence of major effects of beta-AR blockers on the pulmonary vasculature and fear of side-effects have prevented their use in PAH patients until now.
We conducted two independent pre-clinical studies to assess the effects of chronic beta-AR blocker treatment in experimental animal models of PAH-associated RV failure. The two studies showed that Bisoprolol and Carvedilol reverse maladaptive RV remodeling and improve RV function and animal survival. Strengthened by these results we propose a proof-of-concept clinical study, assessing the safety and efficacy of beta-blocker treatment in 30 stable human iPAH patients.

Study objective

The main question of this study is: *Is selective beta-blocker treatment safe and effective in reducing sympathetic overdrive, thereby improving RV function and remodeling in patients with iPAH?*.
In addition to the determination of RVEF, we will explore how beta-blocker therapy affects sympathetic overdrive, remodeling of the RV, single beat elastance, exercise capacity and mechanical efficiency.

Study design

This study is a randomized, placebo controlled, double blind cross over study.

Intervention

After obtaining informed consent, these 30 iPAH patients will be randomized to either Bisoprolol- or placebo-treatment in a double-blinded fashion. A cross-over trial design will be used to increase the power of the study and to assess long-term effects of Bisoprolol-treatment and -withdrawal. The medication will be given in an escalating dose regimen (as described in the *farmacotherapeutisch kompas*, www.fk.cvz.nl) and treatment will be monitored along the guidelines of the American Heart Association.

Study burden and risks

Safety monitoring will include two- and later on four-weekly visits to the outpatient clinic, with physical examination and measurements of body weight, blood pressure, ECG evaluation and 6MWD.
Time points 1, 3 and 5 (6 months periods): this includes a complete assessment of the patient
* Clinical assessment: physical examination, NYHA class, ECG, routine lab including NT-proBNP and urine tests for proteinuria.
* Imaging of right ventricular function: the primary measure of this study will

be right ventricular ejection fraction measured by means of MRI. Additional MRI and echocardiographic measurements will be performed.
* Right Heart Catheterization (performed under local anesthesia): Measurements of pressures in the pulmonary artery, right ventricle and right atrium, while patients are breathing room air and at end-expiration.
* Exercise capacity by means of a maximal incremental cycle testing (CardioPulmonary Exercise Test) to measure maximal work load, VO2 max, anaerobic threshold, heart rate response, oxygen pulse and ventilatory efficiency. And by means of 6 minute walking distance.
* Heart Rate Variability (HRV)
* Nuclear scanning: a comprised PET protocol will be performed to measure 11C-acetaat, oxygen-15-labeled water (H215O) and ^{11}C-HED uptake in the right ventricle.
Every 2 weeks the patients will be seen on the outpatient clinic for physical examination, laboratory tests and a questionnaire.

PAH is characterized by progressive pulmonary vascular remodeling and the associated increased right ventricular (RV) afterload eventually leads to right heart failure and premature death. Even with maximal treatment, prognosis remains poor: 5 year survival is about 50%.
Radiation limits is * 18,3 mSv during the whole study. This is a small exceeding of the allowed limit of 10mSv/year. Because the risks of exceeding radiation limits are a long term risk, we believe that the poor prognosis of patients with iPAH and the relevance of the study question justify these PET-scans.
The most common adverse reaction reported by patients who have used Bisoprolol is (orthostatic) hypotension and mild ankle edema. Other possible side-effects are bradycardia and any degree heart block. Although Bisoprolol has a very favorable safety profile, side-effects may occur and frequent communication between the patients and study investigators/coordinators will likely be necessary.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Idiopathic PAH patients
Stable on PAH specific treatment defined
No change in PAH specific treatment in the past 6 months
No change in functional class in the past 6 months
<10 % change in 6 minute walk distance in the past 6 months
Functional class 2 or 3
In sinus rhythm

Exclusion criteria

History of systemic hypertension, ischaemic heart disease, valvular disease or cardiomyopathy.
Asthma
Use of concomitant medication other than diuretics, acenocoumarol and PAH targeted therapy
History of cardiac arrhythmias or the use of anti-arrhythmic drugs
Sick sinus syndrome
Systolic hypotension < 90 mmHg
AV-block
Clinically relevant sinus-bradycardia

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-02-2011
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Emcor
Generic name:	Bisoprolol
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-10-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-01-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2010-020424-21-NL
CCMO	NL32515.029.10