Pulmonary Hypertension REversal in Clusters of Patients With Identical Pathobiological Substrates. 6-Mercaptopurine Proof-of-Concept Trial

Published: 23-05-2017
Last updated: 13-04-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Pulmonary vascular disorders
Study type	Interventional

Summary

ID

NL-OMON45698

Source
ToetsingOnline

Brief title
PRECISE-MP

Condition

- Pulmonary vascular disorders
- Vascular hypertensive disorders

Synonym
Pulmonary arterial hypertension

Research involving
Human

Sponsors and support

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

Intervention

Keyword: 6 mercaptopurin, pulmonary arterial hypertension, pulmonary vascular resistance

Outcome measures

Primary outcome

Changes in pulmonary vascular resistance

Secondary outcome

Change in cardiac function (right heart catheterization, MRI), exercise

tolerance and quality of life.

Study description

Background summary

Pulmonary arterial hypertension is an incurable disease of pulmonary vascular remodelling and right heart failure. Exuberant lung microvascular endothelial proliferation is one of the lead causes of PAH bul is currently not specifically targeted by medica! treatment. Treatment with 6 mercaptopurine (6-MP) showed encouraging results, mitigating endothelial proliferation in vitro and reversing pulmonary vascular remodelling in relevant anima! models. Lung vascular proliferation in PAH patients is heterogeneous , however, and can be estimated by transcriptome analysis of lung educated platelets (LEPs). Patients with a LEPs profile consistent with exuberant proliferation are expected to respond better to 6-MP treatment than patients with LEPs profiles consistent with quiescent lung vascular remodeling.

Study objective

The primary objective of this clinical trial is to obtain pilot safety and efficacy data on treatment of PAH patients by 6-MP. The secondary objective of this clfnical trial is to determine whether LEPs transcriptome analysis will identify a subset of PAH patients that responds to 6-MP treatment with

hemodynamic and functional improvement

Study design

Open label proof of concept study of treatment for 4 months with 6-MP, in a dose of 1.5mg/kg (up to 150mg) once daily.

Intervention

-

Study burden and risks

6-MP is currently used in haematological disorders and inflammatory bowel disease with an acceptable and manageable toxicity profile. No specific toxicity is expected in PAH. If effective, 6-MP could improve morbidity and mortality of PAH. For individual patients, participation in this study involves one or two extra right heart catheterizations and before and at the end of the study performance of exercise tests, MRI and quality of life assessment. In our experience, these procedures are safe.

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

- Age > 18 years
- Diagnosis of idiopathic, hereditary or drug-induced PAH
- New York Heart Association functional class (FC) II, III or IV
- Prior to their screening right heart catheterization, patients in FC II received * 3 months of at least oral monotherapy (PDE5-inhibitors, soluble guanyl cyclase stimulators, endothelin receptor antagonists or prostacyclin receptor agonist), patients in FC III received * 3 months of at least oral combination therapy, patients in FC IV received * 3 months triple therapy including a parenteral prostacyclin, unless intolerant for these medications
- Stable on mono- or any combination therapy for at least 30 days prior to enrollment, as evidenced by stable drug doses (PAH medications and diuretics), no change in FC, < 15% change in 6 minute walk distance (6MWD)
- Right heart catheterization no longer than 4 weeks prior to enrollment showing precapillary pulmonary hypertension with mPAP * 25 mmHg (at rest), Pulmonary artery wedge pressure (PAWP) * 15 mmHg, PVR > 6 WU
- Negative test results in regard to HIV, Hepatitis C/B, not older than 4 weeks
- Able to understand and willing to sign the Informed Consent Form
- PAH following one year repair of congenital heart defect (atrial septal defect, ventricle septal defect or persistent ductus arteriosus)
- PAH responsive to calcium antagonsists.

Exclusion criteria

- PAH of any cause other than permitted in the entry criteria
- Contraindication for right heart catheterization or CMR imaging
- Any subject who had received any investigational medication within 1 month prior to the start of this study or who is scheduled to receive another investigational drug during the course of this study
- Known intolerance to 6-MP
- Active liver disease, porphyria or elevations of serums transaminases >3 x ULN (upper limit of normal) or bilirubin > 1.5 x ULN - History or suspicion of inability to cooperate adequately.
- Cancer or other malignant haematological disease
- eGFR <30 ml/min
- White blood count < 4.0 109/l
- Hemoglobin < 6.0 mmol/l
- Thrombocytes < 100 109/l

- Transfer capacity for carbon monoxide (TLCO) < 40% of predicted
- Total lung capacity (TLC) < 60% of predicted
- Use of xanthineoxidase inhibitors
- Pregnant female subjects
- Breastfeeding female subjects
- Female subjects unwilling or unable to use a highly effective method of contraception
- Thiopurine S-methyltransferase (TPMT) enzyme deficiency

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-08-2017
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Puri Nethol
Generic name:	6 mercaptopurine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	23-05-2017

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-12-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-01-2018
Application type:	Amendment
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	EUCTR2017-000137-31-NL
CCMO	NL60538.029.17