PHOspholamban RElated CArdiomyopathy STudy - intervention (i-PHORECAST)

Published: 18-11-2013
Last updated: 24-04-2024

The primary objective is to show that eplerenone treatment reduces progression of disease in presymptomatic PLN R14del-carriers

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

Summary

ID

NL-OMON41504

Source
ToetsingOnline

Brief title
i-PHORECAST

Condition

- Other condition
- Myocardial disorders

Synonym
Phospholamban related Cardiomyopathy; Phospolamban heart muscle disorder

Health condition

genetische aandoeningen: erfelijke cardiomyopathien (late-onset)

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: ZonMW en CVON

Intervention

Keyword: Cardiomyopathy, Eplerenone, Phospholamban

Outcome measures

Primary outcome

The primary endpoint is a composite of at least one the following components:

• LV enddiastolic volume, increase >10%

• LV ejection fraction, absolute decrease >5%

• RV enddiastolic volume, increase >10%

• RV ejection fraction, absolute decrease >5%

• late enhancement, absolute increase >5%

(all the above parameters to be assessed with MRI)

• QRS voltage, decrease >25% (ECG, measured in lead I, II and III in mV)

• the occurrence of non-sustained ventricular tachycardia (Holter monitoring, exercise testing)

• symptoms/signs of heart failure and/or arrhythmias necessitating treatment according to the attending physician and likely due to arrhythmogenic cardiomyopathy

• cardiovascular death, including sudden death, likely due to arrhythmogenic cardiomyopathy

Secondary outcome

• Diagnosis of DCM

• Diagnosis of ARVC (according to task force criteria)

• Development of global or regional dysfunction and structural alterations,

(according to task force criterion)

• All individual components of the primary endpoint

• QRS-axis on 12-lead ECG

• Conduction intervals (PR-interval, QRS-duration) on 12-lead ECG and SA-ECG

• STT-segment changes on 12-lead ECG

• Change in biomarkers

• Occurrence of sustained ventricular tachycardia or ventricular fibrillation

• Hospitalization for a cardiovascular reason

Study description

Background summary

In the Netherlands *15% of idiopathic dilated cardiomyopathy (DCM) and *10% arrhythmogenic right ventricular cardiomyopathy (ARVC) patients carry a single (founder) mutation in the gene encoding Phospholamban, PLN R14del. Analogous to other inherited cardiomyopathies, the natural course of the disease is age-related (*age-related penetrance*); after a presymptomatic phase of variable length many PLN R14del-carriers progress to overt disease, and are diagnosed with either DCM or ARVC. PLN is a regulator of the sarcoplasmic reticulum Ca2+-ATPase (SERCA2a) pump in cardiac muscle and thereby important for maintaining Ca2+ homeostasis. Cardiac fibrosis appears to be an early manifestation of disease. We hypothesize that treatment of presymptomatic PLN R14del-carriers with eplerenone, which by virtue of its mineralocorticoid(aldosterone)-blocking properties is a strong antifibrotic agent, reduces disease progression and postpones onset of overt disease.

Study objective

The primary objective is to show that eplerenone treatment reduces progression of disease in presymptomatic PLN R14del-carriers

Study design

Multicenter, prospective, randomized trial with blinded assessment of endpoints (PROBE design).

Intervention

One group receives once daily a 50 mg tablet of eplerenone and the other group receives no treatment. Duration of treatment: 3 years.

Study burden and risks

The burden for the study subjects is limited.
All participants are followed according to routine patient care, which includes baseline assessments (i.e. after identification as PLN R14del-carrier) and yearly assessments. All these assessments are non-invasive, except for blood sampling.
Half of the subjects (control group) will not take study medication and they will receive care as usual. The only additional measurement is blood analysis (venous puncture) at the start of the study and at the end of the study. The other half of the study subjects will receive eplerenone 50 mg for 3 years once daily and they will pay an additional visit to check serum potassium.
Eplerenone is usually very well tolerated and has minimal side-effects. The most important side-effect is hyperkaliemia but in clinical practice this occurs only in the setting of concomitant use of other potassium-sparing drugs, e.g. ACE-inhibitors and renal impairment. The risk associated with eplerenone is hyperkaliemia but the likelihood of hyperkaliemia in this study group is very low (given the exclusion criteria). Moreover, serum potassium will be checked yearly and the dose of eplerenone will be lowered if needed.
On the other hand, the potential benefit of the study is large. If our hypothesis is confirmed that eplerenone retards disease progression in this patient group, this will have immediate beneficial consequences for these subjects. Treatment with eplerenone can be instituted right away in all study subjects as well as the other presymptomatic PLN R14del-mutation carriers in the Netherlands and elsewhere.

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

PLN R14del mutation carriers
Age >=18 and <= 65 years
New York Heart Association functional class <= 1
LV ejection fraction >=.45 (measured with MRI)

Exclusion criteria

•Palpitations necessitating treatment (at the discretion of the attending physician)
•A diagnosis of DCM (see appendix 1). Note: regional LV wall motions abnormalities are acceptable.
•A diagnosis of ARVC (according to the task force criteria)
•Global or regional RV dysfunction and/or structural alterations (according to task force criterion 1).
•Ventricular premature complexes >2500 during 24hours Holter-monitoring
•Non-sustained ventricular tachycardia during Holter-monitoring or exercise-testing
•History of sustained ventricular tachycardia or ventricular fibrillation
•Hypertension requiring the use of antihypertensive drugs, or when this is anticipated within the coming 3 years
•Evidence of ischemic heart disease
•Treatment with cardioactive medication
•Hyperkaliemia (serum potassium >5.0 mmol/l)
•Severe renal dysfunction (eGFR <30 ml/min/1.73m^2)
•Severe hepatic impairment (Child-Pugh class C)

•Women who are currently pregnant or report a recent pregnancy (last 60 days) or plan on becoming pregnant.
•Concomitant use of CYP3A4-inhibitors
•Concomitant use of NSAIDs
•Concomitant use of potassium highering/sparing-agents
•Known intolerance or contraindication to aldosterone antagonists
•Participation in another drug trial in which the last dose of drug was within the past 30 days.
•Contra-indications for MRI (claustrophobia, metal devices)
•Subjects unable or unwilling to provide written informed consent
Note: presence of late gadolinium enhancement on MRI is not an exclusion criterion

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-05-2014
Enrollment:	150
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Inspra
Generic name:	Eperenone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-11-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-02-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-11-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-01-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2013-001067-23-NL
ClinicalTrials.gov	NCT01857856
CCMO	NL43771.042.13