Institut thématique
Santé publique
Pôle Recherche Clinique

Institut national
de la santé et de la recherche médicale

SYNOPSIS

Study Number : C09-44 **Coordinating Investigator :** Philippe Charron
VERSION : 1.0, 22 Mar 2011

PRE CLINICAL MUTATION CARRIERS FROM FAMILIES WITH DILATED CARDIOMYOPATHY AND ACE INHIBITORS (OR PRECARDIA STUDY)

OBJECTIVES

Primary Objective Study the impact of ACE inhibitors (ACEi) in subjects who carry a mutation (leading to a genetic form of heart failure) but have not yet developed DCM (dilated cardiomyopathy).

Secondary Objectives Not applicable

SUMMARY :

This study is part of a broader research program, “INHERITANCE” (INtegrated HEart Research In TrANslational genetics of dilated Cardiomyopathies in Europe) research project, submitted to EU (FP7 European Union, HEALTH-2009-2.4.2-3: Translation of basic knowledge on inherited cardiomyopathies into clinical practice) and accepted in 2009 (Grant agreement n° 241924, global coordinator: Pr Eloisa Arbustini, Pavia, Italy).

Multicentre European double-blind,randomized and controlled trial with 2 parallel groups (1 study medication, 1 placebo) in order top analyse the impact of ACE inhibitors (ACEi) in subjects who carry a mutation but have not yet developed DCM.

Context. Dilated Cardiomyopathy (DCM) is one of the leading causes of Heart Failure due to systolic dysfunction and at least 30% of DCM are of familial/genetic origin, usually with autosomal dominant inheritance, and underlying genes and mutations are increasingly identified. Familial Dilated Cardiomyopathy (fDCM) is characterized by age-related penetrance (or delayed-onset), that means that the cardiac expression of the disease (echocardiographic abnormalities) is usually absent for a long period and progressively appears with advanced age, usually after 20 years of age

Hypothesis : ACEi may delay or prevent the occurrence of DCM in these subjects (pre-clinical stage).

Expected results: If the hypothesis is confirmed, and as a consequence, the knowledge derived from basic research (genes identification in DCM) will be translated into clinical practice (early identification of subjects at high risk of developing heart failure through predictive genetic testing) with the development of new therapeutic management (early ACEi) that will help to decrease the morbidity and mortality associated with the disease. This will constitute a paradigm of the development of preventive medicine thanks to the development of genetics in the cardiovascular field.

Precardia/Workpackage coordinator: Dr Philippe Charron, France
FP7 Global Inheritance network coordinator: Pr Eloisa Arbustini, Italia
8 countries (one center per country) will participate.

Key words (5) : treatment, heart failure, genetics, dilated cardiomyopathy

METHODOLOGY

☒ **Trial on health product (PS)** (drug, medical device, …)

Phase ☐ I ☐ II ☒ III ☐ IV | ☒Controlled ☒Randomized | ☒Parallel groups ☐Cross over | ☒Double Blind ☐Single Blind ☐Open

☐ **Trial not on health product** (physiology, physiopathology, …)

☐ **Epidemiologic study**

PROJECTED STUDY TIMETABLE

Inclusion period : 2 years
Duration of the follow-up and treatment for each participant: 3 years
Total duration of the protocol :5 years
Total duration (enrolment + follow-up + analyses) :6 years

PARTICIPANTS

Number of participants
1. Healthy volunteers : 0
2. Patients : 200

Participation of vulnerable persons
☐ Participant < 18 years : 0
☐ Participant under legal guardianship: 0
☐ Pregnant women : 0

Recruitment method
Participants will be recruited at the outpatient clinic in each investigating centre, selected by the local team of the investigator (cardiologist/geneticist). The participant might have been referred first by a physician out of the investigation centre (during a familial screening) or can be self-referred (through announcements by Associations of patients or the web site of the investigation centres who are usually “Reference centres for cardiac hereditary diseases”).

Number of participants justification
Statistical analysis allowing to have 80% power to detect a relative risk reduction of 60 % of the primary outcome with a 2-sided type I error rate of 0.05.

INCLUSION CRITERIA

- Carriers of the mutation that has been identified in the family as associated with DCM, and who have received appropriate genetic counselling before and after the announcement of the genetic result. The mutation within the family should be considered as disease-causing.
- At least one family member should have a clinical diagnosis of dilated cardiomyopathy (LVEF or left ventricle ejection fraction <45% and LVEDD or left ventricle end-diastolic diameter >112%; WHO & Mestroni et al. 1999 and Mahon et al. 2005: references 3 and 9) (NB in a patient with a mutation in LMNA gene, LVEDD may be normal whereas EF is markedly reduced, so that only a reduced LVEF is mandatory). DCM should not be considered as the burn-out phase of another cardiomyopathy (such as HCM, ARVC). LV non-compaction may co-exist with DCM in this patient. This patient within the family should carry the mutation considered as disease-causing.
- Age : ≥18 years of age and ≤60 years.
- No obvious DCM as assessed by diagnostic criteria on echocardiography (WHO & Mestroni et al. 1999 and Mahon et al. 2005: references 3 and 9): LVEF <45% and enlarged LVEDD (>112% of predicted value according to age, BSA).
- Presence of minor LV abnormality: isolated LVEDD > 112% (Henry Formula, indicated in reference 3) or reduced systolic dysfunction: LVEF < 55%, as assessed on echocardiography.
- Able to provide informed consent, and signed informed consent.
- For some European countries (example France and Spain): participants (by themselves) should have medical health care coverage to be included in a research study (not a problem in some other countries). Nota bene: this is different from the insurance specifically related to this research study that should be obtained by the sponsor for all the participants in all cases.
- Able to understand and accept the study constraints

NON INCLUSION CRITERIA

- Subject < 18 years old or > 60 years
- Other disease or factor that can cause minor LV abnormalities, such as cardiotoxic treatment or significant blood hypertension (with uncontrolled blood pressure or significant hypertrophy on

echocardiography).
- Contraindication to ACE inhibitor (prior intolerance or adverse reaction, e.g. angio-oedeme, patients with hereditary or idiopathic angioedema, hypersensitivity to perindopril or any of the excipients: e.g. hereditary problems of galactose intolerance, glucose galactose malabsorption, or the Lapp lactase deficiency)
- Impaired renal function (serum creatinine > 150 micromol/l).
- Baseline serum potassium >5.5 mmol/L.
- Pregnant, parturient or breastfeeding woman or woman of childbearing potential not under effective contraception or planned pregnancy. Nota bene: a biological diagnostic test will be systematically performed in woman of childbearing potential, and the woman will not be included in case of a pregnancy (positive test). In woman with a negative test that will be included in the study, effective contraception will be mandatory and should be taken during the duration of the study and four weeks after study termination.
- Participation in another therapeutic trial in the previous 3 months
- Participants who are already treated with ACE inhibitor or sartan (for various reasons such as arterial hypertension) can not be included in this study, unless they have been off these drugs for a period of 6 weeks before inclusion.
- Participants treated with lithium
- participant under legal guardianship

Nota bene: MRI (magnetic resonance imaging) can not be performed if there is contraindication to MRI (carrying of pace maker, defibrillator, ferromagnetic foreign body, cochlear auditory implant, ventricular shunt valve and claustrophobia) but in this situation the subject can be enrolled in the study and the cardiac imaging will be performed only with Echocardiography.

ENDPOINTS

Primary Endpoint
Occurrence of DCM or deterioration of LV end diastolic diameter/volume or Ejection fraction (echocardiographic or magnetic resonance imaging).

Rational of the Primary Endpoint's choice : Analysis of the intermediate phenotype because of the insufficient statistical power not allowing to notice « hard » clinical events. Echograpic parameters are predicitive values of the progress to a DCM and to clinical events.

Secondary Endpoint :
Deterioration of LV diameter/systolic function (additional parameters or statistical methods analysis), And deterioration of hormonal biomarkers in serum.

INVESTIGATIONAL MEDICINAL PRODUCTS

Pharmaceutical form : tablets of Perindopril (Angiotensin converting enzyme inhibitor) or placebo

Dose : Initiated at a dose of 2.5 mg (1/2 tablet) per day during one week; then 5 mg (1 tablet) per day during two weeks; then 10 mg (2 tablets), or the maximal dose tolerated.

Route: oral

Duration of the treatment for each participant: 3 years