To study the effect of LDL-cholesterol and LDL-cholesterol lowering on hematopoietic stem cells and circulating immune cells in familial hypercholesterolemia patients.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Observational invasive

Summary

ID

NL-OMON47323

Source
ToetsingOnline

Brief title
PRIME

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
familial hypercholesterolemia, genetic elevated 'bad' cholesterol

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Horizon2020 grant;REPROGRAM

Intervention

Keyword: Familial hypercholesterolemia, Hematopoietic stem cells, Inflammation

Outcome measures

Primary outcome

The main primary outcome is difference in CFU-GM assay (= function) and flow cytometry (=phenotype) of HSCs of FH patients before versus after treatment with a statin/PCSK9-inhibitor compared to healthy HSCs

Secondary outcome

Secondary endpoints are difference in lipid accumulation in FH HSCs and monocytes before and after treatment, flow cytometry (=phenotype) of FH HSCs compared to flow cytometry of circulating monocytes of FH patients and epigenetic and metabolic changes in FH HSCs and monocytes before and after treatment with a statin/PCSK9-inhibitor. This will be compared to healthy HSCs and monocytes

Study description

Background summary

Despite LDL-c optimization with statins, patients with hypercholesterolemia, and in particular patients with FH, have a high residual CV risk. FH patients are characterized by high LDL-c plasma levels, monocytosis and premature development of atherosclerosis. In vivo imaging with 18F-FDG PET/CT scan shows increased 18F-FDG uptake in bone marrow in patients with atherosclerosis, suggesting increased hematopoietic activity in these patients. In vitro co-incubation assays of healthy HSCs with oxLDL showed indeed increased

progenitor capacity, but also a myeloid differentiation bias. Therefore we hypothesize LDL-c can prime HSPCs, resulting in a chronic monocytosis and pro-atherogenic monocytes leading to aggravated atherosclerosis in FH patients despite LDL-c lowering treatment.

Study objective

The main objective is to compare function and phenotype of bone marrow HSCs of FH patients before and after LDL-c lowering by statins/PCSK9-inhibitors with healthy controls. Secondary objectives are to correlate the function and phenotype of HSPCs to lipid accumulation, to compare phenotype of HSPCs with phenotype of circulating monocytes and to determine epigenetic and metabolic changes in HSPCs.

Study design

Single center, observational study

Study burden and risks

The results of this study contribute to the understanding why patients are at risk of cardiovascular events despite optimization of LDL-cholesterol. Individual subjects will gain no direct benefit from this study. The burden and risk of participating in this study are estimated to be low. The study requires a maximum of 2 study visits. Maximum blood withdrawal including clinical laboratory assessment will be 124 ml. Complications of a sternum biopsy are rare, a bleeding or an infection may occur.

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

Patients:
- Age > 18 years old
- Familial hypercholesterolemia (according to Dutch Lipid network criteria)
- No previous cardiovascular events
- No current lipid lowering treatment
- LDL-cholesterol > 4.9 mmol/L;Healthy controls:
- Age >= 18 years old
- No (previous) clinically significant health problems
- No current medication use

Exclusion criteria

1. Malignant diseases or any clinically significant medical condition that could interfere with the conduct of the study in the opinion of the investigator.
2. Chronic or recent (<1 month) infections and/or clinical signs of acute infection and/or CRP>10
3. Auto-immune diseases
4. Recent or chronic immunosuppressant or antibiotic usage
5. Type I or II diabetes mellitus
6. Inability or unwillingness to comply with the protocol requirements, or deemed by investigator to be unfit for the study.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-07-2017
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO Date:	18-01-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-01-2019
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
CCMO	NL59100.018.16