Determination of phenotypic and epigenetic *trained immunity* characteristics of hematopoietic stem and progenitor cells in patients with established atherosclerosis, a proof-of-principle study

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To investigate whether long-term activation of the innate immune system, named *trained innate immunity*, occurs at the level of the bone marrow progenitor cells in patients with significant coronary artery disease and whether this correlates with...

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

Summary

ID

NL-OMON43290

Source
ToetsingOnline

Brief title
Training of hematopoietic stem cells in patients with atherosclerosis

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Cardiovascular disease

Research involving

Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Horizon 2020 grant van de Europese Unie

Intervention

Keyword: Atherosclerosis, Hematopoietic stem cells, Immunology, Trained innate immunity

Outcome measures

Primary outcome

Comparison of HSPC*s of patients with and without significant coronary artery disease on epigenetic and phenotypic characteristics, and relate this with phenotypic appearance of circulating monocytes.

Secondary outcome

Comparison of the pro-inflammatory monocytes and HSPC's phenotype with vascular wall inflammation, bone marrow and spleen activation by measuring FDG uptake in PET-CT scanning.

Study description

Background summary

Atherosclerosis is increasingly being acknowledged as a chronic, low-grade inflammatory disorder of the arterial wall. Patients with CVD show increased FDG uptake in the large arteries and bone marrow, and this strongly predicts resp. correlates with future cardiovascular events. Previously is shown that monocytes/macrophages adopt a long-lasting pro-inflammatory phenotype by epigenetic modulation upon brief exposure to various pro-inflammatory and pro-atherogenic stimuli such as oxLDL and Lp(a), named *trained innate immunity*. Recently, our group has proposed that trained immunity contributes to atherosclerotic vascular inflammation by showing that in patients with elevated levels of Lp(a) monocytes possessed a pro-atherogenic phenotype associated with epigenetic changes (H3K4me3 enrichment), and increased vascular

inflammation on PET-CT. Because these pro-inflammatory changes last longer than the life span of circulating monocytes, up to three months after BCG vaccination, we shifted our attention to the bone marrow progenitor cells. In mice, hypercholesterolemia increases the number of monocytes, and skews their development towards a pro-inflammatory phenotype, via priming of HSPC. Therefore, we hypothesize that functional, transcriptional en epigenetic changes at the level of HSPCs are responsible for the long-term trained immunity phenotype of circulating monocytes, and contributes to the development of atherosclerosis in the context of traditional CVD risk factors. This is the first study to address this issue by directly obtaining bone marrow progenitors from patients with significant coronary artery disease.

Study objective

To investigate whether long-term activation of the innate immune system, named *trained innate immunity*, occurs at the level of the bone marrow progenitor cells in patients with significant coronary artery disease and whether this correlates with the pro-inflammatory phenotype of monocytes.

Study design

An observational pilot proof-of-principle study.

Study burden and risks

There is no direct benefit to the study participants. These results can potentially lead to new therapeutic options for atherosclerosis. The risks for participants are negligible, with the only expected risks being unexpected findings of PET-CT scanning, minor discomfort due to bone marrow aspiration and venipuncture. This will be minimized by the performance of these procedures by experienced personnel.

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 and *75 years
With or without significant coronary artery disease on CCTA as described earlier
Written informed consent

Exclusion criteria

Chronic infections
Diabetes mellitus
Medical history of any disease associated with immune deficiency (either congenital or acquired, including chemotherapy, chronic steroid use, organ transplant)
Clinically significant infections within 3 months prior to study entry (defined as fever >38.5)
Recent hospital admission or surgery with general anaesthesia (<3 months)
Known chronic kidney (MDRD <45 ml/min) or liver disease (ALAT more than three times upper reference limit or known liver disease)
Previous vaccination within 3 months prior to study entry
Inability to personally provide written informed consent (e.g. for linguistic or mental reasons)
Inability to undergo PET-CT scanning
Chronic use of anti-inflammatory drugs such as NSAIDs (acetylsalicylic acid <100 mg/day excluded)
History of haematological malignant disease
Documented bleeding diathesis or thrombocytopenia <50 *10e9/L
Pregnancy

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-07-2017
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	30-01-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-09-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
Other	Clinicaltrials.gov nog niet geregistreerd
CCMO	NL58806.091.16

Study results

Date completed: 22-08-2018

Actual enrolment: 26

Summary results
Trial is onging in other countries