Trained immunity in children with FH that undergo cholesterol lowering treatment

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Objective: The main objective is to evaluate the monocyte phenotype of children with FH compared to normocholesterolemic controls and to explore the effect of statin treatment.

Ethical review	Approved WMO
Status	Pending
Health condition type	Metabolic and nutritional disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON56081

Source
ToetsingOnline

Brief title
Trained immunity in children with FH

Condition

- Metabolic and nutritional disorders congenital

Synonym
Familial hypercholesterolemia, hereditary high cholesterol

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Children, Familial Hypercholesterolemia, Monocytes

Outcome measures

Primary outcome

In the children with FH, blood will be drawn before start of statins and 3 and 12 months after initiation of statin treatment. In the normocholesterolemic controls (only in Oslo), blood will only be drawn once. Plasma will be stored and peripheral blood mononuclear cells will be isolated and viably frozen at each study site. After inclusion is complete, all samples will be shipped to Oslo, Norway for analysis of cytokine production capacity upon ex vivo stimulation with various atherogenic stimuli and flow cytometric analysis. Monocytes will be isolated for RNA sequencing and epigenetic analyses. The primary endpoint is LPS-induced IL-1b release in patients with FH compared to controls. Secondary endpoint is the effect of 3- and 12-month statin treatment compared to the baseline situation in children with FH.

Secondary outcome

Secondary endpoint is the effect of 3- and 12-month statin treatment compared to the baseline situation in children with FH.

Study description

Background summary

Rationale: Familial hypercholesterolemia (FH) is an autosomal dominant dyslipoproteinemia, characterized by elevated low density lipoprotein (LDL) levels, and is an important risk factor for atherosclerotic cardiovascular disease (ASCVD). Due to genetic defects, patients with FH have elevated plasma

LDL cholesterol from birth onwards, and a variety of markers of atherosclerosis are observed already in early childhood. In Europe, about 1:250 people have FH and early treatment is key to lower CVD risk. In the last 10 years, European guidelines have been published for the identification and management of children with FH. In Europe, children with genetically diagnosed FH start LDL lowering treatment with statins from the age of 8 to 10. This treatment is generally very well tolerated, even better than in adults. Over the last decades, it has become apparent that atherosclerosis is a chronic inflammatory disease which benefits from anti-inflammatory treatment. At the same time, it was discovered that the innate immune system is capable of developing a memory, which is termed trained immunity. Trained immunity can be induced by micro-organisms but also by endogenous atherogenic particles, such as (modified) lipoproteins. We have shown in innate immune cells from adults that lipoprotein-trained monocytes have a pro-atherogenic phenotype and furthermore we showed a trained phenotype in monocytes from adults with familial hypercholesterolemia. Furthermore, 3 months of treatment with statins - in adults - did not revert the trained immunity phenotype despite lowering the blood cholesterol levels successfully. It is unknown whether monocytes from children with FH have a trained immunity phenotype similarly to adults and how statin treatment affects this.

Study objective

Objective: The main objective is to evaluate the monocyte phenotype of children with FH compared to normocholesterolemic controls and to explore the effect of statin treatment.

Study design

Study design: Observational cohort study.

Study burden and risks

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: There is no risk associated with participation. After signing for informed consent by the parents and assent by the children if >12 years old, 20 ml of blood will be drawn at the routine diagnostic appointments for the ex vivo experiments.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

8-18 yrs old FH (by genetics or EASCP criteria) and LDLC levels above 3.5 mmol/L and requiring lipid lowering treatment according to the treating physician No previous cardiovascular events. Written informed consent from the parents/legal representatives or patients depending on their age prior to participation in the study

Exclusion criteria

- Current lipid lowering treatment or treatment with lipid lowering drugs in the past year
- Parents inability to provide written informed consent (for linguistic, intellectual or mental reasons)
- Current treatment for malignancy
- Acute or chronic infections with fever at the time of participation
- Medical history of any disease associated with immune deficiency (either congenital or acquired, including chemotherapy, chronic steroid use, organ

transplant)
- Clinically significant infections within 1 months prior to study entry (defined as fever above 38.5)
- Previous vaccination within 1 months prior to study entry
- Chronic use of anti-inflammatory drugs such as NSAIDs (acetylsalicylic acid below 100 mg/day excluded)

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:	Pending
Start date (anticipated):	22-10-2023
Enrollment:	15
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	24-10-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL84300.078.23