Unravelling the role of trained immunity in cardiac allograft vasculopathy

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Primary 1) Establish whether HTx induces a trained immunity phenotype of circulating monocytes in pediatric and adult HTx patients, and compared to healthy controls.2) Investigate whether trained immunity phenotypes in pediatric and adult HTx...

Ethical review	Approved WMO
Status	Pending
Health condition type	Heart failures
Study type	Observational invasive

Summary

ID

NL-OMON56885

Source
ToetsingOnline

Brief title
Trained immunity in heart transplantation

Condition

- Heart failures

Synonym
Cardiac allograft vasculopathy, narrowing of the coronary arteries.

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: Cardiac allograft vasculopathy, Heart transplantation, Immunity phenotype of circulating monocytes, Trained immunity

Outcome measures

Primary outcome

a) Trained immunity: Functional testing of trained immunity is performed using previously established protocols. Levels of the inflammatory cytokines IL1β, IL6 and TNF are measured in culture supernatants upon ex vivo stimulation of whole blood with trained immunity stimuli such as the TLR2 and TLR4 ligands Pam3CysK4 and lipopolysaccharide (LPS), and NLRP3-inflammasome activating cholesterol crystals. The cytokine levels are continuous variables.

b) CAV grading: CAV grading is performed using computed tomography (CT) coronary angiograms, including fractional flow reserve measurement, according to international society for heart and lung transplantation guidelines (ISHLT) and established local protocols. CAV grade is an ordinal variable (grade 0-3).

Secondary outcome

a) Innate and adaptive immune cell phenotypes (secondary objectives):

Compre-hensive phenotyping of circulating immune cells will be performed using:

• Multi-color flow cytometry of circulating monocytes, dendritic cells, T-cells and B-cells (naïve versus effector and memory). Phenotyping will include the expression of activation markers, inflammatory factors and adhesion proteins relevant for CAV development, using previously established protocols. Leukocyte subset frequencies and expression levels of activation markers, inflammatory factors and adhesion proteins are continuous varia-bles.

• Morphological phenotyping of circulating leukocytes, using DeepCell technology. Morphological parameters are continuous variables.

b) Clinical determinants of CAV development: Routine clinical parameters with rele-vance for CAV development and the study objectives will be included in the study database. These parameters include: age, gender, underlying cardiac dis-ease, HTx date, AB0 blood group and antibodies, HLA antibodies / mismatch, re-jection episodes, viral reactivation episodes and immune status, immunosup-pression, and cardiometabolic determinants (dyslipidemia, obesity, dysglycemia, hypertension).

Study description

Background summary

Long-term survival of heart transplantation (HTx) in children and adults is often limited due to cardiac allograft vasculopathy (CAV). CAV is caused by monocytic and lymphocytic inflammation of the intimal layer of the coronary arteries, which results in luminal narrowing of the coronaries, and ultimately in cardiac ischemia. CAV is a leading cause of mortality ten years following HTx, affecting approximately 50% of adolescent and adult HTx patients, with slightly lower numbers in younger children. Here, we investigate whether trained immunity of circulating monocytes is associated with CAV development. Trained immunity is reflected by a hyperinflammatory phenotype of the monocytes, caused by repetitive inflammatory stimulation leading to pro-inflammatory epigenetic changes. If trained immunity is indeed associated with CAV development, inhibition of trained immunity could provide novel avenues to prevent CAV development in the near future.

Study objective

Primary 1) Establish whether HTx induces a trained immunity phenotype of circulating mono-cytes in pediatric and adult HTx patients, and compared to healthy controls.
2) Investigate whether trained immunity phenotypes in pediatric and adult HTx patients are associated with the development of cardiac allograft vasculopathy.
Secondary 1) Explore differences between children and adults in the innate and

adaptive immune phenotypes following HTx. 2) Explore innate and adaptive immune phenotypes associated with viral reactivations, CAV development, and graft rejection.

Study design

Observational.

Study burden and risks

Burden: Whole blood sampling. Sampling will be combined with routine clinical blood sampling whenever possible, to reduce study burden.
a) For pediatric subjects, total volume will be adjusted to circulating volume, in accordance with international standards and EU directive No 536/2014 (2017). Rule of thumb in sick children: blood sampling for research maximum 3% of circulating volume (2.5ml/kg) over a period of 4 weeks, in addition to clinical / routine blood sampling.
b) For primary objective 1, 50 patients will undergo blood withdrawal at 4 timepoints, general-ly more than 4 weeks apart. Blood sampling for research maximum 2.5ml/kg/timepoint for children (or 1.25ml/kg/timepoint if less than 4 weeks from previous blood sampling), and 40ml/timepoint for adolescents and adults.
c) For primary objective 2 and the secondary objectives, patients and controls will undergo one-time blood sampling. Blood withdrawal maximum 2.5ml/kg for children, and 40ml for adolescents and adults.
Risks: addition of extra tubes to routine blood sampling is considered a minimal risk. Benefits: no personal benefits for study participants. On a group level, data from this study may open novel avenues to prevent CAV development in the future.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Patient groups:
- Children and adults undergoing HTx (Primary objective 1) or
- Pediatric and adult HTx patients 5-10 years post-HTx or * 10 years post-HTx (Primary objective 2 and secondary objectives).
- Written informed consent.

Control group:
- Healthy adolescents enrolled in the Whistler birth cohort study.
- Written informed consent, including transfer of data and blood samples to the Trained immunity in heart transplantation study team at the Erasmus MC.

Exclusion criteria

Acute infection (fever >38.5*C and/or clinical infectious symptoms).

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):	01-07-2024
Enrollment:	200
Type:	Anticipated

Ethics review

Approved WMO

Date:	15-07-2024
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	NL86533.078.24