The clinical effect of mTOR inhibition on lipid metabolism in renal transplant recipients

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to study the effect of everolimus (vs. mycophenolate) on dyslipidemia, ectopic fat accumulation, and cardiovascular function against a common calcineurin inhibitor (CNI) background.

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON41053

Source
ToetsingOnline

Brief title
The clinical effect of mTOR inhibition on lipid metabolism

Condition

- Other condition
- Renal disorders (excl nephropathies)

Synonym
dyslipidemia

Health condition

transplantatie onderzoek

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,MRI scans vormen onderdeel van een Nierstichtingsproject

Intervention

Keyword: cardiovascular, dyslipidemia, mTOR, transplant medicine

Outcome measures

Primary outcome

- Fasting serum lipid profile (LDLc, HDLc, TG, Total Cholesterol, lipoprotein

profile)

- Proton-magnetic resonance spectroscopy (1H-MRS) assessed ectopic lipid

accumulation in liver (primary) and heart (secondary).

- Non-contrast MR assessed visceral and subcutaneous adipose tissue (VAT, SAT)

- Non-contrast MR assessed cardiovascular function.

Secondary outcome

not applicable

Study description

Background summary

Long-term patient survival after kidney transplantation is limited by a seven times higher risk of cardiovascular mortality in renal transplant recipients (RTR) compared to the general population. Everolimus, an immunosuppressive drug and mTOR-inhibitor with important anti-proliferative capacity, is associated with significant hyperlipidemia, which limits its widespread use and which seems contra-intuitive to presumed beneficial effects against atherosclerosis. Precise pathways and consequences of mTOR-related hyperlipidemia remain uncertain.

Hypothesis: Hyperlipidemia that is associated with mTOR inhibition in RTR

origins from a diminished ectopic lipid accumulation in nonadipose tissue (such as liver and heart) and is associated with improved cardiovascular function.

Study objective

to study the effect of everolimus (vs. mycophenolate) on dyslipidemia, ectopic fat accumulation, and cardiovascular function against a common calcineurin inhibitor (CNI) background.

Study design

two-year observational study as local add-on of the TRANSFORM Study, a randomized control trial in RTR (P13-233) of everolimus+CNI+steroids vs. mycophenolate+CNI+steroids with assessments of main study parameters at 1 week pretransplant, 1 and 2 years posttransplant.

Study burden and risks

Everolimus has anti-proliferative characteristics that may protect RTR from their high risk of malignancies, viral infections, and cardiovascular disease. However, dyslipidemia is a significant side effect of everolimus, which limits its widespread use and which seems counterintuitive to the presumed beneficial effects on cardiovascular disease. Presently, the clinical significance and pathways of everolimus-induced dyslipidemia are unknown. We hypothesize that everolimus induced-dyslipidemia is a bystander effect of a diminished ectopic lipid accumulation in nonadipose tissue and thus associated with improved cardiovascular and organ function. Gaining insight into the pathways and consequences of mTOR-associated dyslipidemia may improve targeted therapy in the future. The burden of participation in this study is limited. Subjects will already participate in the TRANSFORM Study, and participants to this sub-study will additionally have three noninvasive MRI measurements of approximately one hour at 1 week before, and 1 and 2 years posttransplant in a fasting state. Blood for fasting lipid spectrum will be withdrawn as well. The TRANSFROM Study is a unique clinical setting to observe the effect of mTOR inhibition on ectopic lipid accumulation in relation to dyslipidemia in humans.

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

Renal transplant recipients from Leiden who will participate after informed consent in the global TRANSFORM Study (P13-233).

Exclusion criteria

Any standard contraindications for MRI or 1H-MRS (i.a. claustrophobia, metal parts, etc)

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2014
Enrollment:	30
Type:	Anticipated

Ethics review

Approved WMO

Date:	27-10-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	NL49252.058.14