Pilot study to identify biomarkers for tolerance to liver grafts

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Pilot study to evaluate whether frequencies of donor-specific Teff and Treg in blood differ between tolerant and non-tolerant LTx recipients. Furthermore, the mechanism of tolerance will be studied by characterization of T cells within the blood of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatic and hepatobiliary disorders
Study type	Observational invasive

Summary

ID

NL-OMON47529

Source
ToetsingOnline

Brief title
BIOTOL

Condition

- Hepatic and hepatobiliary disorders

Synonym
liver grafts; rejection

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Stichting Leveronderzoek (SLO)

Intervention

Keyword: biomarkers, immune system, liver graft, tolerance

Outcome measures

Primary outcome

Frequencies of donor-specific CD4+ Teff, CD4+Foxp3+ Treg, and CD4+CD49b+LAG-3+ Treg will be expressed as percentages of CD4+ T-cells. Frequencies of donor-specific CD8+ Teff will be expressed as percentages of CD8+ T-cells. The same calculations will be made for frequencies of T cells responding to 3rd party allo-antigen. A single cell RNA profile for tolerance will be established, as well as a functional immune response and TSDR methylation of immune cells within tolerant and control LTx recipients.

In the case-control study frequencies of donor-specific T cells and 3rd-party specific T cells will be compared between tolerant patients and patients using IS, using the Mann-Whitney test or, if the variables are normally distributed, using the Wilcoxon test for unpaired samples.

In the cohort study at each time point frequencies of donor-specific T cells and 3rd-party specific T cells will be compared between patients that do not reject during or after IS withdrawal and patients that do reject, using the same statistical tests.

Secondary outcome

In tolerant patients only: degree of liver fibrosis (in kPa) as detected by fibroscan and by a combination of serum markers e.g. PINP, PIINP, TIMP, MMP

Study description

Background summary

The life long treatment with immunosuppressive drugs (IS) to prevent graft rejection in liver transplant (LTx) recipients is accompanied by adverse effect such as nephrotoxicity, infections, diabetes and cancer. Gradual withdrawal of IS is possible in about 25% of LTx recipients without signs of graft rejection, and these patients apparently tolerate their liver graft. However, since no biomarkers that identify tolerant LTx recipients are available, deliberate withdrawal of IS has not entered clinical practice. We hypothesize that tolerant and non-tolerant LTx recipients may differ in numbers of circulating donor-specific effector T-cells (Teff) and regulatory T cells (Treg), and in concentrations of immune-regulatory cytokines, such as IL-10 and TGF-beta. Furthermore, the mechanism of tolerance will be studied by characterization of T cells within the blood of tolerant LTx recipients compared to a control group. For patient safety reasons we would like to monitor whether liver fibrosis might develop in the patients without IS. We will use a transient elastography ultrasound technique (Fibroscan), which is a recognized alternative diagnostic technique to asses liver fibrosis but without patient burden.

Study objective

Pilot study to evaluate whether frequencies of donor-specific Teff and Treg in blood differ between tolerant and non-tolerant LTx recipients. Furthermore, the mechanism of tolerance will be studied by characterization of T cells within the blood of tolerant LTx recipients compared to a control group.
Secondary objective: To determine whether long-term absence of IS medication in tolerant LTx recipients might promote fibrosis of the liver graft.

Study design

1). Case-control study in which we compare LTx-recipients in which IS has been stopped for clinical reasons in the past and which are IS-free for at least 6 months (*tolerant patients*) with stable LTx-recipients that are treated with IS and are matched for time after LTx with the tolerant patients. For each patient, two blood samples will be collected during a venapunction performed for diagnostic reasons during a regular visit to our out-patient clinic. IA fibroscan will be performed by tolerant patients. Study duration: 1 year.
2). Cohort study in LTx-recipients in which IS will be gradually withdrawn for clinical reasons. Patients will be followed until signs of acute rejection or until 6 months after complete cessation of IS. Blood will be collected before lowering of IS, during the first visit to the out-patient clinic after IS has been halved, and 6 months after complete cessation of IS. An anual firbroscan will be performed starting 6 month after stopping of IS.

Study duration: 4 years

Study burden and risks

There is no extra risk for the patient.

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

Case control study: The experimental group consists of 8 LTx patients in Erasmus MC that are currently at least 6 months free of IS. 5 additional patients are currently in the process of IS reduction, and will be included as soon as they are 6 months free of IS. As a control group we will include 39 LTx

patients matched with the experimental group for LTx-indication and time after LTx and have been continuously treated with IS., Cohort study: LTx-recipients in Erasmus MC in which for clinical reasons IS will be gradually withdrawn. Our estimation is that we can include 25 patients during the next 4 years, but this is fully dependent on clinical need to reduce and finally stop IS.

Exclusion criteria

Severe recurrence of primary liver disease with development of cirrhosis.

Study design

Design

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

Primary purpose: Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-10-2014
Enrollment:	77
Type:	Actual

Ethics review

Approved WMO Date:	08-08-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	21-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-07-2019
Application type:	Amendment
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	NL48667.078.14