The role of inflammatory mediators (platelet activity,the number and origin of micro particles and levels of mitochondrial DNA) in patient with acute renal transplant rejection.

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The objective of this study is to investigate the role of inflammatory mediators (circulating platelet activity levels, MP numbers, and levels of plasma/urinary mtDNA) to the occurrence and severity of acute rejection and renal outcome.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Observational invasive

Summary

ID

NL-OMON41402

Source
ToetsingOnline

Brief title
Inflammatory mediators in acute renal transplant rejection

Condition

- Autoimmune disorders
- Nephropathies

Synonym
acute renal transplant injury, renal inflammation

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Nierstichting

Intervention

Keyword: AKI, Inflammation, Mediators, rejection

Outcome measures

Primary outcome

The main parameter of this study is the presence and activity of inflammatory mediators, platelet activity (measured as P-selectin positive platelets), the origin and numbers of micro particles, and levels of circulating (plasma) and local (urinary) mtDNA).

Secondary outcome

Concentrations of proinflammatory cytokines and chemokines in plasma and urine (TNF-alpha, IL-1beta, IL-6 and IL-8) and acute tubular injury markers in urine (KIM-1 and NGAL).

Study description

Background summary

Although current immunosuppressive drug therapies are quite successful, acute renal allograft rejection still occurs in approximately 20% of patients after cadaveric renal transplantation and causes graft loss in up to 4% in the first year after transplantation. In the AMC, 120 patients per year receive a kidney transplant, of which ± 22% develop acute rejection. Episodes of acute rejection often have a negative impact on long-term graft survival and are major predictors of chronic allograft nephropathy, which is responsible for most death-censored graft loss after the first year posttransplant. The lack of non-invasive biomarkers for rejection makes it difficult to optimize anti-rejection therapy for transplant recipients. At present, the diagnosis of renal allograft rejection requires a renal biopsy. Clinical management of renal

transplant patients would be improved by the identification of non-invasive markers of rejection that can be measured frequently.
Renal ischemia- reperfusion (I/R) injury is a major cause of acute renal transplant rejection and delayed allograft function. I/R injury is a consequence of a complex interplay between renal hemodynamics, tubular and endothelial cell injury and inflammatory processes. Circulating microparticles (MP), platelets and mitochondrial DNA (mtDNA) have been identified as important inflammatory mediators. Hence, these factors might contribute to induce renal inflammatory responses upon I/R that eventually might lead to allograft rejection.
We therefore hypothesize that inflammatory factors as circulating (plasma) platelet activity levels, MP numbers and the levels of plasma or urinary mtDNA correlate to the occurrence and severity of acute renal transplant rejection and renal outcome.

Study objective

The objective of this study is to investigate the role of inflammatory mediators (circulating platelet activity levels, MP numbers, and levels of plasma/urinary mtDNA) to the occurrence and severity of acute rejection and renal outcome.

Study design

This study will be a prospective longitudinal observational cohort study in the Academic Medical Center, in which we will include the following individuals: Renal transplant recipients from either heart beating, non-heart beating donors and living donors .In these patients blood will be drawn and urine will be collected routinely in order to monitor for clinical signs of acute transplant rejection. Depending on the clinical parameters (creatinine and urea levels in plasma and urine) patients will undergo an indicative biopsy to confirm acute rejection, or a protocol biopsy, which will be in part of the current research protocol.
Patients are then divided into two groups:
1. Patients with clinical signs of acute rejection (according to blood and urine parameters and the indicative biopsy) (n=11)
2. Patients without clinical signs of acute rejection (according to blood and urine parameters and the protocol biopsy in part of the current research protocol) (n=44)
Furthermore, a group of healthy individuals (n=10) will be included to determine basal levels of inflammatory mediators in blood and urine.

Group 1&2

As part of standard care, blood is drawn and urine is collected for monitoring renal functional parameters and graft function.

This will occur in: all patients (group 1 & 2) in the first week post transplantation (at T=0); in patients (group 1) with signs of acute rejection in which the indicative biopsy confirms acute transplant rejection (at T=X), in patients without signs of acute rejection (group 2) which, undergo a protocol biopsy (at T=6).

In addition, blood and urine will be collected 12 months (T=12) post transplantation from both group 1 and 2,
For the purposes of this study 3 additional vials of blood (each 9mL) will be drawn at all indicated time points.
To prevent unwanted activation of platelets and/or mitochondria, the required additional blood will be collected into citrate vials.
Urine (1 mL) will be collected from the catheter in the first week post transplantation and from the urine portion which is collected at all indicated time points.
There are no additional interventions needed for this study

Healthy individuals

Blood will be drawn and urine will be collected from healthy volunteers to asses basal levels of inflammatory mediators in blood and urine. In order to determine the individual variance of these basal levels, blood will be drawn at three time points: T=0, T= 6 and T=12 months.

Study burden and risks

All patients included in the study will receive standard care and medication. As part of postoperative procedure, blood is drawn and urine is collected routinely in the first week, after 6 months and 12 months post transplantation in order to monitor renal functional parameters and graft recovery. Depending on clinical signs of acute rejection (increased creatinine and urea plasma levels or the development of proteinuria) an indicative biopsy will be taken to confirm acute transplant rejection as part of good clinical practice. Furthermore, as part of a current research protocol, a scheduled renal transplant biopsy will be performed 6 months posttransplantation in order to monitor graft condition. At the time of either biopsy, in the first week after transplantation, at 6 and 12 months hereafter, 3 additional vials of blood (each 9 mL) will be drawn and one sample of urine will be collected from the patients.

Besides the donation of an additional 27 ml of peripheral blood (the cumulative amount for the total study period of a year), no additional intervention is necessary for the patients that will be included in this study. Hence, to our opinion no unwanted or unpleasant side effects might occur. In addition, this study will not require more time and will not modify the standard treatment of enrolled patients.
Blood drawing will be exerted by professional nurses and physicians and will be

incorporated in the bloodsampling for clinical purposes. In this perspective, no risks are associated with the participation of patients to this study.

A participating patient will not directly benefit from this observational study. However, patients and volunteers might assess satisfaction of helping others by contributing to medical knowledge, or helping to identify possible new treatments. More knowledge about the possible correlation between platelet activity/ number and origin of micro particles and the occurrence and severity of acute renal transplant rejection, could be beneficial for future renal transplant recipients characterized with acute rejection,

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 heart beating, non-heart-beating donors and living donors. Patients and healthy volunteers have to sign the informed consent form.

Exclusion criteria

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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):	24-01-2013
Enrollment:	65
Type:	Actual

Ethics review

Approved WMO

Date:	31-10-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	NL40978.018.12