The intracellular pharmacokinetics of tacrolimus in CD3+ T lymphocytes

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To prospectively measure the intracellular tacrolimus concentration in CD3+ T lymphocytes in kidney transplant recipients. The area under the concentration-vs-time curve (AUC) of the intracellular tacrolimus concentration will be determined and used...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal disorders (excl nephropathies)
Study type	Observational invasive

Summary

ID

NL-OMON51867

Source
ToetsingOnline

Brief title
INTACT

Condition

- Renal disorders (excl nephropathies)

Synonym
Immunosuppressive drug

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: Intracellular T-lymphocyte concentration, Pharmacokinetics, Renal transplantation, Tacrolimus

Outcome measures

Primary outcome

The intracellular tacrolimus concentration in CD3+ T lymphocytes and a

population pharmacokinetic model to describe tacrolimus.

Secondary outcome

The association between the intracellular tacrolimus concentration in CD3+ T

lymphocytes and IL-2 and IFN-* production by these same cells.

The association between the intracellular tacrolimus concentration in CD3+ T

lymphocytes and clinical events (post-transplant diabetes mellitus and acute

rejection).

Study description

Background summary

The immunosuppressive drug tacrolimus is routinely monitored after kidney transplantation by measuring the whole blood, pre-dose concentration (C0). However, the C0 has a poor correlation with clinical events, most notably the risk of acute rejection. Since tacrolimus* site of action is within immune cells, the intracellular tacrolimus concentration in peripheral blood mononuclear cells (PBMCs) has recently been proposed to better represent the active concentration. However, several studies could not demonstrate an association between the intracellular tacrolimus concentration and acute rejection. One of the possible explanations for this surprising finding is the fact the PBMC fraction is composed of several cells including lymphocytes and monocytes. In this study, the tacrolimus concentration in CD3+ T lymphocytes will be investigated as this may be a more relevant cell population than PBMCs.

Study objective

To prospectively measure the intracellular tacrolimus concentration in CD3+ T lymphocytes in kidney transplant recipients. The area under the concentration-vs-time curve (AUC) of the intracellular tacrolimus concentration will be determined and used for the development of a population pharmacokinetic model. The pharmacokinetics of intra-CD3+ tacrolimus will be compared with the whole-blood concentration and will be related to important clinical events.

Study design

Observational study with additional blood sampling.

Study burden and risks

The participants in this study are de novo kidney transplant recipients transplanted at the Erasmus MC. These patients will receive routine medical care. Twenty mL of venous blood will be sampled from each participant on 4 occasions, including time 0 (pre-dose concentration), 4, and 8 hours after tacrolimus administration on day 5-7 post-kidney transplant and time 0 at day 14 (20 mL at each timepoint for a total of 80 mL per patient for the whole study). No extra-visits are required.

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

- Age * 18 years.
- Recipient of a kidney transplant at the Erasmus MC.
- Use once-daily tacrolimus as part of routine maintenance immunosuppression starting the day of surgery.
- Written informed consent.

Exclusion criteria

Patients who receive lymphocyte depleting agents (thymoglobuline, anti-thymocyte globulin, and alemtuzumab) as an induction therapy or anti-rejection treatment before enrolment. Recipients using medication known to have a pharmacokinetic (drug-drug) interaction with tacrolimus: Antibiotics (Clarithromycin, Doxycyclin, Erythromycin, Rifampicin), Antiepileptics (Carbamazepine, Phenobarbital, Phenytoin), Antihypertensive and antiarrhythmic agents (Amiodarone, Diltiazem, Verapamil), Antimycotic drugs (Fluconazole, Itraconazole, Ketoconazole), Other (HIV protease inhibitors, Theophyllin)

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-05-2022
Enrollment:	25
Type:	Actual

Ethics review

Approved WMO Date:	27-04-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-09-2022
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	NL80363.078.22

Study results

Date completed:	30-11-2022
Actual enrolment:	31