Pharmacokinetics of tacrolimus during pregnancy in kidney and liver transplant recipients.

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

Summary

ID

NL-OMON51032

Source
ToetsingOnline

Brief title
Tacrolimus during pregnancy.

Condition

- Hepatic and hepatobiliary disorders
- Pregnancy, labour, delivery and postpartum conditions
- Renal disorders (excl nephropathies)

Synonym
kidney transplantation and liver transplantation

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: kidney transplant recipient, liver transplant recipient, pregnancy, tacrolimus

Outcome measures

Primary outcome

The correlation between the plasma tacrolimus concentration and whole blood tacrolimus concentration during pregnancy in kidney and liver transplant recipients.

Secondary outcome

Secondary study parameters focus on the change of the fraction of tacrolimus in plasma relative to whole blood before, during and after pregnancy.

- Relating the free tacrolimus and whole blood tacrolimus levels to kidney function.

- Assessing whether there is a difference in the pharmacokinetics and pharmacodynamics of kidney transplant compared to liver transplant recipients.

- To describe the pharmacokinetics of tacrolimus before, during and after pregnancy in kidney and liver transplant recipients in a population pharmacokinetic model using data from the concentration of whole blood tacrolimus, plasma tacrolimus, AUCs, the tacrolimus concentration within CD3+ T lymphocytes, genotyping of CYP3A, ABCB1 and POR, and body composition;

- To perform simulations with the population pharmacokinetic model in order to predict which dosages of tacrolimus are needed to obtain the target trough concentration, for future pregnant patients after kidney of liver transplantation before, during and after pregnancy;

- To define the correlation between whole-blood tacrolimus concentrations and intracellular tacrolimus concentrations and plasma tacrolimus concentrations (prior to conception and during gestation);

- To determine tacrolimus concentrations in umbilical cord blood and analyze the tacrolimus placenta transfer ratio;

- To determine the effect of maternal CYP3A4 and CYP3A5 genotype and foetal CYP3A7 genotype on tacrolimus concentrations;

- To determine the transfer of tacrolimus into breast milk.

Study description

Background summary

In clinical practice, tacrolimus is nowadays often the backbone of immunosuppressive therapy after solid organ transplantation (SOT). Tacrolimus has a narrow therapeutic window and a high degree of intra- and inter-individual pharmacokinetic variability. Therefore, therapeutic drug monitoring (TDM) is routinely performed using whole blood trough levels. However, whole blood trough levels might not be the optimal method since >85% of tacrolimus in the blood is bound to erythrocytes and therefore not therapeutically active. The maternal anatomical and physiological adaptations to pregnancy might affect the pharmacokinetics of tacrolimus but existing knowledge on these affects is scarce. Lastly, little is known about the possible influence of tacrolimus on placental development and exposure to tacrolimus in the foetus.

Study objective

The overall aim of the study is to gain more insight in as well as understand and map the pharmacokinetics of tacrolimus during pregnancy. Therefore, we will study tacrolimus concentrations in maternal whole blood (routine care) and via area under the curve measurements (AUC), in maternal plasma, in maternal CD3+ T lymphocytes, and postpartum in the umbilical cord (foetal compartment), in breast milk and in the placenta. Moreover, we will study the maternal and foetal SNPs/genotypes related with tacrolimus clearance and perform maternal body composition measurements.

Study design

In this prospective two-center cohort study all patients who are planning to become pregnant after a kidney or liver transplantation in the University Medical Centre Groningen (UMCG) or the Erasmus Medical Center Rotterdam (Erasmus MC) are eligible for inclusion. Patients will be identified during the preconception period. The study period is from study inclusion until one year postpartum. The study procedures consist of extra blood samples taken at routinely scheduled venepunctures, AUC measurements using dried blood spots (DBS) via finger pricks at 5 different days (3 finger pricks per day), assessing body composition via bio-impedance spectroscopy at 5 different time-points, one extra venepuncture during delivery, collection of umbilical cord blood and the placenta directly after delivery, collection of foetal residual blood and collection of two samples of breast milk. Besides one extra venepuncture during delivery, no extra venepunctures are needed.

Study burden and risks

The extra burden in this study is limited to an increased amount of drawn blood volume, for a total of 110 mL per patient. These additional measurements will be combined with standard clinical care venepunctures, except for the AUCs via DBS which will require finger pricks at 5 different days (3 finger pricks per day, e.g. a total amount of 15 finger pricks). This approach is minimal-invasive and patient-friendly, collecting very small amounts of blood (typically 50 µL). For patients who will give birth to their offspring in the UMCG or Erasmus MC, 1 extra venepuncture around time of delivery is required with a total amount of 4 mL blood (smallest tube size) and the placenta will be collected (residual material). If a renal allograft biopsy is performed during the study period, we will collect 25 mL blood via 1 venepuncture and 3 finger pricks, if feasible. The burden of possible adverse events from these extra venepunctures is low, since this only includes a superficial and local hematoma and pain. Patients willing to donate their breast milk would need to deliver a total amount of 2 mL, on two different time points postpartum.

There is no burden or risk for the offspring of the patients. The only intervention is a tacrolimus determination and CYP3A genotyping in the umbilical cord blood, and tacrolimus determination in residual blood in the first days postpartum if hospitalized and if possible.

Throughout the study, tacrolimus exposure is closely monitored according to standard care. Tacrolimus dosages are adjusted through pre-dose TDM which is currently standard care. Dosages will not be adjusted on measurements performed for the study. Patients included in this study will not have a therapeutic effect of the measurements and results. All patients will receive identical care to those not included in this study, therefore this is a low risk study. The participants have no benefit of participation in the study. The benefit of

this study is that it may provide a pharmacokinetic model which can be used to give recommendation on tacrolimus treatment during pregnancy in future pregnant patients. Information about patient characteristics and pregnancy follow-up will be obtained from the electronic patient record and therefore will also not burden the patient. Therefore, the benefits outweigh the risks.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Newborns
Premature newborns (<37 weeks pregnancy)

Inclusion criteria

-Kidney or liver transplantation in medical history
-Tacrolimus based immunosuppressive regimen
-Written informed consent

Based on previous experiences with population pharmacokinetic model building, the amount of 24 patients is sufficient to describe the pharmacokinetics during pregnancy. Taking into consideration the already included participants before the amendment, the drop outs and participants who are included during the pregnancy, we estimate that around 50 patients will participate in the study.

Exclusion criteria

• Age <18y
• Albumin concentration below 30 g/L

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-08-2021
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO

Date:	16-08-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	29-05-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL76210.042.20