Personalized tacrolimus treatment for pediatric kidney transplant recipients by using a dosing algorithm and a once-daily tacrolimus formulation.

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This study has been transitioned to CTIS with ID 2024-511585-36-00 check the CTIS register for the current data. The key objective is to personalize tacrolimus treatment for children with a renal transplant by using dosing algorithms to calculate...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON51392

Source
ToetsingOnline

Brief title
TACKI (Tacrolimus dosing in children with donor kidney)

Condition

- Other condition
- Renal disorders (excl nephropathies)

Synonym
immunosuppressant drugs, renal transplantation

Health condition

niertransplantatie

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: pediatric renal transplantation, pharmacokinetics, population based modelling, tacrolimus

Outcome measures

Primary outcome

The percentage of children within the target C0 range of tacrolimus (10-15

ng/mL) on day 3 after kidney transplantation following algorithm-based dosing

Secondary outcome

• The percentage of patients with markedly supra- (> 20 ng/L) or sub- (< 5.0

ng/L) therapeutic tacrolimus C0 on day 3 after transplantation;

• The percentage of patients with a tacrolimus AUC0-8 within the target range

(140 - 180 ng h/mL) on day 9-14 after transplantation;

• The percentage of patients with a sub- and supra-therapeutic tacrolimus

AUC0-8 on day 9-14 post-transplantation;

• The incidence of biopsy-proven acute rejection (BPAR) and serious adverse

events (SAEs);

• The incidence of viral infections (Epstein-Barr virus and Cytomegalovirus)

and diabetes mellitus;

• The role of the human microbiome in intra- and inter-patient variability in

tacrolimus pharmacokinetics;

• The description of the pharmacokinetics of a once-daily tacrolimus

formulation.

Study description

Background summary

Bodyweight-based dosing of the immunosuppressive drug tacrolimus in paediatric kidney transplant recipients is considered standard care, even though the available evidence for bodyweight-based dosing is thin. Other factors, including age, ethnicity, co-medication, cytochrome P450 3A (CYP3A) genotype, and haematocrit, influence the clearance of tacrolimus significantly. Also, the human microbiome might affect tacrolimus pharmacokinetics and thus an individual*s dose requirement. The median time to reach the tacrolimus target pre-dose concentration (C0) is around 7 days but it may take up to 3 weeks in some individuals, even with therapeutic drug monitoring (TDM). Underexposure to tacrolimus is associated with rejection and overexposure to the drug with toxicity. We have developed and improved a tacrolimus dosing algorithm in our paediatric kidney transplant recipient population, which bases the starting dose of tacrolimus on bodyweight and CYP3A5 genotype rather than on bodyweight alone. In part A of this study, this dosing algorithm will be tested prospectively in this study to guide the tacrolimus starting dose. Computerized dosing will then be used to adjust the subsequent tacrolimus doses (once the patient is in steady state) to maintain patients within the target tacrolimus exposure range, aiming for an area under the concentration versus time curve (AUC) of 140-180 ng h/mL on day 9-14 after transplantation. Computerized dosing will not only be based on historical tacrolimus doses and concentrations, but also on bodyweight, serum creatinine, CYP3A5 genotype, and haematocrit. In part B of the study, 4 weeks after transplantation, children will switch from a twice-daily tacrolimus formulation to a once-daily tacrolimus formulation and a second AUC0-12 will be measured with the aim to describe the pharmacokinetics of the once-daily tacrolimus formulation.
The hypotheses are that 1) more patients will be within the target C0 range (10-15 ng/mL) on day 3 after transplantation (primary endpoint; first steady-state) using the tacrolimus starting dose algorithm and 2) that more patients will achieve their target tacrolimus AUC0-8 on day 9-14 after transplantation (secondary endpoint) by using the computerized follow-up dosing.

Study objective

This study has been transitioned to CTIS with ID 2024-511585-36-00 check the CTIS register for the current data.

The key objective is to personalize tacrolimus treatment for children with a renal transplant by using dosing algorithms to calculate both the individual*s tacrolimus starting dose and follow-up doses. Secondary aims are evaluating the role of the gut microbiome in tacrolimus pharmacokinetics, and describing the tacrolimus pharmacokinetics of a once-daily tacrolimus formulation.

Study design

Prospective, multi-centre, single-arm, therapeutic intervention study.

Intervention

All participants will receive a tacrolimus starting dose based on a dosing algorithm which takes bodyweight and genetic factors into account, rather than the standard dose which is based on bodyweight alone. After the first tacrolimus C0 measurement (day 3), computerized dosing will be used to determine subsequent doses, rather than standard TDM by a transplant physician. On day 9-14 an AUC0-8 will be measured as part of standard clinical care. A stool-sample will be collected prior to transplantation and on the day of the AUC0-8 measurement (post-operative day 9-14) to evaluate the effect of the gut microbiome on tacrolimus pharmacokinetics. Four weeks after transplantation, patients will switch from a twice-daily to a once-daily tacrolimus formulation. On the day of the switch a C0 and peak concentration (Cmax) will be measured and two weeks after this switch (after week 6), an AUC0-12 will be measured to describe the pharmacokinetics of the once-daily tacrolimus formulation and compare it to the twice-daily formulation.

Study burden and risks

The extra burden for children in the Sophia Children*s hospital and the Amalia Children*s hospital for the first part of the study (part A) will include the collection of one extra blood sample on day 3 post-transplantation (to determine the tacrolimus peak concentration, Cmax) and the collection of two stool samples (for determination of the microbiome) during hospitalization. As all children will have a central venous catheter or an arterial line during hospitalization, the extra blood sample on day 3 does not require an extra venepuncture. Four weeks after transplantation, in part B of the study, the children will switch from a twice-daily to a once-daily tacrolimus formulation. Before this switch an extra Cmax will be measured using a blood sampling method of the patient*s choice (fingerprick or venepuncture), and after the switch, an AUC0-12 will be measured. Apart from the tacrolimus algorithm-based dosing and the switch to a once-daily tacrolimus formulation, all children will receive identical care to those not included in the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- Age 2-18 years old
- Patients to be transplanted with a kidney allograft
- Patients receiving a kidney from a blood group ABO-compatible donor
- Patients who will receive tacrolimus as part of their initial immunosuppressive therapy
- Signed written informed consent

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Recipients of a non-renal organ transplant at the same occasion
- Recipients of a blood group ABO-incompatible kidney allograft
- Recipients of an HLA-incompatible kidney allograft (positive cross-match)
- Recipients receiving tacrolimus as immunosuppressive treatment within the preceding 28 days.
- Recipients using medication known to have a pharmacokinetic (drug-drug) interaction with tacrolimus

Extra exclusion criteria for participation in study part B:
- Children who are not able to swallow a once-daily tacrolimus capsule
- Children with changes in the administration of drugs interacting with tacrolimus around the switch to the once-daily formulation

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-05-2024
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tacrolimus capsule extended release (ER)

Generic name:	Envarsus capsule extended release (ER)
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	04-08-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-09-2022
Application type:	First submission
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
EU-CTR	CTIS2024-511585-36-00
EudraCT	EUCTR2021-006481-21-NL
CCMO	NL79916.078.22