Personalized Use of Resources study

Published: 18-06-2021
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This study has been transitioned to CTIS with ID 2024-515542-16-02 check the CTIS register for the current data. Primary objective:The objective is to evaluate if the LCPT dose can be reduced in comparison with tacrolimus-ER and still achieve...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional

Summary

ID

NL-OMON54135

Source
ToetsingOnline

Brief title
PURE

Condition

- Renal disorders (excl nephropathies)
- Renal and urinary tract therapeutic procedures

Synonym
immunosuppression after kidney transplant with CYP3A*5 genotyping, preventing rejection kidney after transplant when having a diversion in the CYP3A5 gene.

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Chiesi Pharmaceuticals B.V.

Intervention

Keyword: CYP3A5*1, Envarsus, Kidney transplant, Tracrolimus extended release

Outcome measures

Primary outcome

The dose in mg of Tacrolimus-LCPT (Envarsus) needed to reach adequate levels of tacrolimus trough levels in comparison with Tacrolimus-Extended-Release (Advagraf).

Secondary outcome

Secondary outcomes are:

- variability of trough levels;

- pill burden

- Cmax and Tmax;

- C/D ratio

- 24hour AUC levels;

- side effects;

- CYP3A5 genotypes.

Study description

Background summary

Kidney transplantation is in most cases the best treatment for patients with end-stage renal disease. A significant drawback of renal transplantation is the need for immunosuppressive drugs as long as the transplant is functioning. Tacrolimus is important as first line immunosuppressive in kidney transplantation. In different ethnic groups, polymorphism occurs in the CYP3A5 gene, the so called CYP3A5*1. In the African American patients, the frequency of CYP3A5*1 is, compared to Caucasians, high. The CYP3A5 gene is partly responsible for the breakdown of tacrolimus in the body. With the CYP3A5*1, a

higher dose of tacrolimus is required to achieve a normal tacrolimus level. The transplant population of the AUMC consists of a relative high number of patients from an African or Caribbean background. Up to now the prevalence of the CYP3A5*1 allele in this population remains to be clarified.

Currently there are two extended release tacrolimus formulas on the market. Tacrolimus-Extended-Release (Advagraf) and tacrolimus LCPT (Envarsus). Both formulas have proven their efficacy. Advagraf is currently used routinely as first line immunosuppressive drug after transplantation. Envarsus is designed to be better absorbed via the gastrointestinal tract. Bioavailability is low in patients who require a high dose Advagraf charactarized by a C/D-ratio <1,05 ng/ml × 1/mg. The use of Envarsus can increase bioavailability by 30%. Furthermore, the use of LCPT might result in a lower Cmax, less variability in the trough level, a faster achievement of tacrolimus levels in the therapeutic range, a lower pill burden and less side effects.

Study objective

This study has been transitioned to CTIS with ID 2024-515542-16-02 check the CTIS register for the current data.

Primary objective:
The objective is to evaluate if the LCPT dose can be reduced in comparison with tacrolimus-ER and still achieve similar tacrolimus levels in the therapeutic range in patients who are tacrolimus who need a relatively high dose of tacrolimus a C/D ratio < 1.05

Secondary objectives:
- To evaluate if the switch design of the study leads to a lower pill burden;
- To evaluate if the tacrolimus switch leads to less side effects.
-to evaluate if the tacrolimus switch leads to less variability in trough levels
- to evaluate if patients with CYP3A5*1 allele is a factor to consider when prescribing tacrolimus
-to evaluate differences in Cmax, Tmax and and 24hour AUC levels

Study design

This is a prospective, open label, switch design study.

Intervention

Two treatment arms are used in this study:
- Tacrolimus-Extende-Release (Advagraf);
- Tacrolimus LCPT (Envarsus).

On day 1 the subjects, who are on Advagraf, will be switched to Envarsus in a

rate of 1:0.7 for Advagraf to Envarsus.
Envarsus will then be taken for a period of 3 weeks.
On day 23 all subjects will be switched to their usual dose of advagraf.
At the end of the study, on day 46, the subject have the choice to maintain Advagraf or be switched to Envarsus again.

Study burden and risks

Kidney transplantation is in most cases the best treatment for patients with end-stage renal disease. Tacrolimus is important as a first-line immunosuppressive treatment for kidney transplants. The CYP3A5 gene is partly responsible for the breakdown of tacrolimus in the body. In different ethnic groups, polymorphism occurs in the CYP3A5 gene, leading to CYP3A5*1. In people with the CYP3A5*1 gene variance, a higher dose of tacrolimus is required to achieve normal tacrolimus levels.

In this study, 2 registered immunosuppressive agents are used, namely Tacrolimus-Extended-Release (Advagraf) and Tacrolimus LCPT (Envarsus). People with the CYP3A5*1 gene variant are expected to require a lower dose of Envarsus compared to Advagraf to achieve a good drug level. This leads to a lower pill burden, less side effects and lower toxicity.

Side effects of tacrolimus can be:
- Gastro-intestinal complaints such as abdominal pain, constipation, diarrhea, nausea, vomiting;
- Thirst and excessive urination;
- Increase in hand tremors;
- Blood urination;
- Transplant kidney pain.

The risks/burden associated with the procedures:
- Blood draw: blood draw may cause some discomfort, bruising, minor infections or bleeding.

The following procedures are performed:
- Blood draws at all visits;
- Collection of 24-hours urine before all visits;
- Completion of questionnaire at the initial visit only.

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

a. Patients aged 18 to 70 years, with a stable renal function
b. Patients who are at least 6 months until five years after first transplantation, who are not immunized (PRA<5%) with therapeutic tacrolimus concentrations between 4-9 ng/L and on a stable tacrolimus dose (are using the same dosage of Tacrolimus extended release for the last month) with Tacrolimus-Extended-Release with a C/D ratio < 1.05 ng/mL×1/mg
c. Patients must provide written informed consent
d. Patients of childbearing potential must agree to use highly effective methods of contraception during the study.

Exclusion criteria

a. Patient received or is receiving treatment for acute rejection prior to initiation of study
b. Donor Specific antibody positivity and patients who are immunized (PRA>=5%)
c. Chronic diarrhoea
d. Use of phenytoin, carbamazepine, phenobarbital, primidone, rifampin,

caspofungin, erythromycin, clarithromycin, fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole, fluoxetine, fluvozamine, sertraline, venlafaxine, mirtazapine, paroxetine, diltiazem, verapramil, amiodaron
e Thyroid dysfunction
f. Excessive use of caffeine (more than use of 5 IE daily)
g. Excessive use of alcohol (more than 2 IE daily)
h.. Patients who are pregnant.

Study design

Design

Study type:	Interventional
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):	07-02-2022
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Advagraf
Generic name:	Tacrolimus ER
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Envarsus
Generic name:	Tacrolimus LCPT
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	18-06-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-08-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	09-08-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389

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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	CTIS2024-515542-16-02
EU-CTR	CTIS2024-515542-16-03
EudraCT	EUCTR2020-001101-22-NL
CCMO	NL73399.018.20