CONVERSION TO TACROLIMUS MELTDOSE (ENVARSUS), A PK GUIDED EVALUATION STUDY IN STABLE LIVER TRANSPLANT RECIPIENTS

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To develop a population pharmacokinetic model of Envarsus in stable liver transplant recipients and to evaluate the effect of CYP3A5*3, CYP3A4*22 and IL-polymorphisms of both donor and recipient on Envarsus pharmacokinetics for initial dose...

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

Summary

ID

NL-OMON47419

Source
ToetsingOnline

Brief title
PK guided evaluation study of Envarsus

Condition

- Other condition

Synonym
liver transplantation

Health condition

levertransplantatie

Research involving

Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Chiesi Farmaceutici

Intervention

Keyword: liver transplantation, pharmacogenetics, pharmacokinetics, tacrolimus melt dose

Outcome measures

Primary outcome

a: Population Pharmacokinetic parameters of tacrolimus (Envarsus)

b: PK dependency on CYP3A5*3, CYP3A4*22 and IL genotypes of recipient and of

donor.

Secondary outcome

a: Limited PK samplingmodel for accurate AUC estimation

b: Trough - AUC correlation

c:: Changes in Quality of Life before and after conversion.

Study description

Background summary

Prolonged release tacrolimus (Envarsus), is a new formulation of the calcineurin inhibitor tacrolimus. This product was originally developed to improve bioavailability and to provide more consistent tacrolimus exposure. Envarsus has also demonstrated a lower peak (Cmax) and reduced peak-to-trough fluctuations which is associated with decreased tremor incidence. For this reason doctors are already prescribing Envarsus for liver transplant recipients. Its pharmacologically active compound tacrolimus is characterized by a narrow therapeutic window, and highly variable pharmacokinetics necessitating Therapeutic Drug Monitoring (TDM) to individualize the dose and prevent rejection or toxicity such as leukopenia and renal toxicity.
Currently in LUMC in daily routine clinical practice tacrolimus (for every

formulation) is dosed based on a limited sampling AUC. Tacrolimus AUC correlates better with efficacy and side effects than trough concentrations. For AUC calculation a population PK model is required. However, at the moment there is no population pharmacokinetic model available for envarsus in contrast to prograft and advagraf. Tacrolimus is primarily metabolized by the cytochrome P450 enzymes CYP3A4 and CYP3A5. Genetic polymorphisms in CYP3A4 and CYP3A5 are known to cause clinically relevant variability in tacrolimus pharmacokinetics in solid organ transplantation. Therefore transplant recipients at LUMC are currently genotyped on a routine basis for CYP3A5 polymorphisms in order to adjust the initial starting dose. Several studies investigated the role of genetic variants encoding for CYP3A5 in tacrolimus (prograft and advagraf) pharmacokinetics in liver transplant recipients but genetic variants were never investigated in relationship with patients receiving Melt Dose tacrolimus (Envarsus). Since Envarsus has a more prolonged release than the other formulations and CYP3A4 enzymes are more expressed in the lower tract of the intestine the effect of CYP3A4 and CYP3A5 polymorphism might be different compared to prograft and advagraf . Furthermore evidence is accumulating that pro-inflammatory cytokines are able to down-regulate CYP enzymes. Interleukin levels and IL-10, IL-6, IL-18 and TNF-alpha polymorphisms have been associated with altered tacrolimus pharmacokinetics.

We designed this study protocol to develop a population pharmacokinetic model of Envarsus in stable liver transplant recipients and to evaluate the effect of CYP3A5*3, CYP3A4*22 and IL-polymorphisms of both donor and recipient on Envarsus pharmacokinetics for initial dose differentiation and compare it to Advagraf (the current standard in liver transplantation). Furthermore, we will study two secondary objectives:
1. Development of a limited sampling strategy to enable accurate prediction of Envarsus exposure in liver transplant recipients in an efficient way and to compare it with widely used Ctrough monitoring and the results of Advagraf.
2. Evaluation Quality of life before and after switch to Envarsus therapy using validated QOL questionnaires, i.e., Short-Form 36 (SF-36), Multidimensional Fatigue Index-20 (MFI-20), Euroqol 5D (EQ-5D) and adjusted Liver Disease Symptom Index (LDSI).

Study objective

To develop a population pharmacokinetic model of Envarsus in stable liver transplant recipients and to evaluate the effect of CYP3A5*3, CYP3A4*22 and IL-polymorphisms of both donor and recipient on Envarsus pharmacokinetics for initial dose differentiation and compare it to the current standard Advagraf.The first secondary objective is to develop a limited sampling strategy for accurate AUC estimation of Envarsus. The second secondary objective is the evaluate quality of life of patients on both tacrolimus formulations.

Study design

An open-label, prospective conversion PK evaluation study

Study burden and risks

Burden:
In addition to regular care (potential burden)
- completing questionnaires during advagraf and envarsus therapy
- whole pk curve measurement via venapuncture including venflon
- use of Dried Blood Spot technique to sample blood to determine drug exposure

Benefit:
Patients on Advagraf will be converted to Envarsus, which might be accompanied by less adverse effects based on reduced peak-to-trough fluctuations. This is associated with decreased tremor incidence. Envarsus based immunosuppressive therapy has been shown to have an improved bioavailability and provide a more consistent tacrolimus exposure suggesting an overall benefit for the patients of conversion. This study has been designed to develop a population pharmacokinetic model of Envarsus in stable liver transplant recipients to be able to perform AUC based dosing in the future.

Risks:
Participation within the trial comes with minimal risks (if present).
Monitoring of tacrolimus blood concentration
via fingerprick can result in some discomfort. Venapunctures at the hospital could eventually result in hematoma.

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

1. Patient is recipient of a liver transplant at least 6 months prior to entry into the study.
2. Patients are between 18 and 70 years old.
3. Patient is stable on an Advagraf (tacrolimus) based immunosuppressive regimen for at least 3 months.
4. The Advagraf based immunosuppressive regimen remained unchanged for a minimum of 2 months prior to enrolment.
5. The function of the graft is stable.
6. Patients capable of understanding the purpose and risks of the study, has been fully informed and has given written informed consent to participate in the study and at time of conversion.
7. Patients haven*t infections or other complications during inclusion into the study.

Exclusion criteria

1. Patient with infections or other complications during inclusion.
2. Patients with direct bilirubin >10 µmol/L or albumin level outside the clinical reference range.
3. Patients allergic or hypersensitive to tacrolimus
4. Patients with an estimated glomerular filtration rate (eGFR) <30 mL/min at time of screening.
5. Patients with unstable dosing and the concomitant use of medications known to affect the PK profile of tacrolimus at the time of conversion.

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):	13-09-2017
Enrollment:	55
Type:	Actual

Ethics review

Approved WMO

Date:	22-03-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	11-09-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	27-09-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL59447.058.16