Modifying tacrolimus related toxicity after liver transplantation. A randomized controlled trial comparing Envarsus® and Advagraf® in de novo liver transplant recipients.

Published: 30-10-2018
Last updated: 15-05-2024

To investigate whether Envarsus® leads to a significant reduction in new onset diabetes, chronic kidney disease and new onset hypertension.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON55491

Source
ToetsingOnline

Brief title
MOTTO

Condition

- Hepatic and hepatobiliary disorders

Synonym
liver transplantation

Research involving
Human

Sponsors and support

Primary sponsor: Stichting Leveronderzoek
Source(s) of monetary or material Support: Chiesi Farmaceutici,Stichting Lever en Maag Darm onderzoek

Intervention

Keyword: - liver transplantation, - tacrolimus, - toxicity

Outcome measures

Primary outcome

The primary endpoint is a composite endpoint of any of three events: sustained

(>3 months post randomization) new onset diabetes mellitus, eGFR < 60

ml/minute/1.73 m2 for >3 months or new onset hypertension. Therefore, patients

will reach the primary endpoint if any of the three events occurs.

Secondary outcome

- The individual components of the composite end-point will also be analysed as

separate secondary study outcomes.

- Graft survival

- Recipient survival

- Number of episodes and severity of acute cellular rejection

- Differences in prevalence and severity of tremor

- Intra-patient variability

- Metabolizing status of tacrolimus

- Liver steatosis and fibrosis

- Quality of life

- patients will have AUC measurements of tacrolimus concentrations.

Study description

Background summary

Chronic use of tacrolimus is associated with significant side effects including new onset diabetes after transplantation (NODAT), renal impairment, hypertension, hyperlipidemia and tremor and other neurotoxic traits. It is known that toxicity of tacrolimus is (partly) related to higher peak serum blood concentrations in the first year after transplantation. Reducing peak levels without reducing effective inhibition of the immune response could therefore theoretically attenuate the toxic effects of tacrolimus. Envarsus®, a prolonged release formulation of tacrolimus which gives less fluctuation of whole-blood tacrolimus concentrations and requires lower dosage for similar systemic tacrolimus exposure has the potential to lower the toxic effects of tacrolimus and decrease the amount of metabolic side effects, as compared to the current standard, Advagraf®.

Study objective

To investigate whether Envarsus® leads to a significant reduction in new onset diabetes, chronic kidney disease and new onset hypertension.

Study design

Randomized controlled two-arm phase 4 intervention trial comparing Envarsus® with the current standard treatment Advagraf® after liver transplantation.

Intervention

At discharge post transplantation patients will be initiated on prolonged release tacrolimus, which, according to randomization, will either be standard Advagraf® or Envarsus®.

Study burden and risks

The study resembles our standard clinical practice in that recipients are always converted from an immediate release tacrolimus (i.e. Prograft®) to an extended release formulation (previously exclusively Advagraf®) at hospital discharge. Furthermore, the study visit schedule is an exact copy of our regular outpatient visit schedule post-transplantation and does not include any invasive interventions. All blood draws scheduled in this study are part of routine care.
Patients will have AUC measurements of tacrolimus concentrations.
Throughout the study participants will be closely (monthly) monitored for adequate tacrolimus exposure. As both tacrolimus formulations are approved for

this indication and the active drug on both formulations is the same, this study is considered a low risk study. The anticipated benefit of this study is that it may lead to lowering of the metabolic side effects, nefrotoxicity and neurotoxicity of long term tacrolimus treatment. Thus, we believe that the benefit-risk assessment for this study is favourable.

Contacts

Public
Stichting Leveronderzoek

Dr. Molewaterplein 40
Rotterdam 3015 GD
NL
Scientific
Stichting Leveronderzoek

Dr. Molewaterplein 40
Rotterdam 3015 GD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• First liver transplantation
• Age between 18 and 75
• Using immediate release tacrolimus
• Female subjects of childbearing potential must agree to practice effective birth control during the study

• Informed consent

Exclusion criteria

• Pregnancy
• eGFR < 30 mL/min/1.73m2
• Systemic infection
• Combined organ transplantation
• Use of a mTOR inhibitor
• Use of other tacrolimus formulations
• Hepatic artery trombosis
• Known allergy to the study drug or any of its components

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-04-2019
Enrollment:	106
Type:	Actual

Medical products/devices used

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

Brand name:	Envarsus
Generic name:	Tacrolimus
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	30-10-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-03-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	08-06-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-06-2021
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

ID: 24720
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2018-002856-34-NL
CCMO	NL67040.078.18
OMON	NL-OMON24720