MOdifying Tacrolimus related TOxicity after liver transplantation

Published: 20-09-2018
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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	-
Study type	Interventional

Summary

ID

NL-OMON24720

Source
NTR

Brief title
MOTTO

Synonym
LTx, HCC,

Health condition

Liver transplantation

Research involving
Human

Sponsors and support

Primary sponsor:	Stichting Lever en Maag Darm onderzoek, Erasmus MC
Secondary sponsors:	Chiesi Pharmaceuticals B.V.
Source(s) of monetary or material Support:	Chiesi BV

Intervention

Explanation

Outcome measures

Primary outcome

A composite endpoint of any of three events: sustained (>3 months post transplantation) new onset diabetes mellitus, eGFR < 60 ml/minute/1.73 m2 for >3 months or new onset hypertension.

Secondary outcome

- Drug compliance

- Quality of life

- Neurotoxicity in terms of tremors, cognitive impairment, sleep quality

- Pharmacokinetics and –dynamics

- Drug metabolism

- Liver steatosis and fibrosis

- Efficacy in terms of graft and patient survival and episodes of acute cellular rejection, chronic rejection, antibody mediated rejection

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
tacrolimus

Study burden and risks
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.

Contacts

Public

Scientific

Eligibility criteria

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

Inclusion criteria

- First liver transplantation

- Age between 18 and 75

- Using immediate release tacrolimus

- written informed consent

- Female subject of childbearing potential must agree to practice effective birth control

Exclusion criteria

- Pregnancy or breast feeding

- 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
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

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

IPD sharing statement

Plan to share IPD: No

Ethics review

Approved WMO Date:	01-03-2019
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

ID: 55491
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL7372
NTR-old	NTR7580
CCMO	NL67040.078.18
EudraCT	2018-002856-34
OMON	NL-OMON55491

Study results

Results posted:	27-10-2023
Actual enrolment:	106

Summary results
Significantly less liver transplant recipients reached the composite primary endpoint at 12 months in the LCP-tacrolimus group compared to the extended-release tacrolimus group (50.9%, 95%-CI 37.9% - 63.9% versus 71.2%, 95%-CI 57.7% - 81.7%, p=0.005). This significant difference was observed both in the intention-to-treat and in the per protocol analysis. No differences in rejection rate, graft and patient survival were found. In conclusion, LCP-tacrolimus has a more favorable cardiovascular risk profile and results in less chronic kidney disease as compared to ER-tacrolimus in the first year after liver transplantation with comparable efficacy.

Baseline characteristics
106 included were adult patients, between 18 and 75 years, after a primary LT.

Participant flow
"A total of 106 patients was included, of whom 52 randomized to the ER-tacrolimus and 54 to the LCP-tacrolimus arm. Most of the patients was transplanted because of HCC (31/106, 29.2%), primary sclerosing cholangitis (18/106, 16.9%) or (non)alcoholic stea

Adverse events
"In total, 160 SAEs were reported: 47.5% (76/160) in the ER-tacrolimus group and 52.5% (84/160) in the LCP-tacrolimus group. SAEs most frequently reported were fever (23.1%, 37/160), cholangitis and bile duct obstruction (10%, 16/160) and infections (10%,

Outcome measures
"In this randomized controlled study, it was observed that LT recipients using LCP-tacrolimus have significantly better clinical outcomes, i.e. lower incidence of CKD, PTDM and new-onset hypertension compared to LT recipients using the ER-tacrolimus at no

First publication
30-06-2023