A multi-center randomized, open label, controlled study in primary liver transplantation comparing long term renal function in recipients treated with standard dose extended release tacrolimus alone and recipients treated with a combination of low dose extended-release tacrolimus and low dose sirolimus.

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To evaluate the effectiveness and safety of concentration controlled combination of once daily dosed low-dose sirolimus (trough levels: 3-5 ng/ml) and extended-release tacrolimus (trough levels:3-5 ng/ml), in order to provide superior renal function...

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

Summary

ID

NL-OMON44991

Source
ToetsingOnline

Brief title
LOL III

Condition

- Hepatic and hepatobiliary disorders
- Nephropathies

Synonym
Liver transplantation, replacing a bad functioning liver by an organ from a donor

Research involving
Human

Sponsors and support

Primary sponsor: Stichting Leveronderzoek
Source(s) of monetary or material Support: Astellas Pharma,farmaceutische industrie

Intervention

Keyword: Advagraf, Efficacy and safety, Liver transplantation, Optimizing immunosuppressive therapy

Outcome measures

Primary outcome

Primary endpoint:

* Percentage of patients with cGFR < 60ml/min at 36 months after

transplantation

Secondary outcome

Secondary study parameters and endpoints

* Incidence of and time to de novo malignancy at 36 months after transplantation

* Incidence of and time to recurrent malignancy

* Biopsy proven rejection

* Retransplantation

* Percentage of patients with cGFR <60ml/min at 12 and 24months after

transplantation

* cGFR at 12, 24 and 36 months after transplantation

* Incidence of De novo diabetes mellitus at 12, 24 and 36 months after

transplantation

* Quality of life using SF-36 questionnaires at 12, 24 and 36 months after

transplantation

* Severity of fatigue using FSS at 12, 24 and 36 months after transplantation

* Safety (serious adverse events)

* Tolerability of combination sirolimus and extended release tacrolimus

(percentage of patients completing treatment and reasons

for dose adjustments)

* Percentage of patients on combination sirolimus and extended release

tacrolimus converted to monotherapy extended release

tacrolimus due to lack of tolerability or efficacy of

combination sirolimus and extended release tacrolimus.

Study description

Background summary

Calcineurin inhibitors (CNIs), since their introduction in the 1980s, have been the cornerstone of maintenance immunosuppressive regimens in liver transplantation. The use of CNIs has substantially decreased the risk of acute rejection and improved short-term outcomes. The current most used combination is tacrolimus, prednisolone and mycophenolate mofetil with in some centers an induction therapy with IL-2 antagonists basiliximab or dacluzimab. The incidence of biopsy-proven acute rejection within the first year after transplantation ranges between 19 - 30 % (Yoshida, Marotta et al. 2005; Neuberger, Mamelok et al. 2009).
The use of CNI may have a negative influence on kidney function, induce

diabetes mellitus and hypertension, however depending on type of CNI, dosing regimes and concomitant immunosuppressive medication. Nephrotoxicity is one of the most serious complications of CNI (Gonwa, Mai et al. 2001). Apart from intestinal transplants, liver transplant recipients have the highest five-year incidence of chronic renal failure (CRF) of any non-renal solid organ transplant recipient; additionally, the risk of death is at least fourfold higher in patients who develop CRF (Flechner, Goldfarb et al. 2007). These problems have leaded to the determination of new strategies of immunosuppressive treatment in liver transplantation patients tot decrease the use of CNIs. The first option was to replace CNIs by mTor inhibitors, but this has resulted in a higher incidence of rejection, vena portae thrombosis, decreased wound healing, thrombocytopenia and proteinuria. An other strategy was to replace the CNI by a mTor inhibitor when CNI toxicity such as renal dysfunction has evolved, but also this strategy has resulted in an increased rejection rate and there was no long term improvement of the renal outcome. The third approach was to completely avoid CNIs and start from the time of transplantation with mTor inhibitors in combination with other immunosuppressive drugs.

Study objective

To evaluate the effectiveness and safety of concentration controlled combination of once daily dosed low-dose sirolimus (trough levels: 3-5 ng/ml) and extended-release tacrolimus (trough levels:3-5 ng/ml), in order to provide superior renal function while maintaining comparable rates of patient and graft survival, compared to concentration controlled once - daily extended release tacrolimus (trough levels:5-10 ng/ml) at 12, 24 and 36 months post-transplant. Moreover, to compare the incidence of de novo malignancy, the quality of life, fatigue and side effects between both treatment arms.

Study design

A phase III multicenter, randomized, open label study to evaluate the efficacy and safety up to 3 years of a regimen with a combination of low-dose extended-release tacrolimus and sirolimus in comparison with standard-dose extended-release tacrolimus. The patients are randomized between 80 and 100 days after liver transplantation in 2 arms.
- Arm 1 will receive once daily combination therapy of normal dosed extended-release tacrolimus and prednisone for 3 months and monotherapy once daily extended-release tacrolimus thereafter up to 4 years after liver transplantation.
- Arm 2 will receive once daily combination therapy of low doses sirolimus and extended-release tacrolimus and prednisone for 3 months and combination therapy of low dose sirolimus and extended-release tacrolimus thereafter for up to 3 years after liver transplantation

During the study period all patients will be seen on regular periods according to the local out-patient protocol

Intervention

- Arm 1 will receive once daily combination therapy of normal dosed extended-release tacrolimus and prednisone for 3 months and monotherapy once daily extended-release tacrolimus thereafter up to 4 years after liver transplantation.
- Arm 2 will receive once daily combination therapy of low doses sirolimus and extended-release tacrolimus and prednisone for 3 months and combination therapy of low dose sirolimus and extended-release tacrolimus thereafter for up to 3 years after liver transplantation

Study burden and risks

- extra collection of blood
- adverse events of Sirolimus and possible higher incidence of rejection in the study arm

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

* Primary liver transplantation or retransplantation within 14 days after first transplantation
* Use of Advagraf at least 2 weeks prior to randomization
* Patent hepatic artery
* Closed abdominal wound
* Stable graft function
* Positive informed consent at time of randomization
* Age 18-70 years

Exclusion criteria

*Treatment with investigational drugs within 3 months before start of therapy
*Multi organ transplantation
*cGFR < 30 ml/min
*Proteinuria > 800 mg/24 h
*Hypersensitivity to sirolimus
*Thrombocytes < 50 x 109 /L
*Leukocytes < 2.5 x 109 /L
*Haemoglobin < 6 mmol/L
*Biopsy proven rejection 2 weeks prior to randomization
*HIV positivity
*Signs of recurrent or de novo cancer
*Pregnancy or breast feeding
*Systemic infection
*Any other condition which in the opinion of the investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in and completing the study

Study design

Design

Study phase: 3

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-02-2011
Enrollment:	196
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Advagraf capsule
Generic name:	tacrolimus extented release
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prednison
Generic name:	Prednison
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Sirolimus film coated tablet
Generic name:	rapamune
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	08-10-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	14-10-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-12-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-01-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-12-2017
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-017843-32-NL
ClinicalTrials.gov	NCT01958190
CCMO	NL30908.078.10