A twelve-month, multicenter, open-label, randomized study of the safety, tolerability and efficacy of Certican* with Simulect, corticosteroids and two different exposure levels of tacrolimus in de novo renal transplant recipients

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With the goal of improving kidney function and without causing an increased number of rejections, is it possible to reduce tacrolimus dosage through the use of the previously-mentioned immunosupressives after month three.

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

Summary

ID

NL-OMON30348

Source
ToetsingOnline

Brief title
NA

Condition

- Other condition
- Renal disorders (excl nephropathies)

Synonym
renal transplantation

Health condition

transplantatie geneeskunde

Research involving
Human

Sponsors and support

Primary sponsor: PPD
Source(s) of monetary or material Support: PPD

Intervention

Keyword: immunosuppression, kidney transplantation, rapamycin, transplantation

Outcome measures

Primary outcome

This objective will be assessed by comparing renal function evaluated by calculated glomerular filtration rate (MDRD formula) at 12 months post-transplant (this method has gained favor in the transplant literature above the endogenous creatinine clearance because its reproducibility is far greater).

Secondary outcome

The main secondary objective is to assess efficacy of the two regimens. This will be evaluated by the comparison between the two groups of the incidence of biopsy-proven acute rejection (BPAR) from Month 4 until Month 12 after transplantation

The other secondary objectives are to assess the efficacy and safety of the two regimens. This will be evaluated at 12 months by the comparison between the two groups of:

Incidence of efficacy failure defined as biopsy-proven acute rejection (BPAR), graft loss, death or lost to follow-up

Incidence of each of the components of efficacy failure

Incidence of treated acute rejection

Renal function as measured by serum creatinine value and creatinine clearance (Cockcroft-Gault formula)

Change in renal function evaluated by calculated GFR (MDRD formula) and creatinine clearance (Cockcroft-Gault formula) between Months 4 and 12

Incidence of SAEs

Incidence of AEs

Incidence of new onset diabetes mellitus defined as fasting plasma glucose >= 126 mg/dL or symptoms of diabetes plus casual plasma glucose >= 200 mg/dL or 2h plasma glucose >= 200 mg/dL during an Oral Glucose Tolerance Test (OGTT)

Study description

Background summary

Kidney transplantation without immunosupression is unfortunately not possible. Almost all immunopsupressives have side-effects. The standard-of-care therapy at this moment at the UMC Utrecht consists of tacrolimus, mycophenolate mofetil, and, for a number of months, prednisone.

In patients who are at increased immunsupressive risk, or who are receiving their third transplant, an IL-2 receptor antagonist is added.

One of the most unfortunate side-effects is the nephrotoxicity of calcineuron inhibitors (tacrolimus and cyclosporine). In this protocol we attempt to achieve better kidney function by reducing the dose of tracrolimus. Because we nevertheless wish to provide adequate immunosuppression, other immunospuressives must be prescribed. In this protocol we use a combination made up of basiliximab (Simulect®), tacrolimus, everolimus (Certican*) and

prednisone in dosages which were recently used with success in a study by Cooper et al. Data from this study has been included with application.

A similar study has also already been performed with cyclosporine as calcineuron inhibitor. In most study centers, with Utrecht and Maastricht included, tacrolimus is chosen over cyclosporine because tacrolimus does not induce gingival hyperplasia and also does raises the patient*s blood pressure with less severity.

This study is designed, therefore, to see if fit is possible to lower the tacrolimus dosage even further after three months.

Study objective

With the goal of improving kidney function and without causing an increased number of rejections, is it possible to reduce tacrolimus dosage through the use of the previously-mentioned immunosupressives after month three.

Study design

12 months, multicenter, randomized, open-label.

There are two phases:
In the first three months, the patients are proscribed an accepted treatment consisting of an induction therapy of basiliximab 20 mg at day 0 and 4, everolimus dosed at trough levels of 3 to 8 ng/mL, tacrolimus dosed at a trough level of 4 to 7 ng/mL and a 100 mg pre-operative dose of prednisone, followed by 20 mg per day to eventually tapered to a maintenance dose of 5 mg by 2 months.

After three months, the control arm (B) has their medication continued in this fashion while the study arm (A) has their tacrolimus dosing lowered to a trough level of 1.5-3 ng/mL.

Intervention

At month 3, the tacrolimus dosage in the study arm (A) is lowered.

Study burden and risks

Extra procedures
There are no visits or blood draws for study subjects on top of the regular kidney transplant follow-up, except a 5ml tube of blood to be taken at 13 visits throughout the trial, with the purpose of determining the everolimus trough level.

Risks
As everolimus is a new medicine, this study may bring to light new side-effects that are presently unknown or not expected. Unexpected side effects of immunosupressives are, among others, temporary hormonal changes, lever function abnormalities, bone marrow suppression and increased susceptibility for infection. In a multiple dose study of everolimus in humans it was noted that in some subjects the platelet count (blood cells which stop bleeding) and in some others the white blood cell count dropped. Further, there is the possibility that the triglyceride/cholesterol level will rise. Subjects will, however, receive a low dose of everolimus and should their doctor consider it necessary, they will also receive a lipid-lowering agent (HMG-CoA reductase inhibitor) which will reduce the chance of a raised cholesterol level.

The number of tacrolimus-related side effects will, however, be lower due to the reduced dose. Further, subjects will not experience side effects from mycophenolate mofetil, the medicine usually given concomitantly with tacrolimus.

With every change in the immunosupressive protocol there is a chance for an increased incidence of acute organ rejections. The chance of this is not large during this period (months 4-12), however, and such rejections are nearly always treatable with the standard therapies available (methylsolumedrol and ATG).

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

Male or female 18-65 years old
Primary transplant from cadaveric, living-unrelated or non-HLA identical living related donor
Cold Ischemia time <30 h
Negative pregnancy test in female
Willing and capable to give written informed consent

Exclusion criteria

Multiple organtransplants
Non-heart beating donor
PRA>=50%
Hypercholestrolemia >9,1 mmol/L
Leucocytes <3
HIV, HBSag or anti HBC AB positive
Allergy to one of the drugs
Malignancy apart from localised skin tumors
Unable to cooperate or communicate with the investigator

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):	27-06-2006
Enrollment:	36
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	certican
Generic name:	everolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	prednisolone
Generic name:	prednisolone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	simulect
Generic name:	basiliximab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	tacrolimus
Generic name:	tacrolimus
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	06-06-2006
Application type:	First submission

Review commission:	METC NedMec
Approved WMO Date:	07-04-2009
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2005-001714-41-NL
CCMO	NL11304.041.06