Cardiovascular (CV) risk prediction and CV biomarkers in renal transplant recipients treated with belatacept compared to calcineurin inhibitors (CNI).;Open randomized 12 month study.

Published: 16-03-2015
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The goal of this study is to prove whether kidney transplant recipients can reduce their risk of cardiovascular disease bij converting to Nulojix.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional

Summary

ID

NL-OMON45007

Source
ToetsingOnline

Brief title
Nulojix study

Condition

- Renal disorders (excl nephropathies)
- Vascular hypertensive disorders

Synonym
cardiovascular risk during prophylaxis of graft rejection in renal transplant recipients, cardiovascular risk while preventing rejection of kidney transplant

Research involving
Human

Sponsors and support

Primary sponsor: University Hospital Uppsala
Source(s) of monetary or material Support: Ministerie van OC&W,Bristol-Myers Squibb

Intervention

Keyword: Belatacept, Cardiovascular risk, renal transplant recipients

Outcome measures

Primary outcome

The primary end-point is the estimated risk of major adverse cardiovascular events (MACE). The natural logarithm of the estimated CV risk for MACE will be calculated as previously described by Soveri et al. (2012) as a linear function of the following variables: age, previous coronary heart disease, smoking, serum creatinine, diabetes mellitus, LDL-cholesterol and number of transplants. The primary endpoint will be a comparison of the log of the estimated CV risk between treatment groups (CNI vs. belatacept based immunosuppression) at one year. For patients discontinuing the study before one year, the last available estimate of CV risk will be used in the analysis of the ITT population.

Secondary outcome

The secondary end-points are the comparisons between treatments arms for:

- individual components of CV risk in RTR: blood pressure, lipid profiles and eGFR.

- vascular function measured by EndoPAT.

- biomarkers of ageing (bio-ageing) in RTR: leukocyte telomere length, CDKN2A levels, leukocyte RNA expression profile.

- biomarkers for CV risk factors in RTR measured by Proximity Ligation Assay,

ELISA, multicoloured FACS analyses (Dutch sites only), SDF Imaging (Dutch sites only) and miRNA measurements

- renal transplant biopsy IFTA scores (Banff criteria)

- expression of graft fibrosis markers, and other measures of chronic renal transplant markers in kidney biopsies

- acute rejection

- allograft losses

- CV events occurring during the study, i.e.

o cardiovascular death (due to myocardial infarction (MCI), heart failure or stroke),

o non fatal MCI

o non fatal stroke

o hospitalization due to congestive heart failure

o hospitalization due to angina pectoris

o coronary intervention

- patient survival

- safety and tolerability

Study description

Background summary

The key current problems in adult kidney transplantation are preservation of graft function and patient survival; specifically preventing premature mortality and morbidity due to malignancy and cardiovascular (CV) disease. Calcineurin inhibitors (CNI), which form the mainstay of current immunosuppressive regimens, may contribute to this increased risk through their nephrotoxic effects, and their contributory actions on dyslipidaemia,

hypertension and diabetes.

Study objective

The goal of this study is to prove whether kidney transplant recipients can reduce their risk of cardiovascular disease bij converting to Nulojix.

Study design

Prospective, open, randomized, parallel group, investigator-initiated, *proof of concept* study.

Intervention

Belatacept arm:
Belatacept will be dosed 5 mg/kg IV on day 1, 15, 29, 43, 57 and then every month thereafter. CNI to be tapered as follows: 100% on day 1, to 70-80% on day 7, to 40-60% on day 15, 20-30% on day 23 and none on day 29 and beyond. Infusion doses will be based on the subject*s body weight at the time of baseline visit, day 1. Unless the body weight changes more than +/- 10 % the same infusion dose should be used throughout the treatment period. If the subject's body weight at any study visit has changed more than 10% from V1, a new infusion dose will be calculated from that visit onwards, and serve as a new "baseline" value for dose calculation. Study drug should be administered to the subject at a relatively constant rate over 30 minutes.
CNI-based arm:
Tacrolimus or cyclosporine capsules/ tablets, oral
Cyclosporine doses maintained at through level 75 to 200 ng/ml; tacrolimus concentrations will be kept at 5-10 ng/ml. Target concentrations may be modified according to local directives, and vary with time since transplantation.

Study burden and risks

Participants are requested to visit the hospital more often (to a maximum of 15 times) to provide bloodsamples. The medication used in the study is not expected to have more risks associated than the standard treatment.

Contacts

Public
University Hospital Uppsala

Uppsala University Hospital, MHT Dept. of Nephrology

Uppsala 75185
SE
Scientific
University Hospital Uppsala

Uppsala University Hospital, MHT Dept. of Nephrology
Uppsala 75185
SE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Signed Written Informed Consent
2. Target Population:
2.a Renal transplant recipients of living donor or deceased donor kidney transplant.
2.b Stable renal graft (eGFR > 20 ml/min) with no need for exploratory examination)
2.c Tacrolimus or CsA (Cyclosporine A) standard treatment since transplantation
2.d 3 * 60 months post-transplantation at randomization
3. Age and Sex:
3.a Men and women, aged 18 to 80 years, both inclusive
3.b Women of childbearing potential (WOCBP) must be using adequate method of contraception to avoid pregnancy throughout the study and for up to 8 weeks after the last dose of study drug to minimize the risk of pregnancy. WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who is not post-menopausal. Post-menopause is defined as:
*Amenorrhea that has lasted for 12 consecutive months without another cause, or
*For women with irregular menstrual periods who are taking hormone replacement therapy (HRT), a documented serum follicle-stimulating hormone (FSH) level of greater than 35 mIU/mL.
Women who are using oral contraceptives, other hormonal contraceptives (vaginal products,

skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or who are practicing abstinence or where their partner is sterile (e.g. vasectomy) should be considered to be of childbearing potential.
WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours before the start of the investigational product (belatacept).

Exclusion criteria

1. Sex and Reproductive Status:
1.a Women of Child Bearing Potential (WOCBP) who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and for up to 8 weeks after the last dose of study drug.
1.b Women who are pregnant or breastfeeding.
1.c Women with a positive pregnancy test.
2. Target Disease Exceptions: Subjects who are Epstein-Barr virus IgG negative or have unknown IgG status for EBV.
3. Medical History and Concurrent Diseases:
3.a De novo or recurrent underlying renal disease that, in the investigator's opinion, could adversely influence the current allograft
3.b History of vascular or antibody-mediated rejection in the present transplant
3.c Ongoing serious infections, as per investigator's opinion
3.d Signs of post-transplant lymphoproliferative disorder
3.e History of tuberculosis. If the patient has a history of active TB or a history of latent untreated TB, the patient must be excluded from the study. If the patient has a history of latent treated TB, the patient can be included.
3.f Signs of malignancy. Exceptions are BCC/SCC or non-malignant melanoma
3.g History of malignancy, unless subject has been considered to have fully recovered from malignancy since >1 year, without any signs of relapse
3.h Life expectancy < 3 years at the time of randomization
4. Allergies and Adverse Drug Reactions:
4.a Hypersensitivity to belatacept
4.b Previous/ongoing use of rituximab in connection with the current transplant.
5. Other Exclusion Criteria:
5.a Prisoners, or subjects who are involuntarily incarcerated.
5.b Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g. infectious disease) illness.

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:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-07-2015
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	cyclosporin or tacrolimus
Generic name:	cyclosporin or tacrolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Nulojix
Generic name:	Belatacept
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	16-03-2015
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	28-04-2015
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	27-10-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	27-01-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	28-08-2017
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
EudraCT	EUCTR2013-001178-20-NL
CCMO	NL50627.058.15