Investigating new onset diabetes mellitus in kidney transplant recipients receiving an Advagraf-based immunosupressive regimen with or without corticosteroids - A multicenter, two arm, randomized, open label clinical study.

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

Summary

ID

NL-OMON38176

Source
ToetsingOnline

Brief title
ADVANCE

Condition

- Nephropathies

Synonym
Kidney transplantation, transfer of a healthy kidney in another body with non-functioning

kidneys.

Research involving
Human

Sponsors and support

Primary sponsor: Astellas Pharma B.V.
Source(s) of monetary or material Support: Astellas Pharma Europe Ltd

Intervention

Keyword: Advagraf with or without corticosteroids, Kidney transplantation, New onset diabetes mellitus, Safety and efficacy

Outcome measures

Primary outcome

The primary variable will be the diagnosis of NODAT as per ADA criteria at any

point up to 24 weeks after kidney transplantation.

Secondary outcome

* Efficacy failure defined using a composite endpoint consisting of any of the

following:

a) graft loss (defined as re-transplantation, nephrectomy, death or dialysis

ongoing at study end or at time of discontinuation of the subject from the

study unless superseded by follow-up information)

b) biopsy confirmed acute rejection (BCAR);

c) graft dysfunction (defined as glomerular filtration rate (GFR) <30

mL/min/1.73m2 estimated by MDRD formula at 24 weeks after transplantation).

* Positive Oral Glucose Tolerance Test (OGTT) at 8 weeks (must be at least 4

weeks after treatment with steroids e.g. for treatment of rejection).

* Repeat OGTT at 24 weeks.

* Assess the role of recipient biomarkers on efficacy rate.

* Renal function:

- Renal function assessed by calculated GFR with MDRD4 formula at week 24 after transplantation.

- Renal function assessed by calculated creatinine clearance with Cockcroft and Gault formula at week 24 after transplantation.

- Renal function assessed by calculated creatinine clearance with CKD-EPI formula at week 24 after transplantation.

* Acute rejections by signs and symptoms:

- Incidence of and time to first incidence of acute rejection.

- Incidence of and time to first incidence of corticosteroid-resistant acute rejection.

- Overall frequency of acute rejection episodes.

* Biopsy confirmed acute rejections:

- Incidence of and time to first incidence of biopsy confirmed acute rejection.

- Incidence of and time to first incidence of biopsy confirmed corticosteroid-resistant acute rejection.

- Overall frequency of biopsy confirmed acute rejection episodes.

- Severity of biopsy confirmed acute rejection episodes.

* Subject and graft survival.

* Change from baseline in HbA1C levels at week 12 and week 24

Study description

Background summary

Lifelong immunosuppression to stop the body*s defense mechanism (immune system) from rejecting a new kidney with prescribed medication is necessary after transplantation. Tacrolimus prolonged release formulation, (also called Advagraf®) is approved inside and outside Europe for prevention of kidney transplant rejection and/ or for rescue therapy after rejection in liver and kidney transplantation. Advagraf®, once-daily calcineurin inhibitor (CNI), will be used to induce and maintain suppression of the body*s immune system for prevention of rejection of the new kidney by the body after transplantation. Developments in immunosuppressive medications have provided excellent results in terms of graft and patient survival. Unfortunately, all treatments are associated with side effects. In the case of CNIs an important concern is diabetes mellitus.

In the case of steroids long-term administration is associated with various infectious and metabolic complications including osteoporosis, diabetes mellitus, hypertension and hyperlipidemia.
The concomitant use of high doses of CNIs and steroids increases the risk of glucose metabolism disorders. In the modern era, kidney transplant patients are successfully managed on lower levels of tacrolimus than was the case historically. Furthermore, steroid elimination or avoidance in tacrolimus-based regimens has been shown to provide effective immunosuppression and have beneficial effects on blood pressure, lipid profiles and glucose tolerance.

A combined tacrolimus/MMF (also called CellCept®) regimen is viewed by many clinicians as the current best immunosuppressive regimen in kidney transplantation and is highly effective in prevention of acute rejections.
The use of a monoclonal antibody (also called Simulect®) in combination with tacrolimus and MMF is also common practice and enables safely and efficiently an early steroid-free maintenance.

This study compares two Advagraf-based immunosupressive regimen therapies with regard to incidence of new-onset Diabetes Mellitus after transplantation where the steroid exposure will be minimized during the post-operative period.
Subjects randomized in arm 1 will receive steroids for 10 days and subjects in arm 2 will receive no steroids (other than an optional bolus given during the transplant procedure).
The reduction in overall immunosuppression as a consequence of omitting or reducing steroid exposure will be balanced by the provision of induction therapy with Basiliximab.

Study objective

The primary objective of this study is to compare Arm 1 with Arm 2 with regard to incidence of new onset diabetes Mellitus as per the American Diabetic

Association criteria at any point up to 24 weeks after kidney transplantation.

The secondary objective is to compare the safety and efficacy profiles of the two therapy regimens with each other.

Study design

A multicenter, two arm, randomized, open label study. Phase IV.

The following treatment arms will be compared with each other:

Arm 1: Advagraf + Basiliximab + MMF + steroids (discontinued at 10 days)

Arm 2: Advagraf + Basiliximab + MMF + steroids (optional intra-op Bolus only)

Intervention

The subjects will be entered into the study for 24 weeks. 8 visits are planned for this period.

The study is divided as follow:

- Baseline visit (visit 1, 96 hours prior to transplantation)
- Treatment/research period (Visit 2 until 7)
- End of study visit (visit 8)
- Additional follow-up visit (for subjects who have an acute rejection or elevated glucose level at end of study)

Study burden and risks

The doctor will perform the following tests during the study:

During the baseline visit (visit 1), 96 hours prior to transplantation:
* The subject will be randzomized to one of two treatment arms.
* Subjects and donors medical history including medication, viral status, ABO blood type, PRA grade and HLA type.
* Pregnancy Test (female subjects of childbearing potential) to exclude pregnancy.
* Vital signs, height and weight hip/waist circumference.
* Blood sample for routine safety analysis and monitoring kidney and liver function.
* Blood sample for donor specific antibodies.
* Dispensing study drugs.
* Completion of quality of life questionnaire.

During the treatment period (Visit 2 until Visit 7):

* Vital signs and weight.
* Blood sample for routine safety analysis and monitoring kidney and liver function.
* Dispensing and collecting study drugs.
* Biopsy will be performed in case of rejection.

The following additional assessments will be done during the treatment period:
* Oral Glucose Tolerance Test (visit 6)
* Urine sample for biomarker analyses (visit 4 and 5)
* Completion of quality of life questionnaire (visit 4 until 7)

End of study visit (Visit 8):
* Pregnancy Test (female subjects of childbearing potential)
* Vital signs and weight.
* Blood sample for routine safety analysis and monitoring kidney and liver function.
* Blood sample for donor specific antibodies.
* Urine sample for biomarker analyses
* Oral Glucose Tolerance Test
* Collection study drugs
* Completion of quality of life questionnaire
* Biopsy will be performed in case of rejection.

Suppression of the body*s defense system can increase the risk for bacteria, fungus or virus infections and on long-term could increase the risk of getting cancer. Possible risks of participating include possible side effects of the various drugs. All study drugs have been registered for the therapeutic area kidney transplantation. Therefore, we would like to refer to the attached SPCs for a complete overview of side effects/risks.

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

Subject is eligible for the study if all of the following apply:
1. Age >= 18 years.
2. End stage kidney disease and a suitable candidate for primary renal transplantation or retransplantation (unless the graft was lost from rejection within 1 year).
3. Receiving a kidney transplant from a deceased or living (non Human Leukocyte Antigen [HLA] identical) donor with compatible ABO blood type.
4. Female subject of childbearing potential has a negative serum or urine pregnancy test at enrollment and must agree to maintain highly effective birth control during the study. A highly effective method of birth control is defined as those which result in a low failure rate (CPMP/ ICH/286/ 95 modified) of less than 1% per year when used consistently and correctly such as implants, injectables, combined oral contraceptives, some Intrauterine Devises (IUDs), sexual abstinence or vasectomized partner.
5. Capable of understanding the purpose and risks of the study, fully informed and having given written informed consent (signed Informed Consent has been obtained).

Exclusion criteria

Subject will be excluded from participating if any of the following apply:
1. Receiving or having previously received an organ transplant other than a kidney.
2. Cold ischemia time of the donor kidney > 30 hours.
3. Panel Reactive Antibody (PRA) >20% (highest level within 6 months prior to transplant).
4. Previous renal transplant lost within one year for immunological reasons.
5. Receiving a graft from a non-heart-beating donor other than of Maastricht category 3 (withdrawal of support awaiting cardiac arrest).
6. Significant liver disease, defined as having continuously elevated SGPT/ ALT and/ or SGOT/ AST and/ or total bilirubin levels >= 2 times the upper value of the normal range of the investigational site or is receiving a graft from a hepatitis C or B positive donor.

7. Diagnosis of Diabetes Mellitus prior to transplantation (treated with prescribed medications or diet controlled) or where there is evidence of a previous positive OGTT in the patient's medical history or previous diagnosis of gestational diabetes or pre-Baseline HbA1c >= 6.5 %.
8. Requiring initial sequential or parallel therapy with immunosuppressive antibody preparation(s).
9. Requiring ongoing dosing with a systemic immunosuppressive drug prior to transplantation (e.g. for Lupus Disease, FSGN etc.) other than minimal levels of immunosuppression following failure of previous transplantation without nephrectomy.
10. Where physician considers long term steroid treatment is necessary for the prevention of recurrent auto immune mediated renal disease or if the subject requires ongoing dosing with corticosteroids during the study for any other condition.
11. Significant, uncontrolled concomitant infections and/ or severe diarrhea, vomiting, active upper gastro-intestinal tract malabsorption or active peptic ulcer.
12. Pregnant woman or breast-feeding mother.
13. Subject or donor known to be HIV positive.
14. Known allergy or intolerance to tacrolimus, macrolide antibiotics, corticosteroids, Basiliximab, mycophenolate mofetil or any of the product excipients.
15. Evidence of malignant disease within the last 5 years other than Basal Cell Carcinoma or Squamous Cell Carcinoma.
16. Currently participating in another clinical trial, and/ or has taken an investigational drug within 28 days prior to enrollment.
17. Any form of substance abuse, psychiatric disorder or condition which, in the opinion of the Investigator, may complicate communication with the Investigator.
18. Unlikely to comply with the visits scheduled in the protocol

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):	11-04-2011
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Advagraf®
Generic name:	Tacrolimus prolonged release
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	CellCept®
Generic name:	Mycophenolate Mofetil
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Simulect®
Generic name:	Basiliximab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-12-2010
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-03-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-11-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-12-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2010-019638-28-NL
ClinicalTrials.gov	NCT01304836
CCMO	NL34700.068.10