A multicenter, two arm, randomized, open label clinical study investigating renal function in an advagraf®-based immunosupressive regimen with or without sirolimus in kidney transplant subjects.

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Primary objective: to compare the effect two immunosupressive therapy regimens on GFR estimated by iohexol clearance at week 52 post kidney transplantationSecundary objective: to compare the safety and efficacy profiles of the two immunosupressive...

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

Summary

ID

NL-OMON38063

Source
ToetsingOnline

Brief title
ADHERE

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: Industrie (Astellas Pharma Europe Ltd)

Intervention

Keyword: Advagraf with or without sirolimus, Kidney transplantation, Renal function, Safety and efficacy

Outcome measures

Primary outcome

Primary variable:

GFR estimated by iohexol clearance at Week 52 post kidney transplantation.

Secondary outcome

Secundary efficacy variabeles:

-Efficacy failure. Composite endpoint defined as graft loss

(re-transplantation, nephrectomy, death or dailysis ongoing at the study end)

or subject withdrawal.

- GFR and calculated creatinine clearance at Week 52 post kidney

transplantation by Modification Diet in Renal Disease (MDRD) formula/ Cockcroft

and Gault/ Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).

- Incidence and time to clinical acute rejection and Biopsy Confirmed Acute

Rejection (BCAR).

- Delayed Graft Function (DGF).

- Subject and graft surivival.

- New Onset Diabetis Mellitus (NODM) as per American Diabetic Association (ADA)

criteria.

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 following transplant.
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 renal dysfunction.
Although the use of tacrolimus has markedly improved early graft outcome, nephrotoxicity is associated with its use.

This study will evaluate the potential to reduce nephrotoxic CNI therapy by lowering tacrolimus exposure from Advagraf® in combination with the non-nephrotoxic immunosuppressant sirolimus to avoid the risk of acute graft rejection, compared with an Advagraf® and MMF immunosuppressive regimen.

There may well be a benefit in terms of reducing the potential nephrotoxicity by replacing MMF with sirolimus, in combination with a lower exposure to Advagraf®. Advagraf® also offers the benefit of once daily dosing over other formulations of CNI. As sirolimus is also administered once daily this strategy offers the benefit of a truly once daily immunosuppressive regimen. As no evening dosing is required, this should result in less interference with the routine daily activities of the subject.

Study objective

Primary objective: to compare the effect two immunosupressive therapy regimens on GFR estimated by iohexol clearance at week 52 post kidney transplantation

Secundary objective: to compare the safety and efficacy profiles of the two immunosupressive 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 + MMF + steroids

Arm 2: Advagraf + MMF (withdrawn at week 4) + steroids + sirolimus (introduced at Week 4). At Week 6 the Advagraf dose will be reduced to achieve lower tacrolimus target levels.

Intervention

The subjects will be entered into the study for 52 weeks. 10 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 9)
- End of study visit (visit 10)

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:
* 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.
* Blood sample for routine safety analysis and monitoring kidney and liver function.
* Urine sample for proteinuria analyses.
* Dispensing study drugs.
* Completion of quality of life questionnaire.

During the treatment period (Visit 2 until Visit 9)
* Vital signs and weight.
* Blood sample for routine safety analysis and monitoring kidney and liver function.
* Urine sample for proteinuria analyses.
* Dispensing and collecting study drugs.
* Biopsy will be performed in case of rejection.

The following additional assessments will be done during the treatment period

* The subject will be randomized in one of the two treatment arms (visit 4).
* Completion of quality of life questionnaire (visit 5 and 7).
* Completion of questionnaire regarding study medication intake (visit 4, 5, 7 until 9)

End of study visit (Visit 10)
* Pregnancy Test (female subjects of childbearing potential) to exclude pregnancy.
* Vital signs and weight.
* Blood sample for routine safety analysis and monitoring kidney and liver function.
* Urine sample for proteinuria analyses.
* GFR assessment by iohexol (see section E6).
* Collecting study drugs.
* Completion of quality of life questionnaire.
* Completion of questionnaire regarding study medication intake.

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 6 months).
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.
5. Female and male subjects agree to maintain highly effective birth control during the study and for 90 days after discontinuation of dosing with study drugs. 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.
6. 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%.
4. Receiving a graft from a non-heart-beating donor other than of Maastricht category 3 (withdrawal of support awaiting cardiac arrest).
5. 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.
6. Requiring initial sequential or parallel therapy with immunosuppressive antibody preparation(s).
7. Requiring ongoing dosing with a systemic immunosuppressive drug prior to

transplantation (other than minimal levels of immunosuppression following failure of previous transplantation without nephrectomy).
8. Significant, uncontrolled concomitant infections and/ or severe diarrhea, vomiting, active upper gastro-intestinal tract malabsorption or active peptic ulcer.
9. Pregnant woman or breast-feeding mother.
10. Subject or donor known to be HIV positive.
11. Known allergy or intolerance to tacrolimus, macrolide antibiotics, corticosteroids, sirolimus, MMF or any of the product excipients or iodine.
12. Evidence of malignant disease within the last 5 years, not including non-malignant skin cancers.
13. Currently participating in another clinical trial, and/ or has taken an investigational drug within 28 days prior to enrollment.
14. Any form of substance abuse, psychiatric disorder or condition which, in the opinion of the Investigator, may complicate communication with the Investigator.
15. 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):	10-09-2011
Enrollment:	30
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:	Rapamune®
Generic name:	Sirolimus
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-01-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-05-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-08-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-04-2012
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	EUCTR2010-019639-37-NL
CCMO	NL34168.068.10