Steroid free immunosuppression or calcineurin inhibitor minimization after Basiliximab induction therapy in kidney transplantation: Comparison with a standard quadruple immunosuppressive regimen.

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Objectives: A prospective, open label, randomized trial, in which we aim to achieve optimal immunosuppression after renal renal transplantation with maximal reduction of side effects, especially of vascular injury, chronic allograft nephropathy,...

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

Summary

ID

NL-OMON34397

Source
ToetsingOnline

Brief title
Allegro

Condition

- Renal disorders (excl nephropathies)

Synonym
rejection, renal function

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Astellas Pharma

Intervention

Keyword: immunosuppression, kidneytransplantation, renal function, steroidfree

Outcome measures

Primary outcome

Primary end-points

Renal function parameters, proteinuria and microalbuminuria measured 3, 12 and 24 months after transplantation. Renal function measured by endogenous creatinine clearances, serum creatinine and Nankivell GFR.

Secondary outcome

Secondary end-points

• Rejection episodes

• Graft and patient survival

• The degree of tubular atrophy and interstial fibrosis, inflammation plus the degree of arteriolar hyalinosis in renal biopsies taken at 12 and 24 months after transplantation. Biopsies will be evaluated according to the Banff *07 Criteria for Renal Allograft Biopsy Interpretation (appendix II). Quantitative morphometric analysis of interstitial fibrous tissue will be performed using the digital image analysis technique.

• Cardiovascular incidents, pulse wave velocity measurements and AGEs skin

• Blood pressure (mean of three automated measurements while sitting up) and

the number of antihypertensives

• Lipid profile

• The incidence of malignancies

• Infectious complications

• Dexa bone densitometry

• Miscellaneous; Fasting glucose, oral glucose tolerance, HbA1c, uric acid

Study description

Background summary

Rationale: Quadruple immunosuppression consisting of an induction treatment, followed by mycophenolate mofetil, a calcineurin inhibitor and steroids results in low rejection rates and excellent graft survival. Especially in retransplantation graft survival has been improved in the last decade . Despite this success, mortality and morbidity in transplant recipients is relatively high due to side effects of immunosuppressive strategies. The incidence of hypertension, hypercholesterolemia and diabetes mellitus is relatively high. This is one of the reasons for the high cardiovascular mortality in renal transplant recipients. A potential cause is the use of steroids and calcineurin inhibitors. Calcineurin inhibitors may play an important role in the development of chronic allograft nephropathy causing poor kidney function and cardiovascular disease. However differences between calcineurin inhibitors are shown with regard to the incidence of these side effects and graft function. Also infections and malignancies are the result of immunosuppression in general. In some countries malignancies are the most frequent cause of death in kidney transplant recipients. Steroids play an important role in the development of osteoporosis in renal transplant recipients.

Study objective

Objectives: A prospective, open label, randomized trial, in which we aim to achieve optimal immunosuppression after renal renal transplantation with maximal reduction of side effects, especially of vascular injury, chronic allograft nephropathy, osteoporosis and malignancies. Immunosuppression without steroids and CNI minimization is compared to standard immunosuppression, consisting of tacrolimus OD, mycophenolate mofetil and corticosteroids.

Study design

Group 1 patients will start with quadruple immunosuppression, consisting of basiliximab (Simulect) induction 20 mg intraveneously on day 0 and day 4, three days steroids followed by tacrolimus OD (Advagraf) and mycophenolate mofetil (MMF, Cellcept). Appendix I shows the exact dosage schedule. Advagraf will be given orally in a dosage of 0,2 mg/kg. Trough levels will be monitored. Target values of tacrolimus trough level will be 8-12 ng/ml for the first 5 weeks after transplantation thereafter 6-10 ng/ml. MMF will be given twice daily 1000 mg orally for the first two weeks after transplantation followed by 2 x 750 mg thereafter. Corticosteroids will be given intravenously on day 0, 1 and 2 respectively 500, 250 and 125 mg of methylprednisolone. In group 1 no more steroids will be given other than during rejection episodes. In group 2, induction treatment with basiliximab (Simulect) 20 mg intravenously on day 0 and day 4 is used. Advagraf will be given orally in a dosage of 0,2 mg/kg. Trough levels will be monitored. Target values of tacrolimus trough level will be 8-12 ng/ml for the first 5 weeks after transplantation and thereafter 6-10 ng/ml. MMF will be given twice daily 1000 mg orally for the first two weeks after transplantation followed by 2 x 750 mg thereafter. Corticosteroids will be given intravenously on day 0, 1 and 2 respectively 500, 250 and 125 mg methylprednisolone. From day 3, 10 mg prednisolone orally once daily will be given and from week 6 7,5 mg once daily. Group 3 will receive induction treatment with basiliximab (Simulect) 20 mg intravenously on day 0 and day 4. Advagraf will be given orally in a dosaege of 0,2 mg/kg. Trough levels will be monitored. Target values of Tacrolimus trough level will be 8-12 ng/ml for the first 5 weeks and thereafter 6-10 ng/ml until 6 months after transplantation. After 6 months a fixed dose reduction of 50% of Advagraf will take place and target values of tacrolimus trough level will be 3-5 ng/ml. MMF will be given twice daily 1000 mg orally for the first two weeks after transplantation followed by 2 x 750 mg thereafter. Corticosteroids will be given intravenously on day 0, 1 and 2 respectively 500, 250 and 125 mg methylprednisolone. From day 3 10 mg prednisolone orally once daily will be given and from week 6 7,5 mg once daily.

Intervention

Concomitant therapy
Concomitant therapy will consist of omeprazol, antihypertensives and atorvastatine when needed. Patients at risk for CMV infection (donor or recipient seropositive) wil receive 6 months valgancyclovir prophylaxis. All patients will receive Pneumocystis Jirovecii prophylaxis the first year after transplantation. Rejection documented by percutaneous biopsy, will be treated with 500 mg of methylprednisone (Solu-Medrol) i.v. for six consecutive days according to local practice. Steroid resistant rejection episodes will be treated with rabbit antithymocyte globulin (Thymoglobuline Genzyme) according to local practice. Patients with acute rejection will remain or will resume low dose steroid therapy (7.5 mg prednisolone once daily) after their rejection treatment (37).
Interruption or discontinuation of treatment

Every patient will have the right to discontinue study participation at any time. All data generated up to the time of discontinuation from the study will be analyzed and the reason(s) for discontinuation will be recorded.
Treatment compliance
Compliance to the treatment will be demonstrated by adequate drug levels.

Study burden and risks

The burden associated with participation consists of some more frequent outpatient visits during conversion. In all three groups the amount of examinations is the same.
The risk associated with Advagraf is an increase in new onset Diabetes Mellitus, the risk associated with reducing immunosuppression is a higher incidence of acute rejection.
The benefits associated with reducing immunosuppression are a decreased risk for infections, cardiovascular diseases and malignancies .

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

Inclusion criteria
• Female or male, aged between 18 and 70 years.
• Recipient of a kidney graft (first or second) from a deceased (heartbeating or non-heartbeating) donor or living (non-HLA identical) donor.
• The patient understands the purpose and risks of the study and has given written informed consent to participate in the study.

Exclusion criteria

Exclusion criteria
• Patients with multi-organ transplants
• Patients who are receiving a third or fourth transplant.
• Patients who have > 50 % (current or historic) panel reactive antibodies.
• Female patients who are pregnant or unwilling to use adequate contraception during the study.

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):	27-06-2011
Enrollment:	300
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Advagraf
Generic name:	Tacrolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Bailiximab
Generic name:	Simulect
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Mycofenolate Mofetil
Generic name:	Cellcept
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prednisolon
Generic name:	Prednisolon
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	15-12-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-01-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2010-019854-42-NL
CCMO	NL32205.042.10