

CALciNeurin-inhibitor Nephrotoxicity and Efficacy Study

Submission date 19/12/2005	Recruitment status No longer recruiting	☐ Prospectively registered
Registration date 19/12/2005	Overall study status Completed	☐ Protocol
Last Edited 23/10/2008	Condition category Injury, Occupational Diseases, Poisoning	☐ Statistical analysis plan
		☐ Results
		☐ Individual participant data
		☐ Record updated in last year

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
NTR390

Study information

Scientific Title

A prospective, open, randomised, multicentre study comparing once-daily versus twice-daily dosing of cyclosporin A (Neoral®) or tacrolimus (Prograf®) on renal graft structure and function at 6 and 12 months

Acronym

CANNES

Study objectives

We believe that a routine graft biopsy at 6 and 12 months together with graft function represents the best surrogate marker for late graft loss.

Ethics approval required

Old ethics approval format

Ethics approval(s)

Received from the local medical ethics committee

Primary study design

Interventional

Study design

Multicentre, randomised, active controlled factorial trial

Study type(s)

Treatment

Health condition(s) or problem(s) studied

Renal transplant

Interventions

Before transplantation, patients will be randomised 1:1 to receive either a standard CsA-based or tacrolimus-based immunosuppressive regimen and either a twice daily (bid) or once daily (od) dosing schedule.

In the first four days after implantation Neoral or Prograft will be given twice daily schedule at approximately 12 hours intervals starting before surgery. The initial target 12 hours trough level (= C₀) in these first days will be aimed at 225 ng/ml (range 200 to 250) and 12.5 ng/ml (range 10 to 15) for Neoral and Prograft respectively.

On day 4, in patients assigned to the once daily schedule the total bid dose of CsA or tacrolimus will be given once daily in the morning. At the end of the first week CsA or tacrolimus full 'area under the concentration curves' (AUCs) will be studied to assess true drug-exposure.

Subsequent dose-adjustments will be made to achieve the defined AUCs for Neoral (AUC₁₂ = 5400 ng*h/ml) and Prograft (AUC₁₂ = 210 ng*h/ml) using a three-point sampling method (at C₀, C₂, C₃). Such an approach is required since CsA trough levels do not predict drug exposure 6,9 while the experience with tacrolimus pharmacokinetics is limited.

AUCs will be calculated with an algorithm based on three-point sampling. After the first 6 post-transplant weeks the defined AUC for Neoral (AUC₁₂) is 3250 ng*h/ml and for Prograft (AUC₁₂) 125 ng*h/ml. In the first 6 weeks after transplantation C₀, C₂ and C₃ hour levels will be assessed weekly.

Thereafter these levels will be assessed at the regular visits to the out-patient clinic. Dose-adjustment in each patient will be guided by computer-assisted AUC extrapolation based on C₀, C₂, C₃ drug levels.

Intervention Type

Other

Phase

Not Specified

Primary outcome(s)

1. To investigate which drug regimen is associated with the best graft structure and function at 6 and 12 months
2. Degree of inflammation and fibrosis in renal biopsies taken at 6 and 12 months after implantation. Biopsies will be evaluated according to the Banff '97 Criteria for Renal Allograft Biopsy Interpretation and morphometric analysis of the interstitial fibrous tissue will be performed using the digital image analysis technique available in our department.
3. Graft function will be assessed by measuring glomerular filtration rate (GFR) using 125I-iothalamate and protein excretion rate

Key secondary outcome(s)

1. Patient and graft survival
2. Rejection episodes: number of (biopsy-proven) acute rejection episodes, their severity, histopathological pattern and time to first rejection episode
3. Side effect profile: blood pressure, cholesterol, fasting glucose, HbA1c, uric acid, need for supportive treatment, infectious complications, lymphoproliferative disorders
4. Calcineurin inhibition
5. Plasma levels of TGF- β
6. MPA-levels and IMPDH activity over time
7. mRNA expression of collagen in biopsies
8. Functional analysis of T lymphocytes. Assessment of the CMV-specific CD4⁺ T cell proliferation

Completion date

21/10/2002

Eligibility

Key inclusion criteria

1. Female or male, aged between 18 and 70 years
2. Recipient of a kidney graft (first or second) from a cadaveric donor or living (non-human leukocyte antigen [HLA] identical) donor
3. The patient understands the purpose and risks of the study and has given written informed consent to participate in the study

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Adult

Lower age limit

18 Years

Sex

All

Key exclusion criteria

1. Patients who are receiving a simultaneous pancreas kidney transplant or a double kidney transplant
2. Patients who are receiving a third or fourth transplant
3. Patients who have greater than 50% (current or historic) panel reactive antibodies
4. Female patients who are pregnant or unwilling to use adequate contraception during the study
5. Patients on other investigational drugs
6. Patients who are unable to take medication orally
7. Patients with a life expectancy less than 1 year

Date of first enrolment

29/09/2000

Date of final enrolment

21/10/2002

Locations**Countries of recruitment**

Netherlands

Study participating centre

Leiden University Medical Centre

Leiden

Netherlands

2300 RC

Sponsor information**Organisation**

Leiden University Medical Centre (LUMC) (The Netherlands)

ROR

<https://ror.org/027bh9e22>

Funder(s)

Funder type

Not defined

Funder Name

Not provided at time of registration

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration