Calcineurin-inhibitor Nephrotoxicity and Efficacy Study.

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON21129

Source
NTR

Brief title
CANNES

Health condition

De novo renal transplant recipients.

Intervention

Outcome measures

Primary outcome

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 (appendix) 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.

Secondary outcome

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-b;

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.

Study description

Background summary

Several multicenter studies are currently underway to define the immunosuppressive regimen that is associated with the best long-term outcome.

The primary end-point in such studies is usually graft survival and function, albeit that prevention of acute rejection is sometimes used as the primary end-point. The disadvantage of such studies is that large numbers of patients need to be followed for relatively long periods of time, which is often confounded by frequent cross-overs. Thus, although such studies are of great importance, smaller studies with well-thought of surrogate end-points are more flexible and allow the efficient design of larger multi-center studies.

The current study is designed to compare AUC-controlled dosing of CsA with AUC-controlled of tacrolimus to prevent functional and structural changes at 6 and 12 months post-transplantation. After the first year patients will be followed according to standard clinical

practice, with at least yearly documentation of graft function and protein excretion rate at the transplant center.

To study the relationship between CsA or tacrolimus levels (peak, trough), drug exposure (area under the concentration curve) and the level of immunosuppression in-vivo, we propose to study the level of calcineurin inhibition 34,35 in lymphocytes obtained for the pharmacokinetic study.

The degree of calcineurin inhibition will be correlated with graft function and structure as well as clinical events such as acute rejection episodes and infectious complications. The calcineurin inhibition assay will be performed by Dr G Remuzzi, Bergamo, Italy, who has extensive experience with this assay.

It has been proposed that TGF-b is an important mediator of chronic CsA nephrotoxicity 14,32 and we will therefore measure TGF-b levels in the different treatment groups and correlate TGF-b AUC and urinary TGF-b excretion with drug exposure and histological and clinical evidence of nephrotoxicity.

The active metabolite of mycophenolate mofetil is rapidly de-esterified to mycophenolic acid (MPA) and further metabolized to the glucuronidated metabolite MPA-glucuronide. MPA and to a lesser degree MPA glucuronide 27 reversibly inhibit the enzyme inosine-5'-monophosphatedehydrogenase (IMPDH), the rate-controlling enzyme in the de-novo biosynthesis of guanosine and deoxyguanosine nucleotides. Whereas interactions between tacrolimus and MMF have been reported 32, opposite interactions with CsA have been presented (unpublished). The degree of inhibition of IMPDH will be correlated with graft function and structure as well as clinical events like acute rejection episodes and infectious complications.

Experimental studies in animal models of chronic renal disease and scarring have shown that upregulated expression of a(1)(I) procollagen mRNA is a sensitive and discriminating surrogate end point over a wide range of injuries to predict renal sclerosis. mRNA will be extracted from biopsies and stored in liquid nitrogen. If indeed the primary end-point shows

differences in fibrosis between different treatment groups at 12 months, early biopsies will be analyzed for collagen mRNA levels.

Study objective

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.

Study design

N/A

Intervention

Before transplantation, patients will be randomized 1:1 to receive either a standard CsA-based or tacrolimus-based immunosuppressive regimen and either a twice daily (b.i.d.) or once daily (o.d.) 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 b.i.d. 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.

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Eligibility criteria

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-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.

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 > 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.

Study design

Design

Study type:	Interventional
Intervention model:	Factorial
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-09-2000
Enrollment:	126
Type:	Actual

Ethics review

Positive opinion

Date:	13-09-2005
Application type:	First submission

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
NTR-new	NL351
NTR-old	NTR390
Other	: N/A
ISRCTN	ISRCTN55817881

Study results

Summary results
J Am Soc Nephrol. 2006 Sep;17(9):2622-32. Epub 2006 Aug 9.