ISRCTN39668614 https://doi.org/10.1186/ISRCTN39668614

A pharmacogenetic approach to immunosuppression for renal transplantation

Submission date	Recruitment status	[_] Prospectively registered
28/09/2007	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
28/09/2007	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
31/10/2019	Urological and Genital Diseases	[_] 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
N0236169543

Study information

Scientific Title
A pharmacogenetic approach to immunosuppression for renal transplantation

Study objectives
Individualisation of initial tacrolimus dosing based on the CYP3A5 genotype will increase the proportion of patients who achieve target blood concentrations during the early period after transplantation with the potential to reduce the rate of allograft rejection without increasing drug toxicity. Sub Study of 'The effect of a genetic polymorphism that determines the expression of cytochrome P450 on tacrolimus pharmacokinetics'.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Primary study design
Interventional

Study design
Randomised controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Urological and Genital Diseases: Renal transplantation

Interventions
Patients identified as being genetic expressors of CYP3A5 (at least one CYP3A5*1 allele in the absence of CYP3A5*6 or 7*) will be randomised to initial tacrolimus dosing on their CYP3A5 genotype or to our current empirical starting dose.

From our previous observations, we would predict that 25% of the individuals typed will fall into this group, giving 20-25 eligible patients annually. With our current protocol patients receive an initial loading dose of 0.2 mg/kg tacrolimus followed by 0.1 mg/kg twice daily. CYP3A5 expressers will be randomised to this starting dose or a loading dose of 0.4 mg/kg followed by 0.2 mg/kg twice daily. Subsequent drug dosing will be modified based on whole blood 12-hour post dose (trough) blood concentrations of tacrolimus measured three times weekly for the first two weeks of the study using an immunoassay (Tacrolimus II, Abbott Diagnostics, performed on an IMx clinical analyser). The laboratory is a member of the International Tacrolimus Proficiency Testing Scheme. The target range will be 15-20 ng/ml during the first 7 days after transplantation and 10-15 ng/ml during the following 3 months.

The following clinical data will be recorded at the time of transplant: age, sex, ethnic group, original renal disease, serum albumin and haemoglobin concentrations, concurrent medications, type of transplant: cadaveric/asystolic donor/live-donor, degree of HLA mismatch, % panel reactivity (peak and current), history of diabetes mellitus.

Calcineurin inhibitor toxicity will be defined as follows:
Diabetes mellitus will be diagnosed by the requirement for any hypoglycaemic treatment in patients who had not been diabetic pre-transplant. A glucose tolerance test will be performed at

3 months post-transplant with a 2-hour glucose of greater than 11.1 mmol/L taken as diagnosing diabetes mellitus will be taken as all patients still requiring hypoglycaemic treatment one year after transplantation.

Neurotoxicity is difficult to define with objectivity. A pragmatic approach will be employed. The following symptoms, recorded prospectively either reported by the patient or found on physical examination, will be regarded as evidence of neurotoxicity: tremor, paraesthesia, acute confusion.

Nephrotoxicity will be diagnosed when a renal biopsy performed to diagnosed renal dysfunction excludes rejection and shows changes compatible with calcineurin inhibitor toxicity (tubular vacuolation, hyaline deposits in arterioles), or there is a fall of at least 20% in serum creatinine on reduction of the tacrolimus dose for clinical suspension of toxicity.

Intervention Type
Other

Phase
Not Applicable

Primary outcome(s)
The proportion of patients achieving target blood tacrolimus concentrations, tacrolimus measurements within the target range of 15-20 ng/ml during the first 7 days after transplantation and 10-15 ng/ml during the following 7 days.

Key secondary outcome(s)
1. The incidence of all episodes of rejection including episodes treated as rejection without biopsy confirmation
2. The serum creatinine concentration at one year after transplantation with glomerular filtration rate calculated using the MDRD formula
3. The incidence of calcineurin inhibitor toxicity

Completion date
19/09/2007

Eligibility

Key inclusion criteria
All non-black (genetically from Sub-Saharan Africa) patients on the transplant waiting list for St George's Hospital will be invited to participate. We already give black patients an increased starting dose of tacrolimus as standard practice. At present there are 170 patients on the waiting list and we would anticipate performing 80-100 renal transplant operations annually. All subjects will be given written informed consent.

Individuals will be genotyped for SNPs using DNA prepared from peripheral blood leucocytes. We will type for CYP3A5*1/*3, CYP3A%*6 and CYP3A5*7. CYP3A5*6 and CYP3A5*7 are present in <10% of the population and may coexist with CYP3A5*1 resulting in non-expression of CYP3A5. We will determine the genotype of the SNPs in exons 12,21 and 26 of MDR-1 to define the haplotypeas has been recently suggested to be a more satisfactory approach than looking at

single polymorphisms. We have established methods based on reverse transcriptase polymerase chain reaction (PCR) followed by use of restriction fragment length polymorphisms (RFLP) for MDR-1 genotyping. CYP3A5 genotyping will be performed using a LightCycler™.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Not Specified

Sex
Not Specified

Key exclusion criteria
Not provided at time of registration

Date of first enrolment
19/09/2005

Date of final enrolment
19/09/2007

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Division of Renal Medicine
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Sponsor information

Organisation
Record Provided by the NHSTCT Register - 2007 Update - Department of Health (UK)

Funder(s)

Funder type
Government

Funder Name
St George's Healthcare NHS Trust (UK)

Funder Name
NHS R&D Support Funding (UK)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration