

A pharmacogenetic approach to immunosuppression for renal transplantation

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Registration date 28/09/2007	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan
		<input type="checkbox"/> Results
Last Edited 31/10/2019	Condition category Urological and Genital Diseases	<input type="checkbox"/> Individual participant data
		<input type="checkbox"/> Record updated in last year

Plain English summary of protocol

Not provided at time of registration

Contact information

Type(s)

Scientific

Contact name

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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

Study design

Randomised controlled trial

Primary study design

Interventional

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 expressors 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, CYP3A5*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 haplotypes 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**

London

United Kingdom

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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