ISRCTN24376050 https://doi.org/10.1186/ISRCTN24376050

# Research on individualisation of tacrolimus regimen based on the CYP3A5, MDR1 and PXR genotypes

| Submission date | Recruitment status | [ ] Prospectively registered |
|---|---|---|
| 21/08/2009 | No longer recruiting | [ ] Protocol |
| **Registration date** | **Overall study status** | [ ] Statistical analysis plan |
| 23/09/2009 | Completed | [ ] Results |
| **Last Edited** | **Condition category** | [ ] Individual participant data |
| 23/09/2009 | Injury, Occupational Diseases, Poisoning | [ ] 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

**EudraCT/CTIS number**

**IRAS number**

**ClinicalTrials.gov number**

**Secondary identifying numbers**
N/A

# Study information

## Scientific Title
Research on individualisation of tacrolimus regimen based on the CYP3A5, MDR1 and PXR genotype-guided combination therapy (coadministration with diltiazem or Schisandra sphenanthera extract): a randomised controlled trial

## Study objectives
Tacrolimus is widely used in solid organ transplantation to prevent allograft rejection. It has a narrow therapeutic window and highly variable pharmacokinetic characteristics. Though therapeutic drug monitoring (TDM) is adopted universally to monitor trough concentration and adjust doses, its hysteresis makes it still not an optimal solution. Many studies suggested that genetic polymorphisms in drug-metabolising enzymes (mainly CYP3A5), drug transporters (P-glycoprotein, encoded by MDR1) and upstream regulators (PXR) may be responsible for the inter-individual differences in pharmacokinetics, so using of genetic information to plan drug dosing has great potential for improving safety and efficacy profile of tacrolimus.

Tacrolimus is expensive and theoretically a life-long medication, so it's undoubtedly a heavy financial burden for medical insurance system and patients, especially for those high-dose users. Therefore, efforts have been made to decrease patients' consumption of tacrolimus yet still keep its blood concentration within target therapeutic window. Coadministration with agents that inhibit the metabolism and facilitate the absorption of tacrolimus has been proved to be a useful method. For example, diltiazem, an anti-hypertensive agent from calcium channel blocker family, would inhibit CYP3A and P-glycoprotein and has been used as a tacrolimus-sparing agent for many years. Recently, it has been found that coadministration with Schisandra sphenanthera extract (SchE, a prescribed hepatoprotective drug) could significantly increase in vivo whole blood concentration of tacrolimus, indicating that SchE may also be an efficient tacrolimus-sparing agent with potential therapeutic and financial saving benefits. Studies about substances in SchE revealed that some of them are strong CYP3A inhibitors, while some act on P-glycoprotein, these may be the primary reasons for its potent tacrolimus-sparing effect.

On the basis of our previous retrospective studies and reports from other researchers, we propose the hypnoses as follows:
1. Verifying the polymorphism of CYP3A5, MDR1 and PXR could predict necessary dose for individuals.
2. Schisandra sphenanthera extract can affect tacrolimus pharmacokinetics, increase its bioavailability. The above effect is of clinical significance, safe and stable, which makes it meaningful for tacrolimus-sparing in clinical settings.
3. Pharmacogenetic-guided combination therapy (coadministration with diltiazem or SchE) can decrease the needed tacrolimus dose to reach therapy window by about 15%-30% or 50%-70% respectively.

## Ethics approval required
Old ethics approval format

## Ethics approval(s)
The study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-Sen University on 30 June 2008. (ref: [2008]21-23)

## Study design

Retrospective study + randomised controlled trial

## Primary study design
Interventional

## Secondary study design
Randomised controlled trial

## Study setting(s)
Hospital

## Study type(s)
Treatment

## Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

## Health condition(s) or problem(s) studied
Renal transplantation/ allograft rejection

## Interventions
1. Retrospectively assess the correlations between CYP3A5, MDR1 and PXR polymorphisms and tacrolimus pharmacokinetics.
i. A loading dose (0.05-0.075 mg/kg twice daily) of tacrolimus (was started on the second day after transplantation and subsequently adjusted to achieve target trough concentration (C0) between 5 and 10 ng/mL. Supplementary immunosuppressive drugs include mycophenolate mofetil 0.5-0.75 g twice daily and prednisolone 30 mg per day.
ii. Body weight, tacrolimus dosage, combination (none, dilitiazem or SchE), whole blood concentration were recorded at day 7 after transplantation. The pharmacokinetics were assessed when the patients took tacrolimus alone or coadministered with diltiazem (30 mg, three times daily ) or SchE (0.54 g, three times daily) for two weeks, body weight and tadrolimus dosage were also recorded. Venous blood samples (2 mL) were obtained before drug administration and 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 h after dosing. The quantification of tacrolimus in human whole blood was achieved by liquid chromatographytandem mass spectrometry.
iii. The subjects were genotyped for the CYP3A5*3 (6986 A>G) and MDR1 SNPs 1236 C>T, 2677 G>T/A and 3435 C>T using polymerase chain reaction (PCR) restriction fragment length polymorphism methods.
iv. Correlations between genetic polymorphisms and tacrolimus were separately assessed according to the combination (none, diltiazem or SchE).

2. Investigate the effects of diltiazem or SchE on tacrolimus pharmacokinetics.
Patients who had oral administered tacrolimus alone (without coadminitration with diltiazem or SchE ) for two weeks were enrolled and randomly assigned into diltiazem group or SchE group. Venous blood samples (2 mL) were obtained before drug administration and 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 h after dosing. After last sampling, diltiazem (30 mg, three times daily) or SchE (0.54 g, three times daily) was initially coadministered in diltiazem group or SchE group, respectively. Two weeks later, another ten blood samples were collected. The quantification of tacrolimus in human whole blood was achieved by liquid chromatography-tandem mass spectrometry. Doses of tacrolimus were adjusted according to the C0.

3. A prospective randomised controlled study to compare the pharmacogenetic-guided combination therapy (coadministration with diltiazem or SchE) and conventional therapy. When retrospective study was completed, a prospective randomised controlled study was conducted to to validate the results obtained from the retrospective study and compare the pharmacogenetic-guided combination therapy (coadministration with diltiazem or SchE) and conventional therapy. Patients were genotyped for the polymorphisms that can influence tacrolimus pharmacokinetics before transplantation, and enrolled and randomly assigned to the "control" or the "study" group. In control group, patients administered conventional loading dose of tacrolimus without coadministration with diltiazem or SchE. In the study group, loading dose of tacrolimus was calculated by the results of retrospective study, and diltiazem (30 mg three times daily) or SchE (0.54 g, three times daily) was concomitantly administered. Supplementary immunosuppressive drugs used in these two groups were the same as in retrospective study.

The primary end points were the comparisons between the study and control groups of the C0 after the initial dose and the percentage of out-of-range C0 after first dosing. The target C0 range was 5-10 ng/mL. Secondary end points were to compare the number of dose adjustments made to achieve therapeutic range and the dose requirement to reach therapeutic range in both groups.

In all above studies, enrolled patients are followed once per week for the first months after transplant, once every two weeks for the second and third month, and once per month thereafter. Kidney function, liver function, blood counting and all medical problems of the patients are recorded besides the whole blood concentration of tacrolimus. These results are compared between groups to see whether the combination therapy would influence the allograft function, rejection rate and other physical parameters, especially those related to side effects of immunosuppressants.

### Intervention Type
Drug

### Phase
Not Applicable

### Drug/device/biological/vaccine name(s)
Tacrolimus

### Primary outcome measure
1. Distribution of CYP3A5, MDR1 and PXR polymorphisms in Chinese kidney transplant patients.
2. Correlation between dose-adjusted C0, Cmax, AUC0-12 h and CYP3A5, MDR1, PXR polymorphisms when tacrolimus is administered alone or co-administered with diltiazem/ SchE (See Interventions for details of assessment methods).

### Secondary outcome measures
Comparisons between the pharmacogenetic-guided combination therapy (co-administration with diltiazem or SchE) and conventional therapy:
1. The first C0 of tacrolimus after the first dosing of tacrolimus alone or in combination with diltiazem/SchE. The first C0 was measured 72 h (3 days) when plateau concentration can be reached for most people.
2. Percentage of out-of-range C0 after the first dosing of tacrolimus alone or in combination with diltiazem/SchE

3. Number of dose adjustments made to achieve therapeutic range (5-10 ng/mL)
4. Dose requirement to reach therapeutic range(5-10 ng/mL)
5. 1-year patient/graft survival and 2-year patient/graft survival
6. Incidence of acute rejection, drug-related adverse events and side effects. Duration of follow-up: 2 years.
7. Serum creatinine level will be assessed every 2 weeks for the first 3 months post-transplant and monthly thereafter for 2 years

### Overall study start date
01/12/2005

### Completion date
31/12/2011

## Eligibility

### Key inclusion criteria
1. Adult (both males and females, 18-60 years) recipients underwent single primary renal transplantation in the First Affiliated Hospital of Sun Yat-sen University
2. Only for retrospective study: Used a triple regimen with tacrolimus, mycophenolate mofetil and prednisone after transplantation (Note: In prospective study, patients were enrolled before immunosuppresants were used)
3. Wish to participate in the study
4. Informed consent for the trial

### Participant type(s)
Patient

### Age group
Adult

### Lower age limit
18 Years

### Upper age limit
60 Years

### Sex
Both

### Target number of participants
Retrospective study: 300; prospective study: 200

### Key exclusion criteria
1. Patients with abnormal hepatic function, serious infection, malignant tumour, and diabetes mellitus
2. Patients with ABO-incompatible renal transplantation
3. Panel reactive antibody (PRA) levels greater than 30% before transplantation
4. Underwent combined organ transplantations
5. Except for diltiazem and SchE, other medication known to affect tacrolimus blood levels, such

as verapamil, ketoconazole, itraconazole, erythromycin or clarithromycin was used
6. Allergic history to study medicines
7. During pregnancy or plan to get pregnant during the study period

**Date of first enrolment**
01/12/2005

**Date of final enrolment**
31/12/2011

# Locations

**Countries of recruitment**
China

**Study participating centre**
**Institute of Clinical Pharmacology**
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# Sponsor information

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University/education

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https://ror.org/0064kty71

# Funder(s)

### Funder type
Government

### Funder Name
National Natural Science Foundations of China (China) (refs: 30873124, 30873125)

### Funder Name
Science and Technology Foundation of Guangdong Province (China) (refs: 2008B030301309, 2007B031511001)

## Results and Publications

### Publication and dissemination plan
Not provided at time of registration

### Intention to publish date

### Individual participant data (IPD) sharing plan

### IPD sharing plan summary
Not provided at time of registration