

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

<b>Submission date</b> 21/08/2009	<b>Recruitment status</b> No longer recruiting	<input type="checkbox"/> Prospectively registered
<b>Registration date</b> 23/09/2009	<b>Overall study status</b> Completed	<input type="checkbox"/> Protocol
<b>Last Edited</b> 23/09/2009	<b>Condition category</b> Injury, Occupational Diseases, Poisoning	<input type="checkbox"/> Statistical analysis plan
		<input type="checkbox"/> Results
		<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**  
Ms Jiali Li

**Contact details**  
Institute of Clinical Pharmacology  
School of Pharmaceutical Sciences  
Sun Yat-sen University  
74 Zhongshan Road  
Guangzhou  
China  
510080

## Additional identifiers

**Protocol serial number**  
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 hypotheses 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

## Study type(s)

Treatment

## 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 (C<sub>0</sub>) 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, diltiazem 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 tacrolimus 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 chromatography-tandem 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 coadministration 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 C<sub>0</sub>.

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 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 C<sub>0</sub> after the initial dose and the percentage of out-of-range C<sub>0</sub> after first dosing. The target C<sub>0</sub> 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(s)**

1. Distribution of CYP3A5, MDR1 and PXR polymorphisms in Chinese kidney transplant patients.
2. Correlation between dose-adjusted C<sub>0</sub>, C<sub>max</sub>, AUC<sub>0-12 h</sub> and CYP3A5, MDR1, PXR polymorphisms when tacrolimus is administered alone or co-administered with diltiazem/ SchE (See Interventions for details of assessment methods).

### **Key secondary outcome(s)**

Comparisons between the pharmacogenetic-guided combination therapy (co-administration with diltiazem or SchE) and conventional therapy:

1. The first C<sub>0</sub> of tacrolimus after the first dosing of tacrolimus alone or in combination with diltiazem/SchE. The first C<sub>0</sub> was measured 72 h (3 days) when plateau concentration can be reached for most people.
2. Percentage of out-of-range C<sub>0</sub> 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

### **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 immunosuppressants were used)
3. Wish to participate in the study
4. Informed consent for the trial

**Participant type(s)**

Patient

**Healthy volunteers allowed**

No

**Age group**

Adult

**Lower age limit**

18 years

**Upper age limit**

60 years

**Sex**

All

**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**  
Guangzhou  
China  
510080

## Sponsor information

### Organisation

Sun Yat-sen University (China)

### ROR

<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

### Individual participant data (IPD) sharing plan

### IPD sharing plan summary

Not provided at time of registration