

Title: A Safety and Efficacy Study of a Chronopharmacokinetic Model–Guided Individualized Tacrolimus Dosing Regimen in Kidney Transplant Recipients

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1. Research Abstract

Tacrolimus (TAC) is the most commonly used calcineurin inhibitor after kidney transplantation; however, it has a narrow therapeutic window, high inpatient variability, and exhibits marked diurnal (chronopharmacokinetic) differences in its pharmacokinetics. Our center performs approximately 100 kidney transplant surgeries per year and routinely uses a classic triple immunosuppressive regimen based on TAC combined with mycophenolate mofetil (MMF)/mycophenolate sodium (MPS) and glucocorticoids, providing a stable foundation for follow-up and research implementation in kidney transplant recipients. Both previously published literature and our center's earlier TAC pharmacokinetic (PK) data suggest that when the immediate-release (IR) formulation of TAC is administered as twice-daily equal doses, significant chronopharmacokinetic differences emerge: the morning dose produces higher exposure and peak concentration, whereas the evening dose yields relatively lower exposure—that is, a "high in the morning, low in the evening" biphasic concentration–time profile. Morning exposure is generally higher than evening exposure, and large peak-to-trough fluctuations may increase the risks of nephrotoxicity, metabolic abnormalities, and neurotoxicity.

This study will employ a multicenter, prospective, randomized controlled design and plans to enroll 100 stable-phase kidney transplant recipients, who will be randomized at a 1:1 ratio to either the chrono-individualized dosing group (receiving a "low in the morning, high in the evening" individualized dose regimen guided by the chronopharmacokinetic model) or the conventional equal-dose control group, with a total observation period of 12 months. The primary study endpoints include changes in graft renal function (eGFR) and the incidence of biopsy-proven or clinically diagnosed acute rejection. Secondary study endpoints include the incidence of adverse drug reactions (ADRs) and adverse events (AEs); 1-year patient and graft survival rates; TAC morning and evening trough concentrations and the AUC fluctuation index; the degree of fluctuation in AUC₀₋₂₄; the degree of fluctuation in calcineurin (CN) activity; the trough concentration-to-daily dose ratio (C₀/D); TAC inpatient variability (IPV); and the number of dose adjustments. In addition, we will explore the correlation between biomarkers—including metabolomics, lipidomics, and gut microbiota—and TAC

chronopharmacokinetic characteristics, and, depending on the data, perform a pharmacoeconomic evaluation. The results of this study will provide prospective evidence for chronopharmacokinetic model-guided precision dosing of TAC and for routine clinical monitoring.

2. Research Background and Rationale

Kidney transplantation is the optimal treatment for patients with end-stage renal disease. Calcineurin (CN) inhibitors, of which TAC is representative, serve as first-line antirejection drugs after organ transplantation and have enabled long-term survival of kidney transplant recipients [1]. However, TAC has a narrow therapeutic window, and the high inpatient variability (IPV) caused by factors such as metabolic enzyme activity and the type and state of food intake directly affects graft survival [2-3]. In addition, the *in vivo* pharmacokinetics (PK) of TAC exhibit typical chronopharmacological phenomena: under a twice-daily equal-dose regimen, the concentration–time curve is characterized by high morning and evening peaks, large peak-to-trough fluctuations, and marked differences in morning versus evening exposure (Figure 1A) [4-6]. This fluctuation in exposure and the out-of-window concentrations are closely associated with the renal and pancreatic (islet) toxicity of TAC and are also key factors limiting the long-term survival of grafts maintained on TAC in kidney transplant recipients [7-10]. Currently, routine monitoring of the TAC steady-state trough concentration (C_{trough}) cannot reflect the degree of intra-day fluctuation, and, as a post-hoc measurement, it is associated with a certain delay [11]. We therefore proposed the research concept of improving the TAC daily dosing regimen by exploiting this chronopharmacological phenomenon (Figure 1B) and attempted to establish a TAC chrono-population pharmacokinetic (PPK) model using data from 18 kidney transplant recipients at our center. On the premise of not reducing total exposure (AUC_{0-24}), the TAC "low in the morning, high in the evening" dosing regimen simulated by the chronopharmacokinetic model reduces morning–evening fluctuation while also achieving a saving in daily dose, and at the same time preserves room for individualized dose individualization. We call this the "3S" dosing regimen, representing greater Safety, Smartness, and Smoothness, which is expected to provide an effective, feasible, safer, and more economical long-term TAC regimen for kidney transplant recipients.

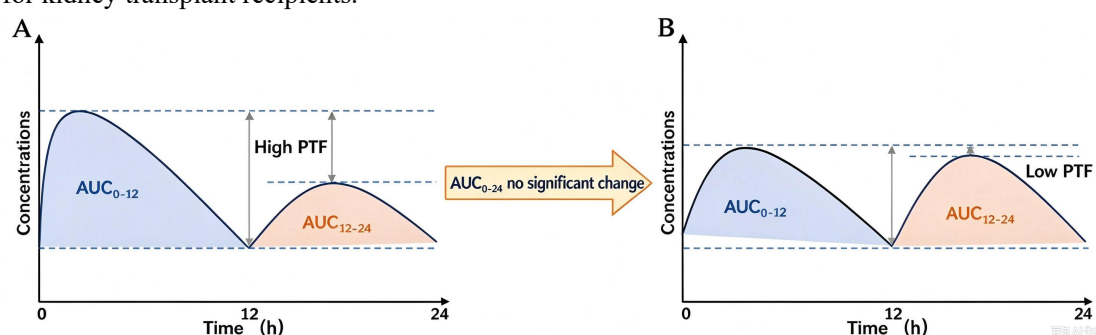


Figure 1. Chronopharmacological characteristic-based individualized TAC dosing regimen

3. Study Objectives

(1) Primary objective:

To evaluate the efficacy and safety of the tacrolimus "3S" dosing regimen in stable-phase kidney transplant recipients.

(2) Secondary objectives:

- 1.To evaluate, using metabolomics, lipidomics, and chronopharmacokinetic modeling analyses, the biomarkers affecting the pharmacokinetic and pharmacodynamic chronopharmacological characteristics of tacrolimus in kidney transplant recipients and their correlations;
- 2.To evaluate the pharmacoeconomic value and compliance of the tacrolimus "3S" chrono-model-guided dosing regimen in stable-phase kidney transplant recipients.

4. Study Methods and Design**4.1 Study design type**

This is a multicenter, randomized, controlled study, with a preliminary plan to enroll 100 participants. In the first phase, 50 participants will be enrolled; after screening, they will be randomized at a 1:1 ratio into the experimental group or the control group to receive TAC treatment. At the study midpoint (Month 6), an interim statistical analysis of the study results will be performed to determine the sample size needed for the subsequent phase, continuing until the statistical requirements are met.

The observation period is 1 year. During the study, participants will undergo safety and efficacy assessments at the times and in the manner specified in the study flow table (Table 1). Participants may continue receiving TAC therapy until clinically diagnosed acute rejection, loss of clinical benefit, occurrence of an unacceptable adverse event (AE), death, loss to follow-up, withdrawal of informed consent, or study completion, whichever occurs first.

4.2 Study population and selection criteria

Study population:

The study population comprises patients who underwent living-donor or deceased-donor kidney transplantation at our center or at collaborating institutions, aged 18–70 years, who are in a stable phase (more than 3 months after transplantation) and receiving long-term TAC therapy. Participants must meet all of the following inclusion criteria and none of the exclusion criteria to be enrolled.

Inclusion criteria:

- Sex not restricted; age 18–70 years (inclusive);
- First living-donor or deceased-donor kidney transplantation;
- For deceased-donor transplantation, kidneys from donation after brain death (DBD);
- ABO blood type compatibility between donor and recipient;
- Negative panel reactive antibody (PRA) result within 6 months before surgery;
- Post-transplant immunosuppressive regimen must be the triple regimen of TAC + mycophenolate mofetil (MMF)/mycophenolate sodium (MPS) + glucocorticoids;
- More than 3 months after kidney transplantation, with stable graft function;
- Stable TAC dose regimen and Ctrough results, and stable concomitant medication regimen;

Voluntarily participate in the clinical study, fully understand the study and voluntarily sign the informed consent form (ICF), and be able to complete all study procedures.

Exclusion criteria:

Multiple organ combined transplantation;
History of prior organ transplantation other than the kidney;
History of acute rejection after transplantation, or currently receiving treatment for acute rejection;
Evidence of active systemic or localized infection;
Currently severe diarrhea, vomiting, active peptic ulcer, or other gastrointestinal diseases affecting TAC absorption;
Allergy to TAC or its ingredients, or other contraindications precluding the use of TAC;
Pregnant women, or women of childbearing potential who plan to become pregnant;
Use of strong CYP3A inhibitors or strong inducers within 2 weeks before first dosing, or short-term use during the study;
Poor recipient compliance, or other conditions judged by the investigator to make the participant unsuitable for enrollment.

Withdrawal criteria:

This study has established a participant withdrawal mechanism, including withdrawals determined by the investigator and those initiated by the participant themselves, as follows:

The subject does not agree to continue participation at any time;
Occurrence of graft loss, death, or loss to follow-up during the follow-up period;
During the study, the occurrence of any adverse event, abnormal laboratory finding, or other medical condition such that the risks of continued participation outweigh the benefits;
Failure to achieve the target AUC₀₋₂₄ under the chrono-individualized dosing regimen, where the investigator deems that a risk exists;
The investigator considers that the subject is exposed to unexpected, significant, or unacceptable risk, or other reasons that preclude continuation of the study.

4.3 Group assignment of study subjects

Experimental group treatment regimen (n=25): Subjects receive the immediate-release (IR) formulation of TAC twice daily with a "low in the morning, high in the evening" dose ratio. After randomization, the morning and evening dose regimen will be individually determined based on the TAC chronopharmacokinetic model and converted into the "3S" dosing regimen.

Control group treatment regimen (n=25): Subjects receive the IR formulation of TAC twice daily at equal doses. The daily dose will be adjusted according to the TAC C_{trough} and the target therapeutic window (see Dose Adjustment). After randomization, subjects continue the original TAC regimen.

4.4 Study procedures

Subjects first enter a screening period, from Day -14 to Day 0 before randomization. During the

screening period, study personnel will explain the study to potential subjects. After subjects voluntarily sign the ICF, confirmation of the inclusion and exclusion criteria and baseline assessments will be performed. Subjects who meet the enrollment criteria will be allocated at a 1:1 ratio into the experimental group or the control group. The experimental group receives the "low in the morning, high in the evening" individualized unequal-dose regimen; the control group receives the conventional twice-daily equal-dose regimen. All randomized subjects will be followed up at 2 weeks, 1 month, 3 months, 6 months, and 12 months after randomization. An end-of-treatment (EOT) visit will be performed at completion of the 12-month follow-up or upon premature study termination, followed by a 28-day safety follow-up after the EOT visit.

4.5 Follow-up plan

On the basis of the standard post-kidney-transplantation follow-up plan, and in accordance with the study flow table, TAC concentrations and other observational parameters will be measured at 2 weeks, 1 month, 3 months, 6 months, and 12 months after randomization using the limited sampling strategy (LSS). The follow-up plan of this study is divided into the screening period, the study observation period, and the study follow-up period. The follow-up plan and specific observational parameters for each phase are shown in the study flow table (Table 1).

Screening period

Days –14 to 0: confirm that participants meet the study enrollment criteria.

Study observation period

After enrollment, participants who complete screening as required by the protocol are randomized into the experimental group or the control group and receive the respective TAC dosing regimens. The observation period begins at the start of randomized dosing and lasts for 1 year. During this period, clinical data at follow-up visits and all adverse events will be recorded in detail, and subjects will be guided in their treatment. On the basis of the standard post-transplantation follow-up plan, laboratory examinations performed at each visit according to the study flow table include: complete blood count, urinalysis, biochemical parameters, liver and kidney function, blood lipids, TBNK (T-cell, B-cell, and NK-cell subsets), and PK; renal graft color Doppler ultrasound will be performed at screening, Month 3, and Month 12 after enrollment. If any adverse event occurs during follow-up, additional examinations will be performed as needed, and the event will be managed promptly.

Study follow-up period

Participants, including those who withdrew prematurely, enter the follow-up period after completing the final (EOT) visit. The follow-up period comprises the 28-day safety follow-up after EOT, regular efficacy follow-up every 3 months, and survival follow-up, continuing until loss to follow-up, withdrawal of informed consent, study completion, or death, whichever occurs first.

Table 1. Study Flow Table

Study Phase	Content	Screening Period	Enrollment	Randomization	Study Observation Period					Safety Follow-up	Remarks
Randomized Controlled Study	Days	-14d*0d	1d	2d	14d*	1M	3M ±5d	6M ±5d	12M ±5d	28d**	
	Visit	-	V1	V2	V3	V4	V5	V6	V7	V8	Add additional follow-up time in the clinical trial
	Inclusion and Exclusion	X									
	Informed Consent Form Signature	X									
	Demographic Data	X									
	Current and Past Medical History	X									
	Vital Signs	X	X	X	X	X	X	X	X	X	
	Concomitant Medications	X	X	X	X	X	X	X	X	X	
	Surgical and Matching Information	X									
	Pre-enrollment Clinical Laboratory Results	X									
	LSS		X		X	X	X	X	X	X	
	Regimen Switch										
	Clinical Laboratory Results		X	X	X	X	X	X	X	X	
	Pre-transplant Imaging	X					X	X			
	Adverse Event Documentation		X	X	X	X	X	X	X	X	

Note: * = Day 14 after randomization; ** = Day 28 after EOT.

Informed consent: the written ICF signed by the subject must be obtained before all study procedures are performed;

Demographics: including age, sex, ethnicity, height, and weight;

Current and past medical history: including past history and current history; past history records medical/surgical history up to the signing of the written ICF; current history records ongoing conditions at the time of signing the ICF and any conditions newly identified after signing the ICF;

Vital signs: including respiratory rate, pulse, blood pressure, and axillary temperature. Subjects must rest for at least 5 minutes before vital sign assessment. For all patients, blood pressure must be controlled to $\leq 150/100$ mmHg before the first dose. During the study, in addition to the vital sign visits planned in the flow table, the investigator may perform additional vital sign checks based on clinical indications;

Pre-enrollment laboratory examinations (during the screening period, laboratory results obtained before signing the ICF but within 7 days before the first dose are acceptable. In the screening period, clinically significant abnormal laboratory parameters may be repeated once): 1) Complete blood count: including white blood cell count, neutrophil count, eosinophil count, basophil count, lymphocyte count, red blood cell count, hemoglobin, platelet count, hematocrit, and monocyte count; 2) Liver/kidney function and blood biochemistry: including serum creatinine, blood urea/urea nitrogen, total bilirubin, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase, total cholesterol, triglycerides, and alkaline phosphatase; 3) Glucose parameters: blood glucose and glycated hemoglobin (HbA1c), with an oral glucose tolerance test (OGTT) if necessary; 4) Urinalysis: urine protein, urine occult blood, and urine specific gravity/ratio; 5) TBNK results; 6) Tacrolimus Ctrough concentration;

Concomitant medications: includes all current medications and any medications discontinued within 2 weeks before enrollment;

Conversion of dosing regimen: performed after randomization; subjects in the experimental group receive individualized dosing according to the chronopharmacokinetic model, whereas subjects in the control group continue their original dosing regimen;

Standard post-kidney-transplantation follow-up plan: follow-up every 2 weeks during months 3–6; once monthly during months 6–12; and every 1–2 months after month 12. Each follow-up includes complete blood count, urinalysis, liver/kidney function and biochemistry, TBNK, and

tacrolimus Ctrough;

Clinical laboratory results: same content as the pre-enrollment laboratory examinations;

TAC intensive PK blood sampling: blood samples are collected at 0 h (before the morning dose), 1 h, 1.5 h, 2 h, 4 h, 6 h, 9 h, 12 h (before the evening dose), 13 h, 14 h, 16 h, 20 h, and 24 h (before the morning dose)—a total of 13 sampling time points;

Compliance assessment: TAC daily dosing must be administered at 12-hour intervals and during the required fasting window. If a dose is missed, it may be taken within 4 hours of the scheduled time. Medication counts and related information will be assessed at each follow-up visit, and compliance-related information will be recorded.

4.6 Selection and definition of primary and secondary endpoints

Primary endpoints

Change in graft renal function (eGFR, calculated using the Cockcroft–Gault equation);

Incidence of acute rejection (biopsy-proven or clinically diagnosed).

Secondary endpoints

Incidence of adverse drug reactions (ADRs) and adverse events (AEs), including but not limited to: liver function (ALT, AST, TBIL); abnormal glucose metabolism or new-onset diabetes (FBG, HbA1c, OGTT); lipid parameters (TG, TC, LDL); tremor; and post-transplant infection (including pulmonary infection, bloodstream infection, urinary tract infection, gastrointestinal infection, and wound infection).

1-year patient and graft survival rates;

Peak-to-trough fluctuation (PTF) index of TAC morning/evening concentrations and AUC;

Degree of fluctuation of TAC AUC0-24;

Degree of fluctuation of calcineurin (CN) activity;

Trough concentration-to-daily dose ratio (C0/D);

TAC inpatient variability (IPV);

Number of TAC dose adjustments.

Other endpoints

Pharmacoeconomic analysis: if the data permit, a clinical-trial–based economic evaluation will be performed for the two TAC dosing regimens;

Biomarker analysis: on the day of study entry, stool samples will be collected and stored at -80°C .

Metabolomics, lipidomics, and gut microbiota analyses will be used to explore the biomarkers affecting TAC pharmacokinetics and pharmacodynamics and their correlations.

4.7 Sample size calculation

Because this trial is the first of its kind both domestically and internationally, lacking preliminary experiments and literature data from which to estimate the sample size, and given the limited number of patients available for enrollment and the fact that a pilot study of the chrono-individualized dosing regimen cannot be conducted, the multicenter randomized controlled component of this study will adopt a sequential adaptive trial design. To ensure the credibility of the clinical results while taking into account the practical realities of research funding and personnel, an initial 50 patients will be enrolled directly according to the inclusion and exclusion

criteria and randomized at a 1:1 ratio into the chrono-individualized dosing group and the conventional clinical dosing group for a comparative study. A total of 100 patients is planned for enrollment, but the actual number enrolled will be determined by the results of the interim (Month 6) statistical analysis, and enrollment will continue until the results of the two study arms satisfy the statistical requirements.

5. Study timeline

Time Period	Research Plan
October 23, 2026 to February 28, 2027	Complete enrollment of 50 subjects in the multicenter randomized controlled trial
March 1, 2027 to March 15, 2027	Complete interim analysis to determine the subsequent sample size
March 16, 2027 to February 29, 2028	Complete all follow-up procedures
March 1, 2028 to May 31, 2028	Complete data sorting and analysis, manuscript drafting and submission

6. Previous Research Basis

To explore more rationally an improved TAC dosing regimen, our team previously conducted a TAC chrono-population pharmacokinetic (PPK) study in 18 patients during the early phase after kidney transplantation (Figure 2). Consistent with published reports, TAC exhibits marked morning–evening PK differences (Figure 2A); therefore, a single PPK model cannot accurately describe the PK over a full day of TAC dosing. Accordingly, we established separate morning and evening PPK models based on the chronopharmacological characteristics of TAC (Figures 2B and 2C). By combining the chronopharmacokinetic characteristics of TAC, we performed dose simulations on the TAC chrono-PPK model and found that, by rationally allocating the morning and evening TAC doses, not only were the differences and fluctuations in morning and evening TAC concentrations reduced, but it was also possible to achieve a 25%–34% saving in the daily TAC dose while maintaining an equivalent daily exposure (AUC₀₋₂₄) (Figure 2D). These results suggest that chrono-dosing of TAC could become a safer and more economical long-term dosing regimen for kidney transplantation. In addition, PPK modeling provides a basis for TAC dose individualization, reserving the use of individual covariates such as body weight, CYP3A genotype, and hematocrit for individualized dosing, further safeguarding the long-term safe use of TAC.

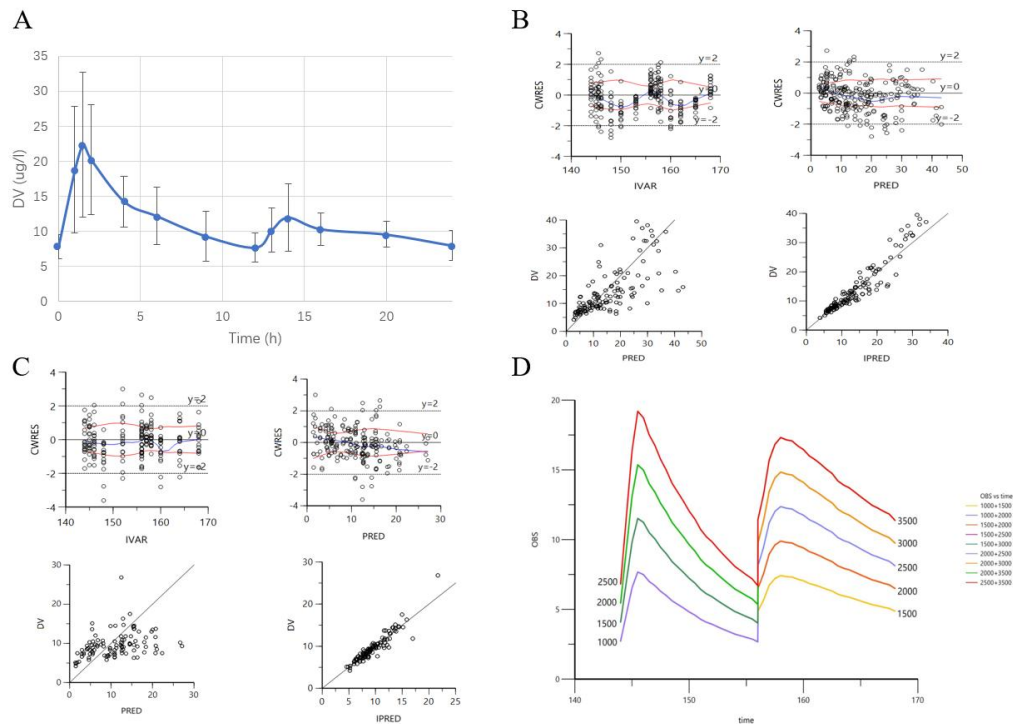


Figure 2. Chronopharmacokinetic study of TAC in early-phase kidney transplant patients

7. Study Sites and Data Management

7.1 Study site

The organ transplantation ward of the Datansha Campus, The First Affiliated Hospital of Guangzhou Medical University.

7.2 Data management

Data sources

The data in this study mainly include: demographic data, general clinical data, laboratory examinations, pathological results, drug concentration results, and patient prognosis information. Demographic data and general clinical data can be obtained at baseline. Laboratory examinations are obtained at baseline and at each follow-up visit as appropriate. Pathological results are obtained after each kidney biopsy. Patient prognosis data are obtained through post-transplantation follow-up.

Data collection

Data are collected using paper case report forms (CRFs). All laboratory and imaging examinations are fully archived at the time of performance. Relevant experimental data are uniformly registered and followed up by designated personnel using a pre-designed template.

Data verification and cleaning

The investigator must review the data to ensure the accuracy and correctness of all data entered into the paper CRFs. At each research center, designated data management personnel will review the paper CRFs and assess their completeness and consistency, and will compare the CRFs against source documents to ensure consistency of key data. After data from the CRFs are entered into

Excel spreadsheets, further checks for completeness, consistency, and logic will be performed using SPSS. If data queries arise, the data management personnel will issue a query, and the research center staff will be responsible for responding. Any changes to the data will be recorded in an audit trail, including the reason for the change, the name of the operator, and the time and date of the modification.

8. Statistical Analysis Methods

1) General principles

- ① Statistical software: SPSS 22.0 will be used for statistical analysis.
- ② Basic principles: all statistical inferences will use two-sided tests; the significance level will be set at 0.05, and parameter confidence intervals will be estimated at the 95% confidence level. Parametric methods will be used wherever possible; when data do not satisfy the assumptions of parametric methods, data transformation may be applied, and, if still not satisfied, non-parametric methods may be considered.
- ③ Missing data: no imputation will be performed for missing data in this study.
- ④ Descriptive statistics: for continuous variables, the mean, standard deviation, and confidence interval will be given, and, where necessary, the minimum, maximum, P25, median, and P75; for paired continuous variables, the mean and standard deviation of the differences will be given; when non-parametric methods are used, the median and mean rank will be given. For categorical variables, the frequency distribution and corresponding percentages will be given. For ordinal variables, the frequency distribution and corresponding percentages, as well as the median and mean rank, will be given. For qualitative variables, the positivity rate, number of positive cases, and the number of denominator cases will be given.
- ⑤ Baseline data analysis: baseline data (including demographic parameters) will be analyzed descriptively.
- ⑥ Factor analysis: between-group differences will be compared using the two independent samples t-test or the Wilcoxon rank-sum test.

2) Efficacy analysis

The incidence of acute rejection will be collected, organized, and compared between the experimental and control groups of the randomized controlled study to measure the difference in efficacy between the two dosing regimens, thereby verifying the advantage of the chrono-individualized dosing regimen over the conventional regimen.

3) Safety analysis

The safety of TAC dosing in the two groups is mainly assessed by comparing the incidence of ADRs during the observation period. ADRs encompass a wide range of events; during the observation period, all adverse events occurring in patients must be recorded and analyzed to determine whether they constitute drug-related ADRs. This will verify whether the chrono-individualized dosing regimen is superior to the conventional regimen with respect to safety.

9. Protection of Human Subjects

In this study, all subjects will be protected in accordance with strict ethical standards, ensuring that

their dignity, rights, and safety are fully respected. Before participating in the study, all subjects must voluntarily sign the informed consent form on the basis of a detailed understanding of the study purpose, procedures, potential risks, anticipated benefits, and other relevant information. All subjects' personal information, medical information, and research data will be kept strictly confidential. The main study risks include pain, bruising, dizziness, or a very small amount of blood loss associated with repeated blood sampling, as well as TAC-treatment-related risks of nephrotoxicity, infection, metabolic abnormalities, neurotoxicity, and rejection. All enrolled recipients will receive professional and timely guidance from the kidney transplant team before, during, and after surgery and throughout follow-up; all examination parameters will be closely monitored, and abnormal findings will be actively tracked and managed.

10. Data Safety and Monitoring Plan

The principal investigator is responsible for overall data management. Data will be stored in both paper-questionnaire and electronic form. Only the study team may access the data; no one outside the team will have access. Each center will designate a data administrator. The lead center will conduct periodic remote monitoring, focusing on informed consent, dosing records, blood sampling times, and laboratory results. Serious adverse events (SAEs) will be reported to the lead center and the ethics committee within 24 hours of notification, followed by a written follow-up report. SAEs, serious protocol deviations, and important information affecting subject safety will be reported to the ethics committee in a timely manner. In the event of unexpected, serious, or unacceptable risks, the principal investigator has the authority to suspend enrollment or terminate the study early and will report to the ethics committee in a timely manner.

11. Participating Centers of the Multicenter Study

An introduction to the lead center and the participating sub-centers is provided.

Role	Site Name	Principal Investigator
Lead Center	The First Affiliated Hospital of Guangzhou Medical University	Liu Xiaoyou
Participating	The Second Affiliated Hospital of Guangzhou Medical University	Chen Zheng
Participating	The Third Affiliated Hospital of Guangzhou Medical University	Zhao Jiqiang
Participating	Zhujiang Hospital, Southern Medical University	Liu Yongguang
Participating	Guangdong Provincial Hospital of Traditional Chinese Medicine	Cao Ronghua

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13. Appendices

None.