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Prograf produces more benefits for CYP3A5 low expression patients in early stage after kidney transplantation

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ABSTRACT

Objective: This study is to analyze concentration changes of the prolonged-release and shorter-acting formulation of tacrolimus in patients with different CYP3A5 genotypes after kidney transplantation.
Methods: A single-factor retrospective analysis was performed in patients underwent allogeneic kidney transplantation with postoperative administration of Advagraf or Prograf in our hospital from May 2013 to June 2014. The CYP3A5 genotypes were determined, and tacrolimus trough concentrations in whole blood were measured within 28 days after transplantation. The rates of acute rejection rate, chronic rejection and infection were recorded and compared after one year follow-up after surgery.
Results: The study included 106 patients administered Advagraf (45 cases) or Prograf (61 cases). The low expression genotype of CYP3A5 was detected in 40 (37.7%) patients. A higher dose of Advagraf was required to increase the tacrolimus trough concentrations within 21 days after transplantation. Moreover, a higher dose for Advagraf than Prograf was required to increase the tacrolimus trough concentrations in low expression patients. In the low expression patients, Prograf more frequently achieved the target tacrolimus trough concentrations within seven days after transplantation (five days: 7.14% vs. 84%, $P=0.001$; seven days: 33.33% vs. 77.78%, $P=0.001$). The patient and kidney graft survival rates one year after transplantation both were 100%. The estimated glomerular filtration rate showed no significant difference between different CYP3A5 phenotypes or formulations of tacrolimus ($P>0.05$). However, the incidence of infections was higher in the Advagraf group in low expression patients ($P<0.05$).
Conclusion: Tacrolimus of different formulations had different impact on patients with different CYP3A5 genotypes after kidney transplantation.

1. Introduction

Tacrolimus is a basic immunosuppressive drug used to prevent rejection of transplanted organs [1]. With a narrow therapeutic window, tacrolimus exhibits great intra and inter individual variability in pharmacokinetics, with a low correlation between the dose and the concentration. Therefore, therapeutic drug monitoring is particularly important for preventing organ rejection and drug toxicity [2]. Despite numerous reports on the pharmacokinetics of tacrolimus, it remains highly difficult to stabilize patients within a target range of tacrolimus blood concentration, especially for those in the early period after transplantation [3]. Originally, the designed dose of tacrolimus consisted of administration two times per day (Prograf®). Later, a prolonged-release formulation for administration once per day (Advagraf®) was developed and became available on the market in Germany and the United Kingdom from 2007. The prolonged-release formulation is advantageous due to its production of more stable blood concentrations and ease of administration [1,2]. A recent meta-analysis by Ho et al. [4] showed that the two formulations of tacrolimus are roughly equivalent in terms of efficacy and safety.

In most cases, the interindividual variability of the pharmacokinetics of tacrolimus is explained based on a single nucleotide polymorphism (SNP). Tacrolimus is a metabolic substrate of cytochrome P450 3A5 (CYP3A5) [5,6]. A homozygous mutation in intron 3 (6986 A> G) of the CYP3A5 gene results in the production of a non-functional CYP3A5 protein [7,8] whereas higher drug dose is required to reach the target blood

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concentration of tacrolimus in patients carrying CYP3A5*1 [6,7]. Compared to those expressing non-functional cytochrome P450 (low expression genotype), patients expressing functional cytochrome P450 (high expression genotype) require nearly a two-fold starting dose to reach the target blood concentration of tacrolimus [9].

It is documented that CYP3A5 genotype has a certain predictive value for the initial dose of tacrolimus in patients, however, to our knowledge, most of the studies are focused on the plasma concentration of stable phase, and few studies have investigated early changes in tacrolimus blood concentrations after transplantation, especially for patients taking prolonged-release formulation. And thereby, in this study, we analyzed the early changes in tacrolimus blood concentrations of two different formulations among kidney transplant recipients within one month after surgery.

2. Materials and methods

2.1. *Pati*ents' data

A single-factor retrospective analysis was undertaken in patients who underwent allograft kidney transplantation with postoperative administration of Advagraf or Prograf in our hospital from May 2013 to June 2014. The inclusion criteria consisted of 1) preoperative use of anti-T lymphocyte globulin (ATG-F) for immune induction therapy with the immunosuppressive regimen of tacrolimus + mycophenolate mofetil (MMF, 1.5 g/d, Roche) + glucocorticoids; 2) patients were negative for donor-specific antibodies; 3) no preoperative dysfunction of the liver or gastrointestinal tract; and 4) no postoperative intake of food or medicine that could affect tacrolimus blood concentrations. All patients were given pantoprazole for acid-suppressive therapy.

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice and the International Conference on Harmonisation guidelines. The protocol was reviewed by the Independent Ethics Committee of Beijing Chaoyang Hospital. Patients gave written informed consent before study enrollment.

2.2. Studying indexes collection

Preoperative (baseline) data were collected, including general conditions (gender, age, height, and weight) and blood indices (aspartate aminotransferase, AST; alanine aminotransferase, ALT; hemoglobin, HGB; albumin, ALB; and serum creatinine, SCr levels). Liver function was assessed before surgery. Tacrolimus trough concentrations (TTC) in the blood was measured on days three, five, seven, 14, 21, and 28 after transplantation, and the medication dose was recorded on the corresponding dates. The CYP3A5 genotypes were determined at one year after transplantation. Patients were divided into two groups according to the CYP3A5 genotype: a high expression genotype (CYP3A5*1*3 and CYP3A5*1*1) and a low expression genotype (CYP3A5*3*3). The TTC, medication dose, concentration/dose ratio (C/D), and percentage of patients achieving the target TTC were compared between the two CYP3A genotypes and formulations of tacrolimus at different time points. The coefficients of variation (CV) of the TTC and C/D within 28 days after transplantation were calculated: CV = mean standard deviation/mean * 100%. The estimated glomerular filtration rate (eGFR) at one year after surgery was calculated from the corresponding SCr, blood urea nitrogen (BUN), and albumin levels (Modification of Diet in Renal Disease (MDRD) = $170 \times [\text{SCr (mg/dL)}]^{(-0.999)} \times [\text{age}]^{(-0.176)} \times [0.762 \text{ women}] \times [\text{BUN (mg/dL)}]^{(-0.170)} \times [\text{ALB (g/dL)}]^{(0.318)}$ [10]) to assess kidney function. The following outcome measures were recorded after one year of follow-up: survival of patient and kidney, acute and chronic rejections proven by biopsy, and infection with etiological evidence.

2.3. Immunosuppressive regimen

Immune induction therapy with ATG-F (3 mg/kg/d) was applied via intravenous infusion for five days (day 0–4) before surgery. Immunosuppressive therapy with tacrolimus + MMF (1.5 g/d, Roche, Beijing, China) + glucocorticoids was performed from day 0 before surgery. Glucocorticoids were administered as follows: intravenous injection of methylprednisolone (500 mg) during surgery and on the first two days after surgery, followed by oral administration of prednisone (30 mg) on the third day after surgery. The starting dose of tacrolimus for preoperative administration was 0.1–0.15 mg/(kg*d). Advagraf was taken once daily at 7:00 am and Prograf was given twice daily at 7:00 am and 7:00 pm The target TTC within the first month after surgery was set to 8–12 ng/mL. Patients received meals two hours before administration or one hour after administration. During the medicine, grapefruit and tea taking were forbidden. Antifungal drugs like ketoconazole, fluconazole, andFushita Yasu; macrolide antibiotics such as erythromycin and clarithromycin; and calcium antagonists that could significantly increase the blood concentration of drug were not allowed. Rifampin, which will significantly reduce the blood concentration of tacrolimus was also prohibited. Once the patients had to take these aforementioned drugs, they were excluded from the study.

2.4. TTC measurement

TTC data were collected from patients on day 3, 5, 7, 14, 21, and 28 after transplantation. Peripheral venous blood specimens were extracted in an EDTA-2Na tube in the morning 30 min before administration. The TTC in the blood was analyzed using a PRO-Trac™ II Tacrolimus ELISA kit (Vendor, City, State, Country). The dose of tacrolimus on the day of TTC measurement was recorded.

2.5. Genetic testing

The frequency of CYP3A5*3 genotypes (Genbank AC005020) in patients was detected one month after surgery. DNA samples were extracted from EDTA-anticoagulated blood specimens using a blood extraction kit (Tiangen, Beijing, China). CYP3A5*3 alleles were detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) [11].

2.6. Statistical analysis

Data were analyzed using the SPSS 19.0 statistical program (IBM SPSS, Somers, NY, USA). Normal distribution of the data was assessed by a Kolmogorov-Smirnov test. The preoperative baseline characteristics of kidney transplant recipients were expressed as mean ± SD. Continuous variables with a normal distribution were analyzed with t test, and those with a non-normal distribution were analyzed with the Mann-Whitney U test. Differences in categorical data were examined by the χ^2 test. Differences with a value of $P < 0.05$ were defined as statistically significant.

3. Results

3.1. General data and genotyping of graft recipients

In order to ensure that there were no differences in the general condition between the two groups pre operation, the general data were analyzed. As shown in Table 1, a total of 106 patients were enrolled in the study, with 45 cases in Advagraf and 61 cases in Prograf. Patients in the two groups showed no significant differences in gender, age, weight, and AST, ALT, HGB, and SCr levels before surgery ($P > 0.05$). Seventy-three patients received a