Limited Sampling Strategy for Estimating Mycophenolic Acid Exposure on Day 7 Post-Transplant for Two Mycophenolate Mofetil Formulations Derived From 20 Chinese Renal Transplant Recipients

W. Cai[a], Q. Cai[b], N. Xiong[c], Y. Qin[c], L. Lai[d], X. Sun[c,**], and Y. Hu[a,*]

[a]Department of Clinical Pharmacy, 303 Hospital of PLA, Nanning, China; [b]Department of Clinical Pharmacy, 458 Hospital of PLA, Guangzhou, China; [c]Guangxi Key Laboratory for Transplantation Medicine, Institute of Transplant Medicine, 303 Hospital of PLA, Nanning, China; and [d]Department of Pharmaceutics, Guangxi Medical University, Nanning, Guangxi, China

ABSTRACT

Purpose. To assess the pharmacokinetic properties of mycophenolate mofetil (MMF) dispersible tablets and capsules by the enzyme multiplied immunoassay technique (EMIT) in Chinese kidney transplant recipients in the early post-transplantation phase and to develop the equations to predict mycophenolic acid (MPA) area under the 12-hour concentration-time curve ($AUC_{0\text{-}12h}$) using a limited sampling strategy (LSS).

Methods. Forty patients who underwent renal transplantation from brain-dead donors were randomly divided into dispersible tablets (Sai KE Ping; Hangzhou Zhongmei Huadong Pharma) and capsules (Cellcept; Roche Pharma, Why, NSW, Australia) groups, and treated with MMF combined with combination tacrolimus and prednisone as a basic immunosuppressive regimen. Blood samples were collected before treatment (0) and at 0.5,1, 1.5, 2, 4, 6, 8, 10, and 12 hours post-treatment and 7 days after renal transplantation. Plasma MPA concentrations were measured using EMIT. LSS equations were identified using multiple stepwise linear regression analysis.

Results. The peak concentration (C_{max}) in the MMF dispersible tablets (MMFdt) group (7.0 ± 2.8) mg/L was reduced compared with that in the MMF capsules (MMFc) group (10.8 ± 6.2 mg/L; $P = .012$); time to peak concentration in the MMFdt group was 3.2 ± 2.3 hours, which was nonsignificantly elevated compared with that of the MMFc group (2.2 ± 1.7 hours). Three-point estimation formulas were generated by multiple linear regression for both groups: $MPA\text{-}AUC_{MMFdt} = 3.542 + 3.332C_{0.5h} + 1.117C_{1.5h} + 3.946C_{4h}$ (adjusted $r^2 = 0.90$, $P < .001$); $MPA\text{-}AUC_{MMFc} = 8.149 + 1.442C_{2h} + 1.056C_{4h} + 7.133C_{6h}$ (adjusted $r^2 = 0.88$, $P < .001$). Both predicted and measured AUCs showed good consistency.

Conclusions. After treatment with MMF dispersible tables or MMF capsules, the C_{max} of MPA for the MMFdt group was significantly lower than that of the MMFc group; there was no significant difference in other pharmacokinetic parameters. Three-time point equations can be used as a predictable measure of the $AUC_{0\text{-}12h}$ of MPA.

W. Cai, Q. Cai, and N. Xiong contributed equally to this work.

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*Address correspondence to Yun Hu, Department of Clinical Pharmacy, 303 Hospital of PLA, Nanning 530021, China. Tel: +86-0771-2870314. E-mail: 19160329@qq.com; and Xuyong Sun, Guangxi Key Laboratory for Transplantation Medicine, Institute of Transplant Medicine, 303 Hospital of PLA, Nanning, China. E-mail: 671854021@qq.com

230 Park Avenue, New York, NY 10169

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MYCOPHENOLATE mofetil (MMF) is an immunosuppressive agent for the prophylaxis of organ rejection in patients receiving renal transplants. MMF has 1 common oral formulations in China: dispersible tablets and capsules [1,2]. MMF taken orally can be absorbed completely and metabolized rapidly; it constitutes a prototype drug that is barely detectable in the body. Therefore, its bioavailability and pharmacokinetic characteristics can be examined by measuring plasma concentrations of its active metabolite, mycophenolic acid (MPA).

Previous studies showed that the MPA area under the 12-hour concentration-time curve (MPA $AUC_{0\text{-}12h}$) is closely related to its antirejection and adverse effects [3,4]. In addition, MPA exposure is particularly associated with postoperative organ function recovery in renal transplantation [5]. However, the trough concentration is poorly correlated to MPA-$AUC_{0\text{-}12h}$, which makes the routine clinical monitoring of MPA exposure difficult.

After the gradual introduction of the death donation organ transplantation policy in China since 2007 [6], an increasing number of kidney transplantation patients have received organs from brain-dead donors. The great differences in temperature, ischemia time, and organ function before donation between such donors and traditional donors mean that the immunosuppressive regimen after renal transplantation should be optimized in terms of higher requirements. Therefore, developing convenient and efficient methods to promote therapeutic drug monitoring of MMF in the clinic is urgent. A limited sampling strategy (LSS) based on multiple linear regression can use few sampling points (usually 2–4 points) to generate results close to full-point AUC data, representing an effective way to solve the current dilemma of MPA therapeutic drug monitoring (TDM) [7–9].

In recent years, after the compatibility of MMF capsules and enteric-coated mycophenolate sodium used in combination with cyclosporine and tacrolimus (Tac) [7–10] following renal transplantation was established, LSS was often carried out. However, reports assessing MMF dispersible tablets are scarce. Our previous study examined the LSS for MMF capsules taken by Chinese patients early after renal transplantation, and obtained a 4-point sampling equation [11]. The present study compared MPA pharmacokinetic parameters and LSS of the 2 formulations of MMF (ie, capsules and dispersible tablets) used in combination with Tac at 7 days after renal transplantation in Chinese adults. Three-point sampling equations were generated for MMF capsules and dispersible tablets, respectively, providing an experimental basis to further clarify the pharmacokinetic characteristics of MMF early after kidney transplantation from brain-dead donors and promoting the clinical development of MPA TDM.

MATERIALS AND METHODS

Subjects

The patients who initially underwent kidney transplantation from brain-dead donors and received a basic immunosuppressive regimen of MMF + Tac + prednisone (Pred) were selected from October 2014 to June 2015 in the People's Liberation Army 303 Hospital, Organ Transplant Center. There were 46 patients aged from 18 to 55 years who met the above-mentioned criteria. The patients were randomly divided into 2 groups (a pair of kidney donors was randomly assigned to MMF dispersible tablets (MMFdt group) or MMF capsules (MMFc group) according to the coin tossing method). The MMFdt group was administered MMF dispersible tablets (Sai KE Ping; Hangzhou Zhongmei Huadong Pharmaceutical Co, Ltd); the MMFc group took MMF capsules (Cellcept; Roche Pharma, Why, NSW, Australia). Individuals who accepted combined multiple-organ transplant or renal transplant from pediatric donors and those with postoperative infection, acute tubular necrosis, or other serious complications within 7 days after surgery were excluded. There were no significant differences between the 2 groups before sampling in terms of gender, age, serum albumin concentration, and creatine clearance rate (Table 1). This study was performed in accordance with the Declaration of Helsinki-Istanbul and Good Clinical Practice; no donors were prisoners.

Immunosuppressive Regimen

The 2 groups of patients were treated with MMF + Tac + Pred, the triple basic immunosuppressive regimen. MMF was administered at a fixed dose of 1500 mg/d (750 mg twice per day). The starting dose of Tac was 0.05 to 0.15 mg/kg/d; it was then adjusted based on the blood concentration and renal function recovery, to maintain plasma concentrations of 10 to 15 μg/L within 1 month after transplantation. Methylprednisolone was administered by intravenous injection of 1.0 g before surgery, followed by 0.5 g and 0.25 g at day 1 and day 2 postoperation, respectively. At day 3, Pred tablets were administered orally instead at 30 mg/d, and then reduced by 5 mg per week to a maintenance dose of 10 mg.

Assessment of MPA Pharmacokinetics

Blood Sample Collection. At day 7 after transplantation, 2 cases in the MMFdt group had delayed graft function (DGF), and 1 case showed acute rejection; 3 cases in the MMFc group had DGF. The other 20 cases in each group continued to the next step of the study. Blood samples (2 mL) were collected before (0 hours) and at 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 12 hours after medication into tubes containing ethylenediaminetetraacetic acid and centrifuged at 1072*g* for 10 minutes. The resulting supernatants were stored at −20°C.

MPA Assay and Determination of Pharmacokinetic Parameters. Serum MPA concentrations were detected using the Viva-E system (Siemens Healthcare Diagnostics Inc, Newark, Del, United States) according to the manufacturer's guidelines. The lower limit of detection was 0.1 mg/L; intraday precision ranged from 2.6% to 8.5%, and interday precision ranged from 3.3% to 6.9%. Enzyme multiplied immunoassay technique (EMIT) 2000 Mycophenolic Acid kits were purchased from Siemens Healthcare Diagnostics Inc. Serum MPA concentrations were obtained at each sampling point: C_{0h}, $C_{0.5h}$, C_{1h}, $C_{1.5h}$, C_{2h}, C_{4h}, C_{6h}, C_{8h}, C_{10h}, and C_{12h}. According to the noncompartmental model using the PKSolver pharmacokinetic and pharmacodynamic data processing software (version 2.0; China Pharmaceutical University, Nanjing, China), the pharmacokinetic parameters of MPA were analyzed, including biological half-life ($t_{1/2}$), time to peak concentration (T_{max}), peak concentration (C_{max}), area under the curve from 0 to 12 hours ($AUC_{0\text{-}12h}$), mean resident time, and oral clearance.