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Correlation Between Mycophenolic Acid Blood Level and Renal Dysfunction in Stable Liver Transplant Recipients Receiving Mycophenolate Monotherapy

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ABSTRACT

Purpose. Mycophenolate mofetil (MMF) is frequently used after liver transplantation (OLT). Mycophenolic acid (MPA) metabolites are eliminated primarily via the kidneys. If renal function declines, clearance is significantly impaired. The aim of this study was to reveal the renal function-dependent changes of MPA level in stable adult OLT recipients receiving MMF monotherapy.

Methods. Sixty-five OLT recipients were selected from our OLT database of >3500 cases. All had undergone MMF monotherapy with a daily MMF dose of 1000 mg or 1500 mg for more than 2 years, primarily because they could not tolerate calcineurin inhibitors. Their clinical profiles, including MPA therapeutic drug monitoring (TDM) and renal function, were analyzed as a cross-sectional study.

Results. For the group treated with 1000 mg MMF ($n = 40$), the 12-hour MPA trough level was 1.20 ± 0.35 μg/mL with serum creatinine (Cr) level ≤1.4 mg/dL in 13 patients; it was 2.78 ± 1.19 μg/mL with Cr >1.4 mg/dL in 16 patients not undergoing hemodialysis and 3.83 ± 0.87 μg/mL in 11 patients undergoing hemodialysis ($P < .001$). For the group treated with 1500 mg MMF ($n = 25$), the MPA trough level was 2.23 ± 0.99 μg/mL with Cr ≤1.4 mg/dL in 6 patients; it was 2.81 ± 0.99 μg/mL with Cr >1.4 mg/dL in 18 patients not undergoing hemodialysis and 3.5 μg/mL in 1 patient undergoing hemodialysis ($P = .21$).

Conclusions. Considering the potential therapeutic range of MPA, the suggested MMF dosage for Korean adult OLT recipients requiring hemodialysis may be set around 1000 mg per day. We suggest adjusting the MMF dosage on an individualized basis according to the results of MPA TDM, particularly for patients with markedly impaired renal function.

MYCOPHENOLATE MOFETIL (MMF) has been frequently used after liver transplantation (OLT) because unlike calcineurin inhibitor (CNI), it does not induce serious side effects such as nephrotoxicity and neurotoxicity [1–3]. Mycophenolic acid (MPA), the pharmacokinetically active product of MMF, has potent inhibitory effects on lymphocyte proliferation. MPA is taken up by the liver, where it is glucuronidated to form an inactive compound. MPA metabolites are primarily eliminated by the kidneys, although biliary excretion makes a significant contribution to overall clearance [4,5].

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MMF has been conventionally regarded as a categorically dosed drug probably due to wide inter- and intraindividual variations of blood concentration [6]. Consequently, this drug has been usually administered on the basis of personal or institutional experience, without generalized suggestion to perform therapeutic drug monitoring (TDM) for dosage adjustment.

If renal function declines, the clearance of MPA metabolites is significantly impaired. According to the MPA pharmacokinetics, blood concentration of MPA metabolites, such as mycophenolic acid glucuronide, is abnormally increased and thus exerts unexpected influence on the level of immunosuppression [7]. When MMF is used as an adjunctive agent with CNIs, such an influence from raised MPA concentration may not be great. In contrast, if it is used as monotherapy in OLT recipients showing renal dysfunction, it is reasonable to pay special attention on MPA pharmacokinetics. However, to our knowledge, there is no clinical suggestion available focused on MMF dosage adjustment according to the renal dysfunction.

The primary goal of the present study was to reveal the renal function-dependent changes of MPA level in stable adult OLT recipients receiving MMF monotherapy, and the secondary goal was to provide clinical suggestions on MMF dosage adjustment according to the degree of renal dysfunction.

PATIENTS AND METHODS

Sixty-five OLT adult recipients were selected from an OLT database of >3500 patients held by our institution. All of the selected patients were stable and had been treated with MMF monotherapy at a daily dose of 1000 mg (500 mg twice per day) or 1500 mg (750 mg twice per day) for more than 2 years, primarily because they were not able to tolerate CNI-associated side effects. Patients receiving different doses of MMF in the morning and evening (eg, 500 mg plus 750 mg per day) were excluded from this study because the morning and evening drug dosages could be switched arbitrarily, thus leading to unwanted bias on 12-hour trough-level MPA TDM. The selected patients underwent transplantation between January 1999 and December 2009. This cross-sectional study was performed during 1-year study period from June 2012 to May 2013. Patients who showed any type of graft dysfunction during the study period were excluded from study. This study was approved by the Institutional Review Board of Asan Medical Center.

The detailed MMF immunosuppression profiles have been described previously [6]. Predose 12-hour blood samples were subjected to MPA TDM using an enzyme multiplied immunoassay technique (EMIT; Dade-Behring, Marburg, Germany) performed on a Cobas Mira analyzer (Roche, Basel, Switzerland). The results of MPA TDM were usually reported within 2 hours after blood sampling because the tests were performed on an outpatient basis.

The clinical profiles of the patients, including MPA TDM and renal function, were analyzed. To avoid bias from intraindividual variations on MPA TDM and serum creatinine level, the mean values of consecutive 3 measurements (usually during 6 months) were used for analysis. To estimate glomerular filtration rate (GFR) in Korean population, Modification of Diet in Renal Disease (MDRD)-GFR was used with a formula as follows: MDRD-GFR (mL/min/1.73 m^2) = 186 × serum creatinine$^{-1.154}$ × age$^{-0.203}$ × 0.742 (if female) [8]. Numerical variables were presented as means with standard deviations and ranges. Continuous variables were compared with the Student t test and one-way analysis of variance. Statistical significance was set at $P < .05$.

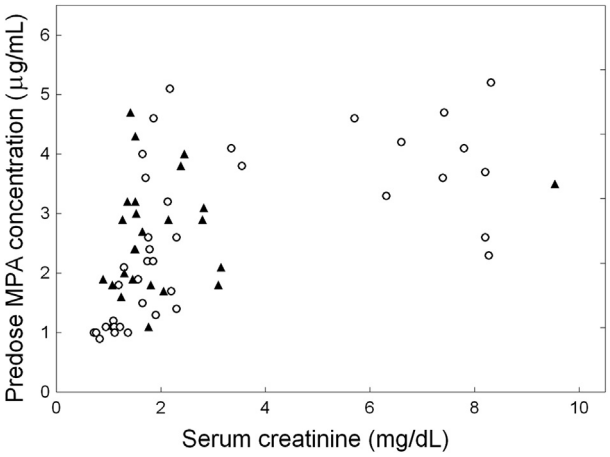

Fig 1. Correlation between the 12-hour predose concentration of mycophenolic acid (MPA) and serum creatinine level. Blank circles and solid triangles indicate the daily mycophenolate mofetil dosage of 1000 mg and 1500 mg, respectively. All patients who showed serum creatinine greater than 4 mg/dL have undergone hemodialysis since liver transplantation.

RESULTS

Patient Profiles

The primary causes of OLT in these 65 patients were hepatitis B virus-associated liver cirrhosis ($n = 52$), alcoholic liver diseases ($n = 7$), and acute liver failure ($n = 6$). There were 59 male patients (90.8%). The mean patient age was 47.4 ± 6.3 years (range, 32–61). Ten patients (15.4%) received deceased donor OLT, and 55 patients (84.6%) received living donor OLT. One patient had undergone deceased donor retransplantation due to chronic rejection. All of the patients had been treated with either CNI-based or CNI-MMF combination immunosuppressive therapy after OLT and gradually converted to MMF monotherapy primarily due to intractable nephrotoxicity or neurotoxicity. These patients were maintained on a fixed daily dose of MMF for more than 2 years, as there was no noticeable change in graft function and no episodes of acute or chronic rejection.

MPA Concentration Regarding MMF Dosage and Serum Creatinine

Forty patients were treated with 500 mg MMF twice per day (MMF 1000 mg group), and their distribution of 12-hour predose MPA TDM is depicted in Fig. 1. The 12-hour MPA trough level was 1.20 ± 0.35 μg/mL with serum creatinine level of ≤1.4 mg/dL in 13 patients, 2.78 ± 1.19 μg/mL in 16 patients not undergoing hemodialysis with serum creatinine level of >1.4 mg/dL (range: 1.56–3.35),