Serum Trough Concentration and Effects of Mycophenolate Mofetil Based on Pathological Findings in Infants After Liver Transplantation

Abstract

Objectives

Mycophenolate mofetil (MMF) is mainly used in conjunction with calcineurin inhibitors as an additional immunosuppressive for renal sparing after liver transplantation. However few reports about MMF use in infants after living donor liver transplantation (LDLT) are available. The purpose of this study was to examine the efficacy and safety of MMF in infants.

Methods

Infants <1 year who received LDLT at our institution were enrolled. Patients received oral MMF twice daily. The initial dose was 40–50 mg/kg/day, which was increased to a target mycophenolic acid (MPA) trough level of 2 mg/L. Body weight, height, MMF dose, MPA trough level, acute cellular rejection (ACR) episodes, pathological findings, and adverse effects were analyzed. Allograft fibrosis was graded using the METAVIR score.

Results

Patients received MMF for refractory ACR (n=2), fulminant hepatitis (n=2), and preexisting antibodies (n=1). Original diseases were biliary atresia (n=3) and fulminant hepatitis (n=2). Mean age at transplant was 8 months (range, 3–10 months). The last available mean trough level was 2.7 mg/L. Mean dose was 66

mg/kg/day or 1,429 mg/m^2/day at the time of the last available through level. The regression line for MMF dose and MPA trough level was $Y=1.8*10^{-3}X$. The correlation coefficient was 0.65. All allografts showed F1–2 fibrosis. Two patients discontinued MMF due to infection and bone marrow suppression respectively. Two patients converted to everolimus. One patient continued on MMF.

Conclusions

After LDLT, infants require a higher MMF dose than older patients based on trough levels, but allograft fibrosis can progress.

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Introduction

In Japan, living donor liver transplantation (LDLT) is the standard treatment of choice for end-stage liver disease in children. After transplantation, continuous immunosuppression is needed to prevent acute and chronic graft rejection.

Mycophenolate mofetil (MMF) is mainly used in conjunction with calcineurin inhibitors as an additional immunosuppressive and anti-rejection agent that is renal sparing after liver transplantation [1]. MMF is an ester prodrug of mycophenolic acid (MPA) that acts through inhibition of inosine monophosphate dehydrogenase. MMF is rapidly converted into MPA by esterases in the intestines and liver. MPA is eliminated by glucuronidation [2].

There have been only a few reports about MMF use in children after liver transplantation [3, 4]. However there is no report for infant. In particular, we have not found any reports about MMF use in infants after LDLT. The purpose of this study was to examine the efficacy of MMF in patients less than 1 year of age based on pathological findings and MPA trough levels.

Methods

Patients aged less than 1 year at the time of LDLT at our institution were enrolled. Patients were tapered from tacrolimus-based immunosuppression and steroids according to our protocol. The standard protocol

for tacrolimus tapering was as follows: the target tacrolimus trough level was 10–15 ng/mL for the first month after transplantation, 5–10 ng/mL until 1 year after transplantation, and 3–5 ng/mL thereafter. Steroids were administered to all patients at least 4 months after LDLT.

In some children, MMF was added for indications including refractory acute cellular rejection (ACR), fulminant hepatitis, and presence of pre-existing antibodies. Oral MMF was administered twice daily. The initial dose of MMF was approximately 40 mg/kg/day, which was increased to a target of MPA trough level 2 mg/L based on previous report [5]. Body weight, height, MMF dose, MPA trough level, ACR episodes, pathological findings, and adverse effects were analyzed.

Serum MPA levels were measured by SRL Inc. (Tokyo, Japan). Quantification of MPA was performed using an enzyme immunoassay and the fully automatic JCA-BM8000 immune analyzer (JEOL Ltd., Tokyo, Japan).

The last available biopsy after MMF therapy began was assessed with hematoxylin-eosin (HE) and Masson's trichrome (MT) stains. Percutaneous liver biopsy was performed with a 16-gauge biopsy needle. The specimens were fixed in 4% phosphate-buffered formaldehyde and embedded in paraffin. After HE and MT staining, the liver specimens were examined microscopically. The degree of liver fibrosis was assessed based on the METAVIR scoring system [6].

Linear regression was performed. Data were analyzed using Excel 2013 (Microsoft Corp., Redmond, WA, USA).

Results

Five patients received MMF for refractory ACR (n=2), fulminant hepatitis (n=2), and presence of preexisting antibodies (n=1), respectively. Original diseases were biliary atresia (n=3) and fulminant hepatitis (n=2). Mean age at transplant was 8 months (range, 3–10 months). Mean body weight was 7.6 kg (range, 4.7–10.7 kg). Mean body surface area (BSA) was 0.35 m^2 (range, 0.26–0.39 m^2). The median duration from transplant to first administration of MMF was 1 day (range, 1–24 days). The median duration of observation was 17 months (range, 6–30 months).

Mean initial dose was 32 mg/kg (range, 23–53 mg/kg) or 770 mg/m^2 (range, 570– 960 mg/m^2). MMF doses were increased until the trough level reached ≥2.0 mg/L. Mean final dose was 66 mg/kg (range, 47–106 mg/kg) or 1430 mg/m^2 (range, 1280–1920 mg/m^2). The last available mean trough level was 2.7 mg/L (range, 2.2–3.5 mg/L). Dose was plotted against trough level in **Fig 1**. The regression line between MMF dose (/m^2) and MPA trough level was $Y=1.8*10^{-3}X$. The correlation coefficient was 0.65. The trough level reached the target level (2 mg/L) at an MMF dose of approximately 1200 mg/m^2. The regression line between MMF dose (/kg) and MPA trough level was $Y=2.6*10^{-2}X+0.78$. The correlation coefficient was 0.53. The trough level reached the target level (2 mg/L) at an MMF dose of approximately 50 mg/kg.

During the observation period, there were no ACR episodes or recurrence of fulminant hepatitis after MMF therapy began. Three patients (60%) experienced adverse effects: *Malassezia* infection (n=1), bacteremia (n=1), and pure red cell anemia (n=1). None of the patients developed cytomegalovirus infection.

Adverse effects were improved after stopping MMF.

All patient had developed allograft fibrosis by the last available biopsy: stage F1 (n=1) and stage F2 (n=4). Two patients discontinued MMF due to infection and bone marrow suppression respectively. Two patients converted to everolimus due to allograft fibrosis. Only one patient continued on MMF.

Discussion

MMF has been successfully used as a prophylactic treatment and rescue therapy for ACR or chronic rejection in adult transplant recipients [7]. MMF is increasingly being used in pediatric transplant recipients [3, 4]. But no clear recommendations about dosing regimens have been made for very young children.

The pharmacokinetic parameters of MPA are highly variable. The therapeutic window has been not been clearly established in the pediatric population with an area under the plasma concentration–time curve from 0 to 12 hours ($AUC_{0–12}$) for MPA. A lower incidence of ACR was reported in pediatric renal transplant patients who achieved AUC_{0-12} greater than 30 mg hour/L [8]. However, in clinical settings the trough level is easier to obtain than AUC because frequent blood sampling is difficult for pediatric patients. MPA trough level monitoring is both clinically effective and cost-effective [5]. The therapeutic range of 1–3.5 mg/L is applicable in adult liver transplant recipients [5].

Tannuri et al reported that 40 mg/kg of MMF promotes prolonged improvement in renal function after pediatric liver transplantation [9]. Barau et al reported that the recommended pediatric dose of MMF is 600 mg/m^2/day [10]. However in our study, young children less than 1 year of age required a higher

MMF dose, 1200 mg/m^2 or 50 mg/kg, to maintain the target MPA trough level.

MMF can increase the efficacy of immunosuppressive therapy and thereby support the treatment of steroid-resistant ACR and chronic graft dysfunction. In our study, no recurrence of ACR or fulminate hepatitis was observed. Regarding recurrence, MMF was effective for infants.

There are only limited data on the long-term histological status of grafts after pediatric liver transplantation. Some studies reported portal fibrosis in pediatric liver transplant biopsy specimens that showed some association with antibody-mediated rejection [11, 12]. MMF, which suppresses de novo purine biosynthesis, results in selective inhibition of T and B cell proliferation. Adding MMF is rational because inhibition of B cell proliferation results in suppression of antibody synthesis [13]. However, in our study, all patients developed graft fibrosis. At least in our relatively small patient population, MMF only had a small effect against graft fibrosis. Therefore, MMF was ultimately switched to everolimus for anti-fibrosis considerations.

Conclusion

After LDLT, infants required a higher dose of MMF than older patients based on trough levels. MMR can prevent recurrent ACR and fulminant hepatitis, but allograft fibrosis can progress.

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