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RAPID COMMUNICATION

Efficacy of mycofenolate mofetil for steroid-resistant acute rejection after living donor liver transplantation

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Abstract

AIM: To discuss the use of mycophenolate mofetil (MMF) as an immunosuppressant in steroid resistant rejection after liver transplantation.

METHODS: The clinical records of 260 adult patients who underwent living donor liver transplantation (LDLT) were reviewed. Tacrolimus and methylprednisolone were used for primary immunosuppression. Acute rejection was first treated with steroids. When steroid resistance occurred, the patient was treated with a combination of steroids and MMF. Anti-T-cell monoclonal antibody was administered to patients who were not responsive to steroids in combination with MMF.

RESULTS: A total of 90 (35%) patients developed acute rejection. The median interval time from transplantation to the first episode was 15 d. Fifty-four patients were steroid resistant. Forty-four patients were treated with MMF and the remaining 10 required anti-T-cell monoclonal antibody treatment. Progression to chronic rejection was observed in one patient. Bone marrow suppression and gastrointestinal symptoms were the most common side effects associated with MMF use. There was no significant increase in opportunistic infections.

CONCLUSION: Our results demonstrate that MMF is a potent and safe immunosuppressive agent for rescue therapy in patients with acute rejection after LDLT.

Key words: Tacrolimus; Rejection; Liver transplantation

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INTRODUCTION

In the majority of transplant centers worldwide, the standard primary immunosuppressive regimen after liver transplantation is based on calcineurin inhibitors (CNIs) and steroids[1]. CNIs exhibit a broad spectrum of nonimmunologic side effects, including renal dysfunction, arterial hypertension, and diabetes mellitus[2]. Despite its potent immunosuppressive effect, acute cellular and chronic rejection can still occur in patients taking CNIs, even when appropriate CNI blood trough levels are maintained[1].

Mycophenolate mofetil (MMF), an enzyme in the guanine nucleotide synthetic pathway, inhibits the proliferation of both B and T lymphocytes[3]. MMF is now accepted as a promising immunosuppressant for liver transplantation. Previous reports have described its efficacy as a CNI-sparing drug to reduce CNI-related toxicity in long-term survivors[4-16]. In contrast, the role of MMF in the immediate posttransplant period is unclear[17-19]. Here, we describe our experience using MMF for patients complicated with steroid-resistant acute rejection after living donor liver transplantation (LDLT).

MATERIALS AND METHODS

Patients

A total of 260 LDLTs (140 men and 120 women; age range: 18-67 years) were performed at the University of Tokyo Hospital between January 1996 and July 2005. The median postoperative follow-up period was 28 mo (range 1-115 mo). The most common indication was virus-related liver cirrhosis (n = 112) secondary to hepatitis C virus infection (n = 78) or hepatitis B virus infection (n = 34), followed by immune-mediated liver cirrhosis (n = 74), including primary biliary cirrhosis (n = 56), autoimmune hepatitis (n = 9), and primary sclerosing cholangitis (n = 9).

The range of pre-operative aspartate transaminase, total bilirubin, and serum creatinine levels were 19-308 IU/L, 4-400 mg/L, and 2-44 mg/L, respectively. The

Table 1 Target trough levels of calcineurin inhibitors and steroid dosage at Tokyo University

	Tacrolimus (ng/mL)	Cyclosporine (ng/mL)	Methylpredonisolone (mg/kg per day)
POD 1-7	15-20	300-350	20-0.75
POD 8-14	14-16	250-300	0.5-0.3
POD 15-90	10-15	200-250	0.3-0.12
POD 91-180	8-10	150-200	0.08-0.12
POD 180-	5-10	100-150	0.05

POD: Postoperative day.

Table 2 Outcome of patients with acute rejection stratified by the rescue treatment

Group	*n*	CMV antigenemia *n* (%)	Systemic infection *n* (%)	Mortality *n* (%)
Steriod	36	14 (39)	5 (14)	7 (19)
Steroid + MMF	44	18 (41)	4 (9)	2 (5)
OKT3	10	7 (70)	4 (40)	4 (40)
Total	90	39 (43)	13 (14)	13 (14)

CMV: Cytomegalovirus; MMF: Mycophenolate mofetil.

median score for model of end-stage liver disease was 13 (range, 4-34).

Operative and postoperative care

Our surgical technique for recipient and donor surgery is described elsewhere[20]. All patients received tacrolimus (FK, Prograf, Astellas Pharma Inc., Tokyo, Japan) and methylprednisolone as primary immunosuppressants (Table 1). When there were FK-related adverse events[21], FK was converted to cyclosporine A (CsA). The cytomegalovirus (CMV) status of the patient was monitored by pp65 antigenemia assay and CMV infection was defined by the presence of more than 5 antigen-positive cells/50 000 white blood cells. Fungal status was monitored by (1-3)-beta-D-glucan assay and antigen assays. Systemic fungal infection was defined as a positive polymerase chain reaction assay or positive culture with the existence of infectious foci. Systemic bacterial infection was defined as a positive culture from the bloodstream or infectious foci.

Management of rejection

Acute rejection was initially suspected by biochemical evidence of deteriorating liver function. After vascular or biliary complications were excluded, liver biopsy was performed to obtain concrete pathologic evidence of rejection. The diagnosis of acute rejection was based on internationally accepted histologic criteria[22]. Our primary treatment for acute rejection was to administer high-dose methylprednisolone (20 mg/kg per day), followed by a gradual dose reduction with the CNI trough level around the upper range of our regimen. When there was no improvement in serum liver function tests, a second biopsy was obtained to confirm the diagnosis of steroid-resistant rejection. In these cases, oral MMF was initiated at the dosage of 3 g three times a d per mo, and then gradually tapered off within 2 to 6 mo. No reduction of CNIs and methylprednisolone was performed when the recipient was under MMF and after treatment with MMF. Anti-T-cell monoclonal antibody (OKT3, Ortho-Biotech Corporation, Raritan, NJ, USA) was used as a tertiary strategy for steroid-resistant refractory rejection under MMF and steroid recycle treatment.

Statistical analysis

Patients complicated by acute rejection were divided into three groups: patients treated with one-time steroid therapy ($n = 36$), those receiving MMF administration ($n = 44$), and those eventually treated with OKT3 ($n = 10$). Inter-group comparisons were performed using the chi-square test or Fisher's exact test for categorical variables. A P value of less than 0.05 was considered statistically significant.

RESULTS

Outcome

A total of 90 out of 260 patients developed acute rejection (35%, 90/260). The median interval time from transplantation to the primary episode of acute cellular rejection was 15 d (range 5-637 d). Fifty-four patients presented with steroid-resistant rejection and were treated with a second steroid recycle in combination with MMF. The median duration of MMF administration in these 54 patients was 74 d (range 36-182 d). Of the 54 patients who received MMF, 10 had refractory acute rejection requiring the use of OKT3. The median interval between the addition of MMF and the use of OKT3 was 5 d (range 2-8 d). Among the patients treated with OKT3, two required the additional use of basiliximab (Simulect, Novartis Pharma, Tokyo, Japan). Chronic rejection was observed in one patient (0.04%, 1/260) who eventually required re-transplantation. Graft failure due to uncontrollable acute rejection was experienced in one patient (0.04%, 1/260) who died 49 d after LDLT, despite the combined use of MMF, OKT3, and basiliximab.

Outcome stratified by treatment

Mortality and systemic bacterial/fungal infections were significantly higher in the patients treated with OKT3 than in the other groups ($P = 0.02$ and 0.04, respectively). The incidence of positive CMV antigenemia tended to be higher in the patients treated with OKT3, although the difference was not statistically significant (Table 2).

Side effects of MMF

MMF-associated side effects were observed in 11 patients (20%), bone marrow suppression in 9 patients (17%), and gastrointestinal symptoms in 2 patients (4%). A dose reduction of MMF and granulocyte colony stimulating factor administration was sufficient for all the patients with bone marrow suppression. Gastrointestinal symptoms disappeared spontaneously under the use of MMF. Cessation of MMF was not necessary due to adverse effects.

DISCUSSION

The results of our study together with those of other studies[17,19] demonstrate that MMF can influence the course of steroid-resistant acute rejection. The main advantage of MMF rescue therapy is the option of continuing the therapy[19]. MMF therapy can be continued in selected patients on an outpatient basis. Rejection rescue therapy with OKT3, anti-thymocyte globulins, and anti-lymphocyte globulin, in contrast, permits only limited use for a short period of time.

Another advantage of MMF is that adverse events related to MMF are infrequent and often mild, which allows for long-term administration when required. In our series, bone marrow suppression and gastrointestinal symptoms were the most common adverse events of MMF. These episodes were easily reversed by dose reduction. MMF was not associated with a significantly increased risk of opportunistic infections. These results are compatible with previous reports[5,7,11].

LDLT theoretically offers an immunologic advantage when the donors are related to the recipients[23]. The overall incidence of acute rejection, however, is similar between LDLT and deceased donor liver transplantation. Our series demonstrated that the overall incidence of steroid-resistant acute rejection was 21%, which was unexpectedly high because LDLT recipients have been reported less likely to develop steroid-resistant or chronic rejection[24]. The 'immunologic advantage' of LDLT might be smaller than previously expected.

In conclusion, the results of our retrospective study suggest that treatment with MMF might be indicated for selected patients with acute rejection and demonstrate the high clinical value of MMF for secondary immunosuppressive therapy after LDLT.

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