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ORIGINAL ARTICLE

The beneficial effect of high-dose mizoribine combined with cyclosporine, basiliximab, and corticosteroids on CMV infection in renal transplant recipients

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Abstract
Background Mizoribine (MZR) has been developed as an immunosuppressive agent, but has a less potent immunosuppressive effect up to 3 mg/kg/day MZR. Therefore, we investigated whether high-dose MZR, at 6 mg/kg/day, would be effective and safe for kidney transplant patients in conjunction with cyclosporine (CsA), basiliximab, and corticosteroids.
Methods A total of 40 living related patients were administered MZR (6 mg/kg/day), CsA (7 mg/kg/day), prednisolone (maintenance dose 10 mg/day), and basiliximab (20 mg/body). A control group ($n = 38$) treated with CsA, mycophenolate mofetil (MMF, 25 mg/kg/day), basiliximab, and corticosteroids was also employed in this study.
Results The 2-year graft survival rates for the MZR and MMF groups were 100 and 94.7 %, respectively. The rejection rate in the MZR group (25 %) was not significantly higher than that in the MMF group (16 %). Serum creatinine level was not significant between the two groups. The number of patients who developed cytomegalovirus (CMV) disease was 0 (0 %) in the MZR group and 7 (18.4 %) in the MMF group ($P < 0.05$). The number of patients treated with ganciclovir was 3 (7.5 %) and 11 (28.9 %) ($P < 0.05$), respectively.
Conclusions The combination of high-dose MZR with CsA, basiliximab, and corticosteroids can establish not only satisfactory immunosuppression but also a low rate of CMV infection in vivo.

Keywords High-dose mizoribine · CMV infection · Acute rejection

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Introduction

Mizoribine (MZR), a novel nucleoside analog, has been developed as an immunosuppressive agent [1] and was placed on the market in 1984 in Japan, where it has now been widely used for 28 years. MZR has been shown to exhibit a low incidence of severe adverse drug reactions and does not enhance oncogenicity [2]. A phase II clinical study of MZR was conducted over 20 years ago [3]. The standard dosage in the 1990s used to be 1–3 mg/kg/day as a substitute for azathioprine (AZA) combined with steroids and cyclosporine (CsA) [4]. However, some reports have indicated that up to 3 mg/kg/day MZR has a less potent immunosuppressive effect but fewer adverse events [5, 6]. Therefore, we investigated whether high-dose MZR, at 6 mg/kg/day, would be effective and safe for kidney transplant patients in conjunction with CsA, basiliximab, and corticosteroids.

Patients and methods

Study subjects and immunosuppression

A total of 92 patients received renal transplants at the Kyoto Prefectural University of Medicine between October

2004 and July 2007. Among the 92 cases, 14 cases were cadaver, ABO-incompatible or crossmatch-positive transplants. The remaining 78 cases were all living donor transplants and the focus of this study. CsA, basiliximab, and corticosteroids were concomitantly administered with either the immunosuppressant MZR or mycophenolate mofetil (MMF). Initially, a concomitant immunosuppression regimen of four agents that included MMF was administered, but when issues arose such as infection, the use of high-dose MZR was investigated. However, since the capability of high-dose MZR was unknown, both the MMF and the MZR protocols were used together for a period of time, and when high-dose MZR appeared to elicit a positive response, further MZR subjects were added to the study. Of the 78 cases, consent was obtained in 40 cases for the treatment protocol with MZR. Since analysis of the patient characteristics of the MZR group and the MMF group showed no statistical differences between the two groups, the safety and efficacy analyses of MZR were compared against the MMF group (Table 1).

Immunosuppressive therapy was initiated with MZR (daily dose 6 mg/kg, given orally twice a day), CsA (trough level 200 ng/mL during the first week and 150–200 ng/mL 1 week after transplantation), and prednisolone (maintenance dose 10 mg/day, after initial dose reduction). Basiliximab (20 mg/body) was administered at days 0 and 4 (Fig. 1a). A control group treated with CsA, MMF, basiliximab, and corticosteroids was also employed in this study. MMF was administered at a dose of 25 mg/kg/day (Fig. 1b). CsA, basiliximab, and steroids were administered using the same protocol as that for the MZR group. All patients were living related, aged between 16 and 66 years old, and excluded both patients with an ABO incompatible relationship or who were crossmatch-positive. The number of patients who were switched from cyclosporine to tacrolimus within 2 years was 4 in each of the groups, with no difference between the two groups.

Table 1 Demographic characteristics

	MZR group	MMF group
Number of recipients	40	38
Recipient age (years)		
Mean ± SD	41 ± 13	35 ± 14
Range	16–64	16–66
Gender (male/female)	23/17	20/18
Donor type		
Parent	22	27
Child	1	1
Brother or sister	6	4
Spouse	11	6

MZR mizoribine, *MMF* mycophenolate mofetil, *SD* standard deviation

All patients gave informed consent, and the study was approved by the institutional review board and complied with the Declaration of Helsinki.

Endpoints

The primary efficacy endpoints of this study were 2-year patient survival, 2-year graft survival, and the acute rejection-free rate within 6 months after transplantation. Major side effects and complications within 2 years were also used as an endpoint. The diagnosis of rejection was established by biopsy. Acute rejection was defined by histopathological findings of grade 1a and over according to the Banff classification.

Pharmacokinetic study of mizoribine

To obtain pharmacokinetic parameters (i.e., AUC), a pharmacokinetic study of MZR was performed at 14 and 28 days after transplantation. For this study, serum samples were obtained at 0, 1, 2, 3, 4, 6, and 9 h after drug administration (AUC_{MZR}^{0-9}). Serum samples to determine the trough blood level of MZR (TL_{mzr}) were obtained each day before dosing until day 14 after transplantation. For MZR pharmacokinetic analysis, serum samples were assayed using a validated HPLC method [7].

Statistical analysis

The Kaplan–Meier method was used to determine patient and graft survival rates, and statistical significance was tested using the log-rank test. The study was approved by the Ethics Committee of the Kyoto Prefectural University of Medicine.

Results

Demographic characteristics

The demographic and baseline characteristics were similar between patients and donors assigned to the MZR and MMF groups (Table 1).

Patient and graft survival

The 2-year patient survival rates for the MZR and MMF groups were 100 and 97.4 %, respectively. The one death in the MMF group was due to fulminant hepatitis B, despite normal renal function for 5 months after renal transplantation. The 2-year graft survival rates for the MZR and MMF groups were 100 and 94.7 %, respectively (Fig. 2). There was no significant difference between the two groups in terms of patient or graft survival rates.

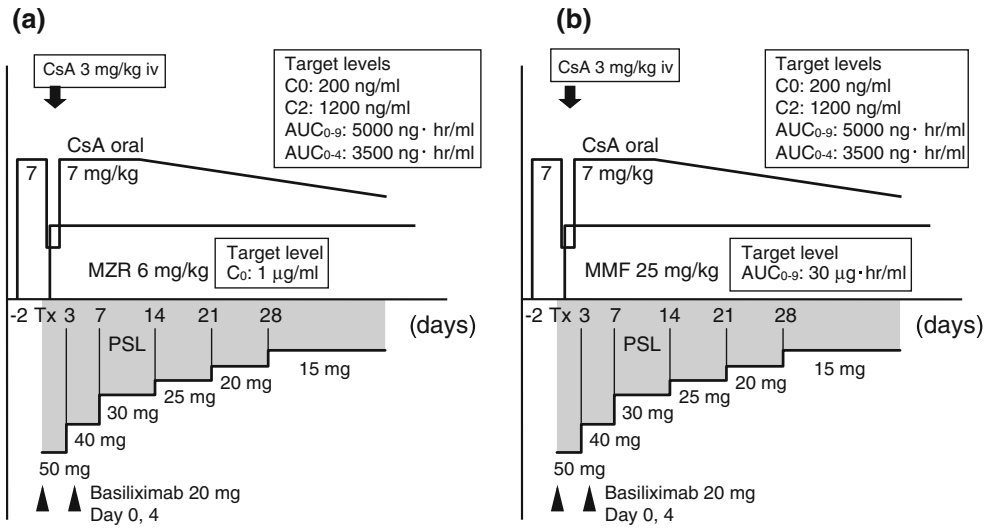

Fig. 1 Immunosuppressive regimens: **a** CsA + MZR + PSL + basiliximab, and **b** CsA + MMF + PSL + basiliximab. *PSL* prednisolone, *Tx* transplant

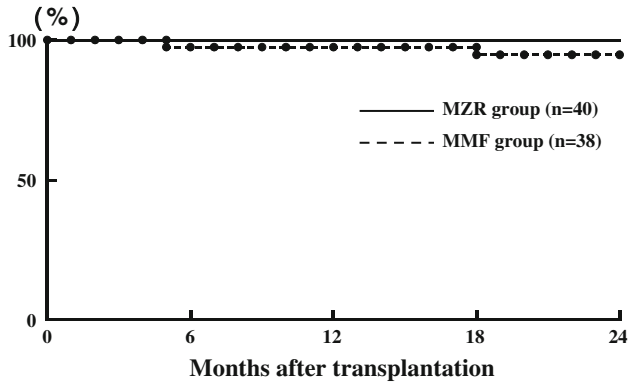

Fig. 2 Graft survival rates in the MZR group and the MMF group. (The one death in the MMF group was from fulminant hepatitis B, and one patient lost graft function and was shifted to the hemodialysis)

Acute rejection-free rate within 6 months after transplantation

Table 2 shows the rejection rate at 6 months after transplantation for each group. The rejection rate observed in the MZR group (25 %) was not significantly higher than that in the MMF group (16 %). The Banff grades confirmed by renal biopsy in the MMF group were borderline, 1 pt.; IA, 3 pts.; IIA, 1 pt.; and IIB, 1 pt., and in the MZR group, borderline, 2 pts.; IA, 7 pts.; and IIA, 1 pt.

Serum creatinine level

Serum creatinine levels for the MZR and MMF groups were 1.24 ± 0.48 and 1.24 ± 0.84 mg/dL at 1 month, 1.28 ± 0.45 and 1.35 ± 0.59 mg/dL at 3 months, 1.32 ± 0.55 and 1.35 ± 0.40 mg/dL at 6 months, 1.30 ± 0.56 and 1.47 ± 0.50 mg/dL at 12 months, 1.41 ± 0.55 and 1.39 ± 0.38 mg/dL at 18 months, and 1.54 ± 0.69 and 1.38 ± 0.36 mg/dL at 24 months after transplantation, respectively (Table 2). There was no significant difference in serum creatinine levels between the two groups.

Adverse effects

The incidences of adverse effects and infections, both drug-related and overall, during the 2 years after renal transplantation were compared between the two groups (Table 3). The MZR group demonstrated a significantly higher rate of elevated serum uric acid values (35 %). The number of patients treated with allopurinol was 10 (25.0 %) of the 40 patients in the MZR group and 1 (2.6 %) of the 38 patients in the MMF group ($P < 0.05$). Mean serum urate levels of the MZR group and the MMF group at 1 month after transplantation were 7.4 ± 2.0 and 5.4 ± 2.2 mg/dL, respectively ($P < 0.05$). There was no significant difference between the two groups in terms of bone marrow suppression or liver dysfunction.

There were 4 occurrences of gastrointestinal symptoms in 2 cases (5.0 %) in the MZR group and 13 occurrences in 9 cases (23.7 %) in the MMF group ($P < 0.05$). Diarrhea occurred in 3 cases in the MMF group, with the severity of the diarrhea in 1 case requiring a reduction in MMF dose that resulted in symptom abatement. Abdominal distension and nausea also occurred with high frequency in the MMF group.

BK polyomavirus infection was not observed in either group.

Table 2 Rejection episodes and outcome of kidney function

	MZR group ($n = 40$)	MMF group ($n = 38$)	P value
Rejection episodes	10 (25 %)	6 (16 %)	NS
Mean serum creatinine level (mg/dL)			
1 month after transplantation	1.24 ± 0.48 ($n = 40$)	1.24 ± 0.84 ($n = 38$)	NS
3 months after transplantation	1.28 ± 0.45 ($n = 40$)	1.35 ± 0.59 ($n = 38$)	NS
6 months after transplantation	1.32 ± 0.55 ($n = 40$)	1.35 ± 0.40 ($n = 37$)	NS
12 months after transplantation	1.30 ± 0.56 ($n = 40$)	1.47 ± 0.50 ($n = 37$)	NS
18 months after transplantation	1.41 ± 0.55 ($n = 40$)	1.39 ± 0.38 ($n = 36$)	NS
24 months after transplantation	1.54 ± 0.69 ($n = 40$)	1.38 ± 0.36 ($n = 36$)	NS

MZR mizoribine, *MMF* mycophenolate mofetil

Table 3 Adverse event profile (excluding CMV infection)

	MZR group ($n = 40$)	MMF group ($n = 38$)	P value
Leucocytopenia	5 (12.5 %)	5 (13.1 %)	NS
Grade 1	5 (12.5 %)	3 (7.9 %)	
Grade 2	0	3 (7.9 %)	
Grade 3	0	0	
Grade 4	0	0	
Hepatic function abnormal	13 (32.5 %)	17 (38.6 %)	NS
Grade 1	9 (22.5 %)	14 (36.8 %)	
Grade 2	4 (10.0 %)	2 (5.2 %)	
Grade 3	0	1 (2.6 %)	
Grade 4	0	0	
Hyperuricemia	10 (25.0 %)	1 (2.6 %)	<0.05
Mean serum urate level (mg/dL)			
1 month after transplantation	7.4 ± 2.0	5.4 ± 2.2	<0.05
3 months after transplantation	7.6 ± 1.6	6.8 ± 1.6	NS
Gastrointestinal	2 (5.0 %)	9 (23.7 %)	<0.05

CMV cytomegalovirus, *MZR* mizoribine, *MMF* mycophenolate mofetil

Cytomegalovirus infection

Transplants from CMV carriers to non-carriers was 15.8 % (6/38) and 17.5 % (7/40), respectively, in the MMF and MZR groups, with no difference between the two groups. All of the non-carrier recipients receiving transplant from a carrier donor were given anti-virus prophylactic treatment. However, the incidence of cytomegalovirus (CMV) infection was significantly higher in the MMF group (Table 4). The number of CMV antigenemia-positive patients was 14 (35.0 %) in the MZR group and 18 (47.4 %) in the MMF group (NS). However, the average peak level of CMV antigenemia was 12 ± 37 in the MZR group and 300 ± 596 in the MMF group ($P < 0.0074$). The number of patients who developed CMV disease was 0 (0 %) in the MZR group and 7 (18.4 %) in the MMF group ($P < 0.05$). Moreover, the number of patients treated with ganciclovir was 3 (7.5 %) in the MZR group and 11 (28.9 %) in the MMF group ($P < 0.05$).

Pharmacokinetics of MZR at 14 and 28 days after transplantation

A 9-h pharmacokinetic study of MZR ($n = 40$) after several administrations revealed that most patients showed a peak at around 4 h (C4) with an average value of 2.87 ± 1.08 μg/mL at 14 days and 3.27 ± 1.01 μg/mL at 28 days, followed by a slow decrease, and the average trough levels (C0) were 1.0 ± 0.5 and 1.1 ± 0.6 μg/mL, respectively (Fig. 3).

Discussion

MZR is a nucleoside of the imidazole class, isolated from a culture medium of the mold *Eupenicillium brefeldianum* M-2166, which was found in the soil of Hachijo Island, Tokyo, Japan, in 1971 (l). Although this compound was found to have weak antimicrobial activity against *Candida*

Table 4 Incidence of CMV infection

	MZR group ($n = 40$)	MMF group ($n = 38$)	P value
CMV disease	0 (0 %)	7 (18.4 %)	<0.05
CMV antigenemia positive	14 (35.0 %)	18 (47.4 %)	NS
Treatment with IV ganciclovir	3 (7.5 %)	11 (28.9 %)	<0.05
Mean antigen-peak level (/50,000)	12.0 + 37	300 ± 596	<0.0074
Mean occurrence time after transplantation (days)	37 ± 14	41 ± 35	NS

CMV cytomegalovirus, *MZR* mizoribine, *MMF* mycophenolate mofetil, *IV* intravenous

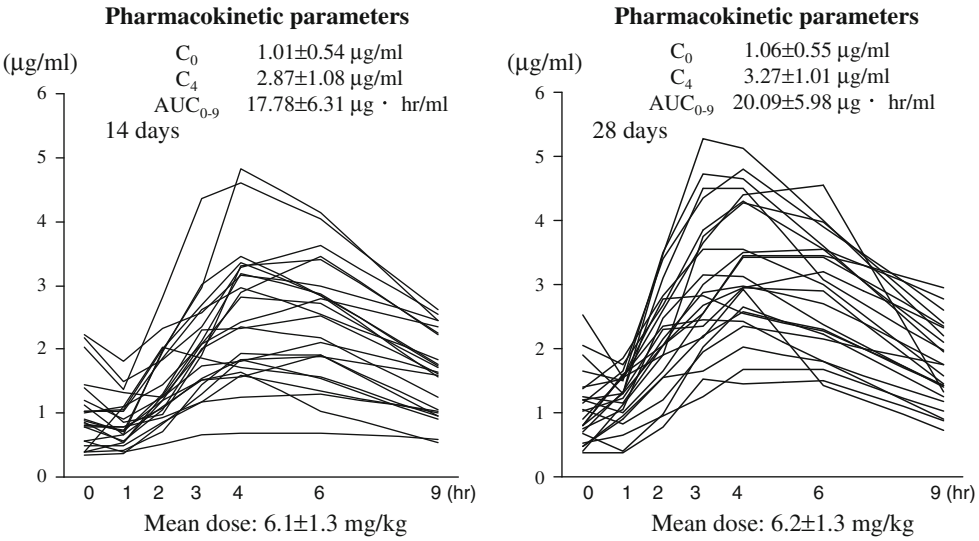

Fig. 3 Pharmacokinetic study of MZR at 14 and 28 days after transplantation

albicans, it proved ineffective against experimental candidiasis. MZR inhibits the de novo biosynthesis of purines. Unlike AZA, the compound is not taken up by nucleic acids in the cell. Instead, after phosphorylation, mizoribine-5′-monophosphate (MZR-5P) inhibits GMP synthesis by antagonistic blocking of IMPDH ($K_i = 10^{-8}$ M) and GMP-synthetase ($K_i = 10^{-5}$ M) in the pathway from IMP to GMP of the purine synthesis system. The drug was found to inhibit both humoral and cellular immunity by selectively inhibiting the proliferation of lymphocytes, and then it was developed as an immunosuppressive agent in Japan. The clinical efficacy of MZR in renal transplantation was studied in various Japanese institutions from 1978 to 1982, the period when immunosuppression was performed mainly with AZA and corticosteroids without immunophilin-binding drugs. The immunosuppressive effect in 57 cases of triple-drug therapy (MZR/AZA/corticosteroids) was compared with that obtained in 72 historical controls treated with AZA/corticosteroids. The graft survival rate for the MZR-treated group, 89.6 %, was significantly higher than that for the non-MZR-treated group (74.6 %). MZR was approved by the Ministry of Health and Welfare, Japan, in 1984. Recently, it has been used most commonly in combination with other immunosuppressants, such as CsA or tacrolimus, and corticosteroids in transplantation.

In 1989, a randomized trial to compare CsA/AZA and CsA/MZR revealed that MZR had an immunosuppressive effect equal to that of AZA and fewer side effects such as myelosuppression and liver dysfunction [8].

The original dosage of MZR, 1–3 mg/kg/day, was decided on the basis of animal experiments that showed good survival rates and no harmful side effects with doses of 1.2 mg/kg in rats and 3 mg/kg in dogs [5]. The mixed lymphocyte reaction revealed that a blood concentration of 1 μg/mL was able to suppress lymphocyte proliferation by 50 % (IC_{50}) [9]. However, blood concentration was not measured in clinical cases. Several Japanese papers reported that MZR at 1–3 mg/kg/day did not bring the blood concentration to an effective range in some cases, and that a higher dosage of 4–5 mg/kg/day was as potent as MMF without major side effects [10]. Therefore, in the present study, high-dose MZR (6 mg/kg/day) was investigated in conjunction with CsA, basiliximab, and corticosteroids.

Measurement of the serum concentration of MZR is important for achieving both efficacy and less toxicity, especially because water-soluble MZR is easily affected by renal function.

The pharmacokinetics of MZR during the 9 h after administration showed a gentle curve to a peak at around

4 h later, followed by a slow decrease toward a trough. Most patients revealed a trough level of over 1 μg/mL at 28 days after transplantation. This indicates that the immunosuppressive effect of MZR appears over a long period when the dosage is regulated to maintain a trough level higher than 1 μg/mL.

In 2004, a multi-center trial in Japan [11] reported that high doses of MZR at 5 mg/kg/day or greater used concomitantly with tacrolimus achieved a significantly higher rejection-free rate within 3 months after transplantation (85.0 %) compared with the <3 mg/kg/day group (64.9 %) and with the 3–<5 mg/kg/day group (65.1 %). In a long-term study, Tanabe et al. [9] reported that a combination of MZR with CsA achieved 10-year patient and graft survival rates equivalent to that of a group receiving AZA and CsA. In the present short-term study, we showed that a combination of MZR with CsA yielded similar results to the MMF/CsA treatment group in terms of patient and graft survival and renal function. Regarding adverse events, many Japanese studies have reported that MZR causes little myelosuppression and hepatic disorder in comparison with AZA, and that MZR causes little gastrointestinal disturbance and viral infection compared with MMF [11]. In this study, our results were similar to those reported previously. The most harmful side effect of MZR is hyperuricemia, and this was also the case in the present study. However, this was easily controlled by administration of allopurinol in most cases.

Although several previous studies noted no increase in the incidence of CMV disease in kidney transplant recipients treated with MMF, our everyday clinical experience and reports from Basic-Jukic et al. [12] and Sarmiento et al. [13] suggest that the number of patients with CMV disease has increased since its introduction.

Basic-Jukic et al. reported that MMF increased the incidence of CMV disease compared with AZA after cadaveric kidney transplantation. In their study, the group treated with AZA included 280 patients (132 females) treated for 17,672 months with AZA/CsA/steroids or AZA/steroids, while the MMF group included 219 patients (112 females) treated for 5,079 months with MMF/CsA/steroids or MMF/steroids. There was no difference in the number of acute rejection episodes between the AZA and MMF groups. The AZA group had 51 CMV disease episodes (1 episode per 346.5 treatment months), and the MMF group experienced 43 episodes (1 per 118.1 months) ($P < 0.01$). Mean onset of CMV disease occurred 32.65 ± 47.69 (SD) months and 3.72 ± 4.43 months after transplantation in the AZA and MMF groups, respectively.

Sarmiento et al. also reported that MMF was associated with more clinically severe forms of CMV disease than AZA. Patients who received MMF were more likely to have CMV disease with organ involvement: 7 of 12 patients (58 %) in the MMF group versus 3 of 17 (18 %) in the AZA group, $P = 0.03$. Furthermore, the median number of organs involved was greater in the MMF group than in the AZA group: 2.0 versus 1.0 ($P = 0.015$).

In our study, the number of patients who developed CMV disease, the number of patients treated with ganciclovir, and the average peak level of CMV antigenemia were significantly lower in the MZR group than in the MMF group.

An inhibitory effect of MZR on CMV infection in vitro was reported by Shiraki et al. [14]. The effect of combination therapy (CsA, prednisolone, MZR) on CMV in vitro was evaluated with fixed concentrations of CsA and prednisolone. Immunosuppressive doses of CsA and prednisolone enhanced CMV replication in vitro and appeared to predispose patients to CMV infection in addition to their suppressive effects on immune function. On the other hand, AZA and MZR suppressed CMV infection in vitro. These results suggested that the combination of CsA and prednisolone with AZA or MZR might suppress CMV replication and help to control CMV infection in vivo.

Shiraki et al. showed that the combination of CsA and prednisolone enhanced CMV replication but that the addition of MZR suppressed CMV replication. Although the antiviral activity might not be as strong as that of ganciclovir and not sufficient to control CMV infection in vivo, it might be able to suppress the initial step of CMV infection and help to lessen the frequency and severity of CMV infection in vivo. The suppressive effect of MZR on replication of human CMV in cells treated with CsA and prednisolone is dose-dependent and about 60, 80, and 90 % that of MZR at 1.0, 2.0, and 10.0 μg/mL, respectively. The pharmacokinetics of MZR at 14 and 28 days in our study revealed a peak level (C4) of 2.87–3.27 μg/mL and a trough level of 1.0 μg/mL, so these levels may be appropriate for yielding anti-CMV activity.

MMF has also been associated with gastrointestinal (GI) symptoms, with diarrhea in particular being frequently difficult to manage. In this study, 3 of the 38 cases in the MMF group presented diarrhea while none presented in the MZR group. While GSRS scoring [15] was not employed in this study, it was clear that there were few GI adverse events in the MZR group compared to the MMF group.

Our findings suggest that a combination of high-dose MZR with CsA, basiliximab, and corticosteroids at the dosages indicated can establish not only satisfactory immunosuppression but also suppression of CMV infection in vivo.

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