Comparison of Mizoribine and Mycophenolate Mofetil With a Tacrolimus-Based Immunosuppressive Regimen in Living-Donor Kidney Transplantation Recipients: A Retrospective Study in China

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ABSTRACT

Background. A retrospective study was conducted to investigate the prevalence of gastrointestinal (GI) symptoms as well as the efficacy and safety of mizoribine (MZR) and mycophenolate mofetil (MMF) in Chinese living-donor kidney transplantation (LDKT).

Methods. Forty-two recipients enrolled between January 2012 and March 2014 were treated with either MZR (n = 22) or MMF (n = 20). All patients were treated in combination with a tacrolimus-based immunosuppressive regimen, besides the study drugs.

Results. GI symptoms were observed in 1 of 22 patients (4.5%) and 10 of 20 patients (50%) in MZR treatment group and MMF treatment group, respectively ($P = .001$), during the post-transplantation 1 year. No significant differences in the incidence of acid reflux, bloated stomach feeling, and constipation were observed between the two groups. No recipient developed diarrhea in the MZR treatment group, whereas 30% of the MMF treatment group developed diarrhea ($P = .007$). The averages of GI symptom severity total score and diarrhea score were significantly lower in the MZR treatment group compare with MMF treatment group. There were no inter-group differences in background characteristics. There were no significant differences in acute rejection rate and clinical findings between these two groups, whereas the prevalence of cytomegalovirus infection and leukopenia were significantly lower in the MZR treatment group. There was no significant difference on adverse events such as hyperuricemia or other adverse events.

Conclusions. This study demonstrated a significantly lower incidence of GI symptoms for treatment with MZR compared with MMF and good efficacy and safety in Chinese LDKT with MZR.

GASTROINTESTINAL (GI) disturbances occur frequently after kidney transplantation, affecting 20% to 40% of recipients. Severity of GI symptoms varies widely, from relatively mild, such as intermittent episodes of diarrhea or nausea, to extremely serious, such as colonic necrosis or perforation in rare cases, resulting in graft loss and/or the patient's death. These symptoms may be related to surgical stress, infections, exacerbation of preexisting GI symptoms, or the administration of medications such as antibiotics, glucose-lowering agents, proton-pump inhibitors, and immunosuppressants [1,2].

Apart from infections and preexisting GI symptoms, the main cause of GI symptoms after kidney transplantation appears to be the use of immunosuppressants, in particular mycophenolic acid (MPA) in the form of mycophenolate mofetil (MMF), affecting up to 45% of patients, in a dose-dependent manner [3]. Various strategies have been tried to ameliorate symptoms, including dose reduction or drug withdrawal. However, the reduction of immunosuppressant doss had been shown to significantly increase the risk of acute graft rejection and to decrease long-term graft survival [4].

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Mizoribine (MZR), another immunosuppressive regimen, blocks the enzyme inosine 5-monophosphate dehydrogenase in the same manner as MMF. It has been demonstrated that there were fewer incidents of GI-associated symptoms with the administration of MZR compared with MMF [5].

To the best of our knowledge, there had been no comparative studies of the incidence of GI symptoms during treatment with either MZR or MMF among Chinese living-donor kidney transplantation (LDKT) recipients.

The primary objective of the present study was to identify the prevalence and severity of GI symptoms in Chinese LDKT recipients, using a tacrolimus-based regimen. We also compared the efficacy and safety of MZR and MMF in Chinese LDKT recipients.

METHODS

This study comprised patients who underwent first LDKT at the General Hospital for the Chinese People's Armed Police Force from January 2012 to August 2014. Routine protocols for patient care and follow-up were the same for all patients in both the MZR-treated group and the MMF-treated group. The following exclusion criteria were implemented: patients who did not receive MZR or MMF; those with less than 1-year post-transplantation follow-up data; pediatric patients; and those whose grafts were lost due to extensive medication or poor compliance. Applying these criteria, 42 patients were included in this study: 22 initially received MZR and 20 were treated with MMF.

Tacrolimus and a steroid were administered according to the protocol of our institution. Tacrolimus was started at 0.08 to 0.12 mg/kg/day and adjusted to maintain a trough level in whole blood of 8 to 12 ng/mL for the first 2 months. From 3 months after transplantation onward, the trough level was adjusted to 5 to 10 ng/mL. With regard to the steroid treatment, methylprednisolone was administered intravenously at a dose of 1.0 g/day on day 0, followed by 0.5 g/day for 3 days and 0.25 g/day for another 2 days after transplantation. Thereafter, a steroid was administered orally at a dose of 30 to 40 mg/day (prednisolone equivalence). The dose was gradually reduced to 8 mg/day after 3 months and 4 mg/day as a maintenance dose half a year after transplantation. Administration of MZR was started at an average dose of 3 mg/kg/day, divided into morning and afternoon doses. MMF was started at an average dose of 1.5 g/day (divided into twice per day) and 1.0 g/day as a maintenance dose after 3 months.

The goal of this study was to compare the two groups in terms of (1) screening for GI symptoms (without GI infection–associated symptoms, such as vomiting or abdominal pain); (2) incidence of rejection episodes; (3) clinical findings, serum creatinine levels (mg/dL), estimated glomerular filtration rates (eGFR) (mg/L), serum urate levels (μmol/L), blood urea nitrogen (BUN) levels (mg/L), and Cystatin C levels (mg/L) at the 1, 2, 3, 6, 9, and 12 months post-transplantation time points; and (4) other adverse effects of each group.

Data are presented as mean ± standard deviations or percentages. Statistical analyses were performed with the use of IBM SPSS Statistics (Version 19.0, Armonk, NY, United States). Nominal data were compared with the use of the χ^2 test or Fisher exact test, and numeric means were compared with the use of the unpaired t test. All tests were two-sided, and a value of $P < .05$ was considered statistically significant.

This study was approved by the local Institutional Review Board and conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent before entering the study. The study was also registered with the Chinese Clinical Trial Registry (Registry No. ChiCTR-ORN-16007878, http://www.chictr.org/cn/).

Table 1. Clinical and Demographic Data for Recipients and Donors

	MZR Group (n = 22)	MMF Group (n = 20)	*P*
Cause of uremia (%)			
Chronic glomerulonephritis	10 (45.5%)	16 (80.0%)	.833
IgA	7 (31.8)	4 (20.0%)	
NS	1 (4.5%)	0 (0%)	
Diabetic nephropathy	1 (4.5%)	0 (0%)	
Membranoproliferative glomerulonephritis	2 (9.1%)	0 (0%)	
Others	1 (4.5%)	0 (0%)	
Recipient sex (%)			
Male	20 (90.1%)	16 (80%)	.400
Female	2 (9.9%)	4 (20%)	
Recipient age, years	30.4 ± 7.7	29.4 ± 84	.690
Recipient weight, kg	67.0 ± 21.8	60.7 ±13.0	.263
Pre-transplant dialysis	22 (100%)	20 (100%)	1.000
Duration of dialysis before transplantation, months	18.3 ± 32.8	16.5 ± 24.6	.841
Donor sex (%)			
Male	8 (36.4%)	9 (45%)	.799
Female	14 (63.6%)	11 (55%)	
Donor age (years)	51.6 ± 6.5	50.2 ± 7.7	.517
Donor type (%)			
Father	7 (31.8%)	8 (40%)	.994
Mother	10 (45.5%)	8 (40%)	
Sibling	4 (18.2%)	4 (20%)	
Others	1 (4.5%)	0 (0%)	
HLA-AB mismatches (%)			
0	3 (13.6%)	2 (10%)	.715
1	6 (27.3%)	2 (10%)	
2	10 (45.5%)	15 (75%)	
3	3 (13.6%)	1 (5%)	
4	0 (0%)	0 (0%)	
HLA-DR mismatches (%)			
0	3 (13.6%)	5 (5%)	.544
1	19 (86.4%)	13 (65%)	
2	0 (0%)	2 (10%)	
ABO blood type (%)			
Identical	20 (90.9%)	20 (100%)	.489
Compatible	2 (9.1%)	0 (0%)	
Lymphocyte cross-match	2.4 ± 0.73	2.7 ± 0.80	.227
PRA I (%)	<10	<10	
PRA II (%)	<10	<10	
CMV status			
D+/R−	0 (0%)	0 (0%)	.988
D+/R+	22 (100%)	20 (100%)	
D-/R−	0 (0%)	0 (0%)	
Valganciclovir treatment (%)	22 (100%)	20 (100%)	1.000

RESULTS

A total of 42 LDKT recipients who had been treated with either MZR or MMF in combination therapy with tacrolimus were included in this retrospective study (Table 1). No significant differences were observed in baseline

Table 2. Comparison of GI Symptoms Between the Two Treatment Groups

	MZR Group (n = 22)	MMF Group (n = 20)	*P*
No. (%) of patients with GI symptoms	1 (4.5%)	10 (50%)	.001
Diarrhea	0 (0%)	6 (30%)	.007
Acid reflux	0 (0%)	1 (5%)	.476
Bloated feeling in stomach	0 (0%)	2 (10%)	.221
Constipation	1 (4.5%)	1 (5%)	1.000

characteristics, including sex, age, body weight, dialysis period, number of human leucocyte antigen (HLA)-incompatible cases, and cytomegalovirus (CMV) status (D+/R−, D+/R+, D−/R+), between the MZR treatment group and the MMF treatment group.

The incidence rate of GI symptoms developing within 1 year after kidney transplantation was compared between the two groups (Table 2). During the follow-up period, the prevalence of GI symptoms in MZR and MMF group were observed as 1 of 22 patients (4.5%) and 10 of 20 patients (50%), respectively ($P = .001$). Diarrhea was the most frequent GI symptom observed in the MMF treatment group, in which the incidence rate was 30%, whereas none of recipients developed diarrhea in the MZR treatment group ($P = .007$). Apart from diarrhea, there were no significant differences in the incidence rates for other GI symptoms including acid reflux, bloated feeling in the stomach, and constipation between the two groups.

In addition, GI symptoms were evaluated through the use of a severity score, which is defined as 0 (no event), 1 (mild), 2 (moderate), and 3 (severe) [6]. The averages for total GI symptoms score, diarrhea score, acid reflux score, bloated feeling score, and constipation score were 0.01 ± 0.10, 0, 0, 0, and 0.05 ± 0.21, respectively. Otherwise, in the MMF treatment group, the score was 0.26 ± 0.79, 0.60 ± 0.99, 0.05 ± 0.22, 0.15 ± 0.49, and 0.15 ± 0.67, respectively (Table 3). These results clearly indicate a significant lower average total score and lower average diarrhea score in the MZR treatment group compared with the MMF group.

The acute rejection (AR) rate at 1 year after the transplantation was 18.2% in the MZR treatment group and 10% in the MMF treatment group, without significant intergroup differences ($P = .665$). Three patients in the MZR treatment group and two patients in the MMF treatment group with AR underwent methylprednisolone pulse therapy (intravenous infusion at 0.5 g/day for 5 consecutive days). One patient in the MZR treatment group with AR was treated with increased doses of tacrolimus (Table 4). All four patients had favorable outcomes after the treatment described above. Patient and graft survival rates were 100% in both groups at post-transplantation 1 year.

Table 3. Comparison of GI Symptom Severity Scores Between the Two Treatment Groups

	MZR Group (n = 22)	MMF Group (n = 20)	*P*
GI symptoms total score	0.01 ± 0.10	0.26 ± 0.79	.002
Diarrhea	0	0.60 ± 0.99	.007
Acid reflux	0	0.05 ± 0.22	.300
Bloated feeling in stomach	0	0.15 ± 0.49	.158
Constipation	0.05 ± 0.21	0.15 ± 0.67	.492

Severity score: 0, no event; 1, mild; 2, moderate; 3, severe.

Table 4. Outcome of Rejection and Treatment

	MZR Group (n = 22)	MMF Group (n = 20)	*P*
Rejection episodes (clinical rejection)	4 (18.2%)	2 (10%)	.665
Treatment			
MP	3 (13.7%)	2 (10%)	
Tacrolimus dose up	1 (4.5%)	0 (0%)	

The clinical findings are shown in Table 5. Serum creatinine levels at 1, 2, 3, 6, 9, and 12 months after transplantation were 1.49 ± 0.76, 1.23 ± 0.37, 1.22 ± 0.36, 1.22 ± 0.33, 1.25 ± 0.34, and 1.23 ± 0.25 (mg/dL), respectively, in the MZR treatment group, and 1.31 ± 0.87, 1.36 ± 0.71, 1.22 ± 0.45, 1.48 ± 0.91, 1.35 ± 0.45, and 1.23 ± 0.30 (mg/dL), respectively, for the MMF treatment group. There was no significant difference in any of the measured values between the two groups. Similarly, eGFR levels (mg/L), serum urate levels (μmol/L), BUN levels (mg/L), and Cystatin C levels (mg/L) were not significantly different between the two groups.

Results of adverse events are summarized in Table 6. No CMV infection was observed in the MZR treatment group (0%), whereas CMV infection was observed in four patients in the MMF treatment group (25.0%), with a significant difference between the two groups ($P = .043$). A significant difference ($P = .018$) occurred in leukopenia between the MZR treatment group (0 case, 0%) and the MMF treatment group (five cases, 20%). Eleven patients had hyperuricemia in the MZR treatment group (50%) and 14 cases occurred in the MMF treatment group (70%), with no significant differences between the two groups ($P = .222$). There were no significant differences in the incidence rates of other adverse events, such as urinary tract infections, pneumonia, anemia, and hepatic amebiasis.

DISCUSSION

MMF is hydrolyzed to its active metabolite MPA, leading to immune suppression effects being observed soon after oral administration. After oral ingestion, MPA is liberated in the GI tract, absorbed, and metabolized in the liver to form MPA glucuronide (MPAG) and two other metabolites, 7-O-glucoside and acyl glucuronide (AcMPAG), which is pharmacologically active and believed to be the cause of some MPA-associated GI tract–adverse effects [7].

Several immunosuppressive drugs, including MPA, used in solid-organ transplantation are known to cause diarrhea [8]. Various possible explanations for patients

Table 5. Comparison of Kidney Function Between the Two Treatment Groups

	MZR Group (n = 22)	MMF Group (n = 20)	*P*
Serum creatinine level (mg/dL)			
l Month after transplantation	1.49 ± 0.76	1.31 ± 0.87	.522
2 Months after transplantation	1.23 ± 0.37	1.36 ± 0.71	.493
3 Months after transplantation	1.22 ± 0.36	1.22 ± 0.45	.964
6 Months after transplantation	1.22 ± 0.33	1.48 ± 0.91	.228
9 Months after transplantation	1.25 ± 0.34	1.35 ± 0.45	.435
12 Months after transplantation	1.23 ± 0.25	1.23 ± 0.30	.986
eGFR (mg/L)			
l Month after transplantation	70.6 ± 25.6	76.1 ± 45.1	.587
2 Months after transplantation	77.5 ± 23.1	71.7 ± 35.8	.554
3 Months after transplantation	78.6 ± 23.1	76.7 ± 24.5	.806
6 Months after transplantation	76.4 ± 18.8	68.5 ± 25.3	.265
9 Months after transplantation	75.3 ± 25.4	68.7 ± 23.8	.409
12 Months after transplantation	74.9 ± 15.9	74.8 ± 25.1	.985
Serum urate level (μmol/L)			
l Month after transplantation	374.2 ± 134.0	366.8 ± 128.0	.867
2 Months after transplantation	331.7 ± 57.7	359.1 ± 97.8	.346
3 Months after transplantation	342.0 ± 80.7	366.8 ± 73.5	.347
6 Months after transplantation	359.4 ± 79.2	384.1 ± 102.9	.428
9 Months after transplantation	361.8 ± 86.9	387.1 ± 63.0	.330
12 Months after transplantation	384.5 ± 94.8	378.9 ± 66.0	.838
BUN (mg/L)			
l Month after transplantation	7.38 ± 3.15	7.88 ± 5.39	.739
2 Months after transplantation	5.96 ± 1.25	7.37 ± 3.99	.185
3 Months after transplantation	5.92 ± 1.25	6.98 ± 2.74	.153
6 Months after transplantation	6.21 ± 1.80	7.67 ± 3.77	.149
9 Months after transplantation	6.09 ± 1.66	6.82 ± 3.11	.376
12 Months after transplantation	5.87 ± 1.26	6.54 ± 1.69	.196
Cystatin c (mg/L)			
l Month after transplantation	1.85 ± 0.51	1.80 ± 0.25	.743
2 Months after transplantation	2.08 ± 0.48	1.92 ± 0.61	.499
3 Months after transplantation	1.65 ± 0.33	2.06 ± 0.98	.186
6 Months after transplantation	1.58 ± 0.28	2.32 ± 1.96	.177
9 Months after transplantation	1.59 ± 0.50	1.96 ± 0.81	.156
12 Months after transplantation	1.40 ± 0.22	1.54 ± 0.50	.363

developing diarrhea have been proposed, including the presence of infectious agents, drug reactions, metabolic alterations, and surgical complications. MPA has been claimed to account for 50% of all cases of drug-related induction of post-transplantation–associated diarrhea [9], whereas it is estimated that 20% of all complications associated with administration of MPA involve the GI tract [1,2].

Table 6. Comparison of Other Adverse Events Between the Two Treatment Groups

	MZR Group (n = 22)	MMF Group (n = 20)	*P*
CMV infection	0	4	.043
Leukopenia	0	5	.018
Urinary tract infection	2	5	.240
Pneumonia	0	3	.099
Anemia	0	1	.476
Hepatic amebiasis	0	1	.476
Hyperuricemia	11	14	.222

The underlying mechanisms of MPA-induced GI toxicity remain unclear. However, several hypotheses have been proposed, including direct toxicity as a result of MPA antiproliferative effects, myelosuppression-induced opportunistic infections, local variations in immune response, and AcMPAG adduct toxicity [1,9,10]. In addition, a previous study has suggested that MPA can induce alterations in myosin light chain-2 phosphorylation, which may have a role in the pathophysiology of intestinal epithelial barrier disruption, and might therefore be responsible for the GI toxic effects of MPA observed in the intestine [11].

In comparison with MMF, MZR is more rapidly absorbed, and levels in the bloodstream decline more rapidly after oral ingestion. Within 24 hours, 85% of the administered dose is excreted in the urine and 1.0% in the bile. An inverse isotope dilution analysis showed that unchanged 14C-mizoribine accounted for more than 99% of

the radioactivity in the plasma 1 hour after dosing, and 85% of MZR excreted in the urine within 24 hours after administration was unchanged [12]. As discussed previously, it is clear that the absorption and metabolism profiles of MZR are different from those of MMF, and these differences are likely to be beneficial with respect to GI symptoms.

In the present study, the primary objective was to compare the prevalence and severity of GI symptoms in the MZR treatment group and the MMF treatment group. The incidence of GI symptoms within 1 year after kidney transplantation was 4.5% and 50% in the MZR treatment group and the MMF treatment group, respectively ($P = .001$). As described above, the incidence of GI symptoms in the MZR treatment group was much lower than in the MMF treatment group, and the symptoms occurred with increased frequency in the patients who were treated with MMF, especially for diarrhea. A similar observation has reported in another study [5]. In addition, results of this study show that diarrhea was the most frequent GI symptom observed in the MMF treatment group. Similar results have been reported in previous studies [13,14]. Furthermore, analysis of the GI symptoms severity scores also shows that the severity of GI symptoms (especially diarrhea) was significantly lower in the MZR treatment group compared with the MMF treatment group in LDKT recipients.

A second objective of this study was to determine the efficacy and safety of MZR and MMF in combination therapy with tacrolimus for LDKT recipients.

In this study, we found that patient and graft survival rates at the first year after transplantation were 100% in both groups, with no significant inter-group difference in the AR rate. Regarding serum creatinine, eGFR, serum urate, BUN, and Cystatin C level, there was no significant difference between the two groups.

We note that suppression of CMV proliferation by MZR in vitro has recently been reported [15], and this activity of MZR appears to contribute to the lower rate of CMV infection in the MZR treatment group. A previous study [16] also demonstrated that there were fewer incidents of CMV infections in patients treated with MZR compared with those treated with MMF. In the present study, the incidence of CMV infection was also significantly less frequent in the MZR treatment group compared with the MMF treatment group (0% vs 20%, $P = .043$).

Both MZR and MMF inhibit the enzyme inosine monophosphate dehydrogenase in de novo pathway of lymphocytes, resulting in the accumulation of inosine monophosphate, leading to higher uric acid production caused by increased concentrations of inosine, hypoxanthine, and xanthine [17–21]. Therefore, careful monitoring is necessary for patients treated with MZR or MMF who are likely to develop hyperuricemia. In this study, the incidence of hyperuricemia was 50.0% in the MZR treatment group and 70.0% in the MMF treatment group, with no significant difference between the two groups ($P = .222$). Similar results have been reported in previous studies [5,22].

Although this study may be still in a preliminary stage because of the small number of patient enrollment in this retrospective study, it can be concluded that the regimen of MZR in combination with tacrolimus and steroids is safe and effective, with beneficial reductions in the frequency and severity of GI symptoms in Chinese LDKT recipients.

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