# Efficacy and Safety of Mizoribine Combined With Tacrolimus in Living Donor Kidney Transplant Recipients: 3-Year Results by a Chinese Single Center Study

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ABSTRACT

Background. Mizoribine (MZR) was effective and safe for living Chinese donor kidney transplantation (LDKT) on tacrolimus-based treatment 1 year after transplantation. We investigated whether MZR was effective and safe for LDKT on tacrolimus-based treatment with long follow-up periods.

Methods. We compared 22 LDKT recipients who were administered MZR, tacrolimus, and corticosteroids with a control group (n = 20) treated with mycophenolate mofetil (MMF), tacrolimus, and corticosteroids. Primary efficacy endpoints were 3-year patient survival, 3-year graft survival, and acute rejection (AR) rate within 3 years after transplantation.

Results. The 3-year patient and graft survival rates for the MZR and MMF groups were 100%. The AR rate after transplantation was 18.2% for the MZR group and 10.0% for the MMF group; the difference was not significant ($P = .665$). There was no significant difference in serum creatinine levels, glomerular filtration rates (eGFR), serum urate levels, blood urea nitrogen, and cystatin C levels 12, 24, and 36 months after transplantation. No significant differences in the CD3, CD4, CD8, CD4/CD8, and CD45 were observed between the 2 groups 12, 24, and 36 months after transplantation. There were no significant differences in adverse events among the MZR or the MMF group, whereas the prevalence of gastrointestinal symptoms were significantly lower in the MZR treatment group ($P = .003$), especially acid reflux ($P = .007$). Compared with the MMF group, the MZR group should lighten the burden on patients.

Conclusion. MZR with tacrolimus and corticosteroids provides satisfactory immunosuppression and higher safety for Chinese LDKT over a 3-year follow-up.

MIZORIBINE (MZR) is an immunosuppressant developed in Japan that inhibits DNA synthesis by selectively inhibiting inosine monophosphate dehydrogenase in the de novo pathway [1–3]. The mechanism of action of MZR is similar to mycophenolate mofetil (MMF) and is used for the suppression of acute rejection in renal transplantation instead of MMF.

A meta-analysis to compare the efficacy and safety of MZR with MMF in Asian renal transplant patients showed that those taking MMF had a higher incidence of diarrhea, leucopenia, viral infection, and liver dysfunction, which indicated that MZR has a stronger safety profile than MMF [4]. However, to the best of our knowledge, there have been no comparative studies of efficacy and safety during treatment with either MZR or MMF among Chinese living donor kidney transplant (LDKT) recipients. Therefore, we investigated the efficacy and safety of MZR and MMF in Chinese LDKT recipients. The preliminary results of this

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**Table 1. Clinical and Demographic Data of the Recipients and Donors**

| | MZR (n = 22) | MMF (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 |
| BMI (kg/m$^2$) | 20.9 ± 3.1 | 23.6 ± 6.9 | .101 |
| Systolic blood pressure (mmHg) | 140.6 ± 15.1 | 145.9 ± 18.8 | .317 |
| Diastolic blood pressure (mmHg) | 90.7 ± 12.0 | 91.8 ± 14.2 | .779 |
| HTN (%) | 10 (45.5%) | 11 (52.4%) | .650 |
| Diabetes (%) | 1 (4.5%) | 0 (0%) | 1.000 |
| Pretransplant 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 Scr (μmol/L) | 63.0 ± 12.2 | 60.9 ± 9.4 | .515 |
| Donor GFR (mL/min/1.73 m$^2$) | 106.8 ± 16.1 | 110.0 ± 9.0 | .433 |
| 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 |
| Panel-reactive antibody PRA I (%) | <10 | <10 | |
| Panel-reactive antibody 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 |

Abbreviations: BMI, body mass index; CMV, cytomegalovirus; GFR, glomerular filtration rate; HTN, hypertension; MMF, mycophenolate mofetil; MZR, mizoribine; PRA, panel reactive antibody; Scr, serum creatinine.

study at 1 year were presented at the Transplantation Science Symposium Asian Regional Meeting 2016, in Tokyo, Japan, on April 8 to 9, 2016, and have been published in *Transplantation Proceedings* [5]. In addition, there was no long-term study with long follow-up periods to investigate the efficacy and safety of MZR and MMF; therefore, the present report details the results of the efficacy and safety studies at the 3-year point.

**Table 2. Tacrolimus Trough Levels**

| | MZR Group | MMF Group | *P* |
|---|---|---|---|
| Trough level of tacrolimus (ng/mL) | | | |
| 12 months after transplantation | 7.45 ± 2.03 | 7.44 ± 3.86 | .991 |
| 24 months after transplantation | 6.38 ± 1.83 | 7.56 ± 4.49 | .296 |
| 36 months after transplantation | 6.81 ± 2.43 | 6.27 ± 2.41 | .524 |

Abbreviations: MMF, mycophenolate mofetil; MZR, mizoribine.

## PATIENTS AND METHODS

### Study Subjects and Immunosuppression

The study subjects comprised 22 patients who underwent the first LDKT at the General Hospital for the Chinese People's Armed Police Force from January 2012 to August 2014. The patients were administered MZR (3 mg/kg/d, given orally twice a day), tacrolimus (0.08–0.12 mg/kg/day; trough level, 8–12 ng/mL for the first 2 months), prednisolone (maintenance dose, 4 mg/d, after half a year post-transplantation). The control group comprised 20 patients who also underwent the first LDKT at the same institutions during the same period. Patients in the control group were administered MMF (an average dose of 1.5 g/day, divided into twice per day), tacrolimus, and prednisolone, and the 2 groups were compared. Tacrolimus and steroids were administered according to the same protocol as that for the MZR 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, those whose grafts were lost due to extensive medication, and patients with poor compliance. There were no intergroup differences in patient background characteristics, such as an underlying disease in the recipient, sex, age, body weight, dialysis period, and number of HLA mismatches.

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 participating in the study.

### Endpoints

Primary efficacy endpoints of this study were 3-year patient survival, 3-year graft survival, and the acute rejection rate within 3 years after transplantation. The other goals of this study were to compare the 2 groups in terms of 1. kidney function, serum creatinine levels, estimated glomerular filtration rates (eGFR), serum urate levels, blood urea nitrogen (BUN) levels, and Cystatin C levels at the 12, 24, and 36 months post-transplantation time-points; 2. lymphocyte subsets, CD3, CD4, CD8, CD4/CD8 and CD45 at the 12, 24, and 36 months post-transplantation time-points; and 3. adverse effects of each group.

### Statistical Analysis

Data are presented as mean ± standard deviations or percentages. Statistical analyses were performed with IBM SPSS Statistics (Version 19.0, IBM, Armonk, NY, United States). Nominal data were compared using the $\chi^2$ test or Fisher's exact test, and numeric means were compared using the unpaired *t* test. All tests were 2-sided, and a $P$ value $< .05$ was considered statistically significant.

## RESULTS

### Characteristics

No significant differences were observed in baseline characteristics, including sex, age, body weight, dialysis period, number of HLA-incompatible cases, and cytomegalovirus

**Table 3. Comparison of Kidney Function Between the 2 Treatment Groups**

| | MZR group | MMF group | *P* |
|---|---|---|---|
| Serum Creatinine Level (mg/dL) | | | |
| 12 months after transplantation | 1.23 ± 0.25 (n = 22) | 1.23 ± 0.30 (n = 20) | .987 |
| 24 months after transplantation | 1.30 ± 0.38 (n = 22) | 1.31 ± 0.45 (n = 19) | .954 |
| 36 months after transplantation | 1.23 ± 0.40 (n = 20) | 1.35 ± 0.66 (n = 18) | .484 |
| eGFR (mg/L) | | | |
| 12 months after transplantation | 74.9 ± 15.9 (n = 22) | 74.8 ± 25.1 (n = 20) | .835 |
| 24 months after transplantation | 74.3 ± 18.8 (n = 22) | 70.0 ± 21.8 (n = 19) | .500 |
| 36 months after transplantation | 80.7 ± 23.1 (n = 20) | 74.7 ± 24.1 (n = 18) | .445 |
| Serum urate level (μmol/L) | | | |
| 12 months after transplantation | 384.5 ± 94.8 (n = 22) | 378.9 ± 66.0 (n = 20) | .838 |
| 24 months after transplantation | 371.3 ± 155.7 (n = 22) | 382.3 ± 157.8 (n = 19) | .661 |
| 36 months after transplantation | 343.8 ± 164.5 (n = 20) | 369.5 ± 161.6 (n = 18) | .352 |
| BUN (mg/L) | | | |
| 12 months after transplantation | 5.87 ± 1.26 (n = 22) | 6.54 ± 1.69 (n = 20) | .196 |
| 24 months after transplantation | 6.66 ± 3.04 (n = 22) | 6.69 ± 1.86 (n = 19) | .969 |
| 36 months after transplantation | 5.80 ± 2.12 (n = 20) | 6.73 ± 3.00 (n = 18) | .316 |
| Cystatin C (mg/L) | | | |
| 12 months after transplantation | 1.40 ± 0.22 (n = 22) | 1.54 ± 0.50 (n = 20) | .363 |
| 24 months after transplantation | 1.66 ± 0.86 (n = 22) | 1.78 ± 1.10 (n = 19) | .729 |
| 36 months after transplantation | 1.37 ± 0.40 (n = 20) | 1.63 ± 0.62 (n = 18) | .154 |

Abbreviations: BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; MZR, mizoribine.

**Table 4. Comparison of Lymphocyte Subsets Between the 2 Treatment Groups**

| | MZR group | MMF group | *P* |
|---|---|---|---|
| CD3 ($10^3$/μL) | | | |
| 12 months after transplantation | 1.66 ± 0.56 (n = 22) | 1.44 ± 0.51 (n = 20) | .254 |
| 24 months after transplantation | 1.86 ± 0.71 (n = 20) | 1.97 ± 0.67 (n = 19) | .631 |
| 36 months after transplantation | 2.01 ± 0.79 (n = 20) | 1.97 ± 0.64 (n = 18) | .876 |
| CD4 ($10^3$/μL) | | | |
| 12 months after transplantation | 0.83 ± 0.32 (n = 22) | 0.72 ± 0.28 (n = 20) | .294 |
| 24 months after transplantation | 0.97 ± 0.40 (n = 20) | 1.02 ± 0.44 (n = 19) | .737 |
| 36 months after transplantation | 1.10 ± 0.40 (n = 20) | 0.99 ± 0.38 (n = 18) | .426 |
| CD8 ($10^3$/μL) | | | |
| 12 months after transplantation | 0.73 ± 0.28 (n = 22) | 0.64 ± 0.23 (n = 20) | .351 |
| 24 months after transplantation | 0.79 ± 0.37 (n = 20) | 0.87 ± 0.29 (n = 19) | .473 |
| 36 months after transplantation | 0.82 ± 0.41 (n = 20) | 0.91 ± 0.35 (n = 18) | .519 |
| CD4/CD8 (%) | | | |
| 12 months after transplantation | 1.18 ± 0.42 (n = 22) | 1.19 ± 0.40 (n = 20) | .953 |
| 24 months after transplantation | 1.44 ± 1.14 (n = 20) | 1.22 ± 0.38 (n = 19) | .464 |
| 36 months after transplantation | 1.59 ± 0.77 (n = 20) | 1.17 ± 0.40 (n = 18) | .067 |
| CD45 ($10^3$/μL) | | | |
| 12 months after transplantation | 2.24 ± 0.78 (n = 22) | 1.80 ± 0.67 (n = 20) | .097 |
| 24 months after transplantation | 2.51 ± 0.88 (n = 20) | 2.28 ± 0.96 (n = 19) | .449 |
| 36 months after transplantation | 2.62 ± 0.93 (n = 20) | 2.48 ± 0.80 (n = 18) | .648 |

Abbreviations: MMF, mycophenolate mofetil; MZR, mizoribine.

status (D+/R-, D+/R+, D-/R-), between the MZR treatment group and the MMF treatment group (Table 1).

### Immunosuppressive Therapy

Administration of MZR was an average dose of 150 mg/d (divided into morning and afternoon doses). MMF was started at an average dose of 1500 mg/d (divided into twice per day) and 1000 mg/d as a maintenance dose after 3 months. Furthermore, as shown in Table 2, the trough levels of tacrolimus at 12, 24, and 36 months after transplantation were 7.45 ± 2.03, 6.38 ± 1.83, and 6.81 ± 2.43 (ng/mL), respectively, in the MZR treatment group and 7.44 ± 3.86, 7.56 ± 4.49, and 6.27 ± 2.41 (ng/mL), respectively, for the MMF treatment group. There were no significant differences in any of the measured values between the 2 groups.

### Patient and Graft Survival

Patient and graft survival rates were 100% in both groups 3 years post-transplantation. During the follow-up period, 2 patients in the MZR group were lost to follow-up 30 months after transplantation, and 2 patients in the MMF group were lost to follow-up 18 and 30 months after transplantation. The above 4 four patients left the study because of a transfer to another hospital for a nonmedical reason.

### Acute Rejection Rate and Graft Function

The acute rejection (AR) rate 1 year after the transplantation was 18.2% in the MZR treatment group and 10% in the MMF treatment group without significant intergroup differences ($P = .665$). On the other hand, no AR was observed between the 2 groups between 2 and 3 years. The kidney functions are shown in Table 3; serum creatinine levels at 12, 24, and 36 months after transplantation were 1.23 ± 0.25, 1.30 ± 0.38, and 1.23 ± 0.40 (mg/dL), respectively, in the MZR treatment group and 1.23 ± 0.30, 1.31 ± 0.45, and 1.35 ± 0.66 (mg/dL), respectively, for the MMF treatment group. There was no significant difference in any of the measured values between the 2 groups. Similarly, eGFR levels, serum urate levels, BUN

**Table 5. Comparison of Adverse Events Between the 2 Treatment Groups**

| | MZR Group (n = 20) | MMF Group (n = 18) | *P* |
|---|---|---|---|
| Between 1 and 3 years | | | |
| No. (%) of patients with GI symptoms | 0 (0%) | 7 (38.9%) | .003 |
| Diarrhea | 0 (0%) | 1 (5.6%) | .474 |
| Acid reflux | 0 (0%) | 6 (33.3%) | .007 |
| Bloated feeling in stomach | 0 (0%) | 2 (11.15) | .218 |
| Constipation | 0 (0%) | 1 (5.6%) | .474 |
| Diabetes | 1 (5.0%) | 0 (0%) | 1.000 |
| Pneumonia | 0 (0%) | 1 (5.6%) | .474 |
| Hyperuricemia | 11 (55.0%) | 8 (44.4%) | .746 |

Abbreviations: GI, gastrointestinal; MMF, mycophenolate mofetil; MZR, mizoribine.

**Table 6. MZR and MMF Costs in China**

| | MZR Group | MMF Group | |
|---|---|---|---|
| Description | 50 mg (100 tablets) | 250 mg (40 tablets) | |
| Unitary cost (RMB) | 13.12 | 12.63 | |
| Average dose (mg/d) | 150 | 1500 (0–3 months) | 1000 (3–36 months) |
| Daily cost (RMB) | 39.36 | 75.78 | 50.52 |
| Monthly cost (RMB) | 1180.8 | 2273.4 | 1515.6 |
| Annual cost (RMB) | 14,169.6 | 20,460.6 (1 year) | 18,187.2 (2–3 years) |
| Total cost within 3 years (RMB) | 42,508.8 | 56,835.0 | |

Abbreviations: MMF, mycophenolate mofetil; MZR, mizoribine; RMB, renminbi (Chinese currency, yuan).
Source: Integrated Management Platform of Beijing Medicine Sunshine Purchase.

levels, and cystatin C levels were not significantly different between the 2 groups.

### Lymphocyte Subsets

The Immunological Index is shown in Table 4. CD3, CD4, CD8, CD4/CD8, and CD45 at 12, 24, and 36 months after transplantation were not significantly different between the 2 groups.

### Adverse Effects

The results of adverse events are summarized in Table 5. Between 1 and 3 years after transplantation, the prevalence of gastrointestinal (GI) symptoms in the MZR and MMF groups were observed as 0 of 20 patients (0%) and 7 of 18 patients (38.9%), respectively ($P = .003$). Acid reflux was the most frequent GI symptom observed in the MMF treatment group, in which the incidence rate was 33.3%, whereas none of the recipients developed acid reflux in the MZR treatment group ($P = .007$). On the other hand, 11 patients had hyperuricemia in the MZR treatment group (55.0%), and 8 cases occurred in the MMF treatment group (44.4%) with no significant differences between the 2 groups ($P = .746$). There were no significant differences in the incidence rates of other adverse events, such as diabetes and pneumonia.

### Cost Effectiveness

The MZR and MMF costs in China are summarized in Table 6. The unitary cost and the total cost, respectively, within 3 years were 13.12 yuan and 42,508.8 yuan in the MZR treatment group and 12.63 yuan and 56,835.0 yuan in the MMF treatment group.

## DISCUSSION

MZR has been approved in Japan for induction and maintenance of immunosuppressive therapy after renal transplantation, and it has also been released in South Korea and China. It is often used in conversion treatment for the maintenance of renal transplant recipients receiving MMF who develop the adverse events of GI symptoms, cytomegalovirus infection, and pneumonia. However, it is used in Chinese de novo kidney transplant recipients only as a second-line choice [6]. Previously, few Chinese studies have suggested that the combination of a calcineurin inhibitor and MZR therapy was effective and safe for de novo kidney transplant recipients [7–9]. However, there are almost no comparative studies of efficacy and safety during treatment with either MZR or MMF among living Chinese donor kidney transplant (LDKT) recipients with long follow-up periods. We therefore investigated the efficacy and safety of MZR and MMF in Chinese LDKT recipients within 3 years of follow-up.

In the present study, the results indicated that patients in the MZR group had outcomes equivalent to those of the MMF group in terms of 3-year patient survival and 3-year graft survival. The AR rate within 3 years after transplantation was 18.2% in the MZR treatment group and 10% in the MMF treatment group without significant intergroup differences ($P = .665$). Regarding serum creatinine, eGFR, serum urate, BUN, and cystatin C level at 12, 24, and 36 months after transplantation, there were no significant differences between the 2 groups (Table 3). The lymphocyte subsets, CD3, CD4, CD8, CD4/CD8, and CD45, at 12, 24, and 36 months after transplantation were also not significantly different between the 2 groups (Table 4). Furthermore, for trough level of tacrolimus at 12, 24, and 36 months after transplantation, there were no significant differences between the 2 groups (Table 2). That is, like MMF, MZR was shown to be an effective immunosuppressive agent in combination with tacrolimus and corticosteroids.

Between 1 and 3 years after transplantation, the prevalence of GI symptoms in the MZR and MMF groups was observed as 0 of 20 patients (0%) and 7 of 18 patients (38.9%), respectively ($P = .003$). Acid reflux was the most frequent GI symptom observed in the MMF treatment group in which the incidence rate was 33.3%, whereas none of the recipients developed acid reflux in the MZR treatment group ($P = .007$). MMF is also known to increase the frequency of GI symptoms of diarrhea. In the present study, the incidence of GI symptoms in the MZR treatment group was much lower than in the MMF treatment group, the symptoms occurred with increased frequency in patients who were treated with MMF, and a similar observation was reported in other studies [5,10]. In addition, numerous studies have confirmed that diarrhea was the most frequent GI symptom observed in the MMF treatment group during the 1-year post-transplantation period [5,11,12]. However, the results of this study show that acid reflux was the most

frequent GI symptom observed in the MMF treatment between 1 and 3 years after transplantation.

Both MZR and MMF inhibit the enzyme inosine monophosphate dehydrogenase in the de novo pathway of lymphocytes, which result in the accumulation of inosine monophosphate and lead to higher uric acid production caused by increased concentrations of inosine, hypoxanthine, and xanthine [1–3,13,14]. As has been reported in previous studies [10–15], in this study, the incidence of hyperuricemia was 55.0% in the MZR treatment group and 44.0% in the MMF treatment group between 1 and 3 years after transplantation with no significant differences between the 2 groups ($P = .746$). Therefore, recipients should monitor serum uric acid levels in both the MZR and MMF treatment groups after transplantation.

There were no significant differences in the incidence rates of other adverse events, such as diabetes and pneumonia. In addition, no notable differences in adverse events were observed between groups.

Although this study had a number of limitations (this study was conducted at a single hospital in a mid-sized city in central China, bias may be present in patient characteristics, and the study sample size was small), it can be concluded that the regimen of MZR in combination with tacrolimus and steroids was safe and effective in Chinese LDKT recipients with long follow-up periods.

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