Mizoribine Versus Mycophenolate Mofetil in Combination Therapy With Tacrolimus for De Novo Kidney Transplantation: Evaluation of Efficacy and Safety

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ABSTRACT

The present study compared the efficacy and safety of mizoribine (MZR) with mycophenolate mofetil (MMF) in kidney transplantation. This multicenter, randomized clinical trial. Employed doses of study drug tailored to the immunosuppressive need. The primary efficacy outcome was the incidence of biopsy-proven acute rejection episodes (BPAR). The safety of the study drug was assessed using the incidences of adverse events, drug discontinuations, and abnormal laboratory results. The 7 (6.4%) BPARs above grade II were observed in the MZR group noninferior to the 2 (1.8%) in the MMF group (95% confidence interval, −0.007–0.097 > noninferiority limit [−0.2]). BPAR was significantly decreased in the MZR group after the dose change (17/41 [41.4%] vs 8/69 [11.6%]; $P < .0001$) and the incidence of BPAR was similar between the MZR and MMF groups after the dose change ($P = .592$). The uric acid level was significantly elevated in the MZR group ($P = .002$). In conclusion, the efficacy and safety of MZR were similar and statistically noninferior to MMF in combination therapy with tacrolimus.

MIZORIBINE (MZR), a nucleoside analogue that was developed as an immunosuppressive agent, inhibits inosine monophosphate dehydrogenase. Bredinin (Asahi Kasei Corp, Tokyo, Japan) is an oral formulation of MZR that is administered at doses of 1–6 mg · kg^{-1} · day^{-1}.[1,2] Previous studies comparing the concomitant use of azathioprine or mycophenolate mofetil (MMF) or MZR in combination with a calcineurin inhibitor showed MZR to achieve earlier restoration of transplant kidney function and fewer adverse events.[2,3] However, MZR is widely used only in Japan; this may be due to the lack of experience with MZR use in other countries. Few multicenter trials have compared the efficacy and safety of MZR with those of MMF.[2,3]

Therefore, the aim of this study was to compare the efficacy and safety of MZR vs MMF in de novo kidney transplantation patients who were treated with immunosuppressive protocol employing a generic tacrolimus formulation (TacroBell [Chong Kun Dang {CKD} Pharmaceutical Corp, Seoul, Korea]).

PATIENTS AND METHODS

This 26-week, multicenter, open-label, prospective, and randomized clinical trial included end-stage renal failure patients undergoing de novo living or deceased donor kidney transplantation at 9 centers in South Korea between July 2008 and January 2011. Among 223 screened patients, 4 were excluded due to screening failure, including 2 surgery cancellations, 1 delayed surgery, and 1 protocol violation before study drug administration (Fig 1).

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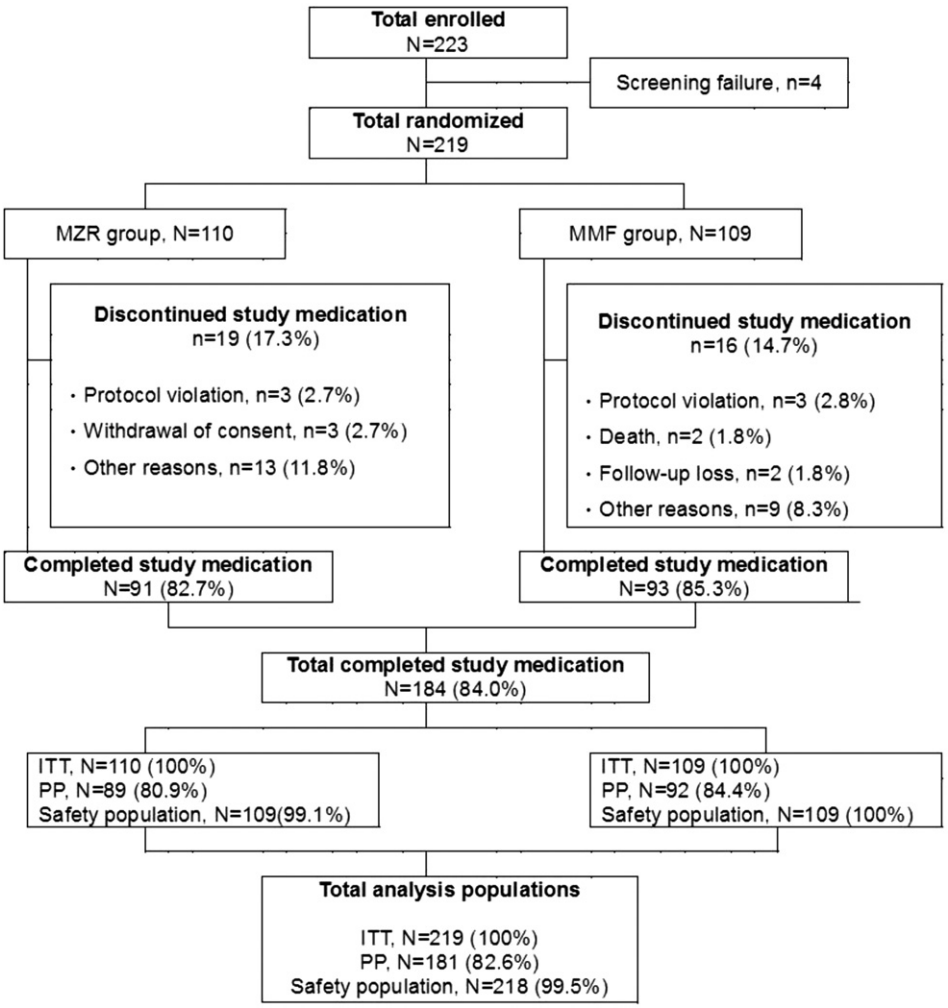

Fig 1. Summary of patient disposition: The intention-to-treat (ITT) set was defined as patients who underwent transplantation and received at least 1 dose of the study drug. The per protocol (PP) set population was defined as patients who completed the study process without protocol violation, and the safety set population was defined as patients who received at least 1 dose of the study drug regardless of transplantation status. Because 1 patient did not receive any study drug after transplantation in the mizoribine (MZR) group, the safety set population number is smaller than the ITT set population number. MMF, mycophenolate mofetil.

The MZR group received generic tacrolimus (TacroBell) plus MZR (Bredinin) and corticosteroids after induction therapy with basiliximab. The MMF group received the same protocol, except that MMF was administered instead of MZR. The initial dose of TacroBell was 0.1 mg/kg twice daily, with dose adjustments according to therapeutic drug monitoring. The target trough level was 5–15 ng/mL during the first 13 postoperative weeks and 3–10 ng/mL thereafter. Corticosteroids were administered based on the participating center's local protocol. The initial dose of methylprednisolone (500–1000 mg) was tapered to oral prednisolone (≥5 mg/d) by 6 months. The MZR dose was adjusted to 100 mg/d in patients with a body weight of 40–80 kg and 150–200 mg/d for greater than 80 kg. The MMF dose was adjusted to 1000 mg/d in patients with a body weight of 40–80 kg and 1500– 2000 mg/d for greater than 80 kg. The maximum permissible doses of MZR and MMF in the study protocol were altered during the study period because of suboptimal immunosuppression. Before changing the maximal permissible dose of the study drug, 17 (31.4%) biopsy-proven acute rejections (BPAR) and 4 (9.7%) BPARs were observed in the MZR group and the MMF group respectively. This observation indicated that the doses of study drugs were insufficient, especially in the MZR group. The revised maximum permissible dose of MZR was 200 mg/d for patients with a body weight below 80 kg and 300 mg/d greater than 80 kg. The revised maximum permissible dose of MMF was 2000 mg/d for patients with a body weight below 80 kg but unchanged for patients with a body weight greater than 80 kg.

We used an intention-to-treat (ITT) set analysis for primary and secondary efficacy evaluations and a safety set analysis for safety evaluation. The primary MZR efficacy was evaluated using the incidence of BPAR ≥ grade II according to the Banff 07 criteria during the study period.[4] The secondary efficacy was investigated using 2 criteria: (1) the incidence of efficacy failure defined as BPAR, graft loss, follow-up loss, and patient death and (2) the gastrointestinal symptom rating scale score and the gastrointestinal-related quality of life index (GIQLI) before and after kidney transplantation.[5,6]

The safety of the study drugs was assessed using the incidence of adverse events, study drug discontinuation, and abnormal results on laboratory tests. The enrolled patients attended 3 follow-up visits for efficacy and safety assessments of MZR at post-transplantation weeks 2, 12, and 24. Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) Version 12.1.[7]

The internal review board of each participating transplantation center approved this trial. It was monitored internally and externally during the study period.

Differences between parameters were analyzed by the Student paired *t* tests or Wilcoxon rank test. Differences between the 2 groups were assessed by the independent *t* test, chi-square test, and Wilcoxon rank sum test. $P < .05$ was considered statistically significant.

RESULTS

Patient Demographics

The ITT set analysis included 70 (63.6%) male and 40 (36.4%) female patients of mean age 44.6 ± 10.9 years in the MZR group vs 64 (58.7%) male and 45 (41.3%) female subjects of mean age of 44.2 ± 11.1 years in the MMF group. No significant differences were observed in patient demographics (Table 1).

Tacrolimus Trough Level and Change in Study Drug Dose

The tacrolimus trough levels were within the target range during the entire study period. Before the maximal permissible dose change, 17 (31.4%) BPARs and 4 (9.7%) BPARs were observed in the MZR group and MMF group, respectively; a significant difference ($P = .040$). After the maximal permissible dose change, 8 (11.6%) BPARs and 6 (8.9%) BPARs were observed in the MZR group and the MMF group respectively; ($P = .592$).

Efficacy Evaluation

Seven (6.4%) BPARs above grade II were observed in the MZR group and 2 (1.8%) in the MMF group. However, the MZR group was not inferior to the MMF group (95% confidence interval, −0.007–0.097 > noninferiority limit [−0.2]). The secondary efficacy evaluation showed that the incidence of efficacy failure was 19.1% in the MZR group and 12.8% in the MMF group. Although 25 BPARs were observed in the MZR group, there was no graft loss, follow-up loss, or death. In the MMF group, 10 BPARs, 1 graft loss, 2 follow-up losses, and 2 patient deaths occurred due to aspiration pneumonia and septic shock. Significantly more BPARs were observed among the MZR group before the change in the study protocol ($P = .040$). Although BPAR significantly decreased in the MZR group after the dose change (17/41 [41.4%] vs 8/69 [11.6%]; $P < .0001$), BPAR did not change significantly among the MMF group after the dose change (4/41 [9.7%] vs 6/68 [8.9%]; $P = .096$). After increasing the maximum permissible dose the inci-

Table 1. Demographic Characteristics of the Study Population

	MZR (%), *n* = 110	MMF (%), *n* = 109	*P* Value
Gender			
Male	70 (63.6)	64 (58.7)	.46
Female	40 (36.4)	45 (41.3)	
Age (yr)	44.6 ± 10.9 (22–74)	44.2 ± 11.1 (18–66)	.760
Height (cm)	165.4 ± 7.8 (148–183)	164.1 ± 9.0 (145–190)	.240
Weight (kg)	61.9 ± 11.2 (39–96)	59.9 ± 11.3 (37–92)	.200
Dialysis			
Hemodialysis	68 (61.8)	64 (58.7)	.680
Peritoneal dialysis	29 (26.4)	26 (23.9)	.756
None	13 (11.8)	19 (17.4)	.257
Donor type			
Deceased	51 (446.4)	43 (39.4)	.340
Living related	33 (33.0)	42 (38.5)	.202
Living unrelated	26 (23.6)	24 (22.0)	.872
HLA mismatch			
0	4 (4.0)	2 (2.0)	.864
1	3 (3.0)	2 (2.0)	
2	11 (1.0)	11 (10.0)	
3	39 (35.0)	45 (41.0)	
4	26 (24.0)	27 (25.0)	
5	19 (17.0)	18 (17.0)	
6	8 (7.0)	4 (4.0)	
Original disease			
Unknown	45 (40.9)	45 (41.3)	.766
Hypertension	33 (30.0)	30 (27.5)	
Glomerular disease	9 (8.2)	14 (12.8)	
Diabetes	8 (7.3)	13 (11.9)	
Polycystic disease	4 (3.6)	1 (0.9)	
Infection	4 (3.6)	1 (0.9)	
Obstructive disorder	0 (0.0)	1 (0.9)	
Other	7 (6.3)	4 (3.6)	

MZR, mizoribine; MMF, mycophenolate mofetil; HLA, human leukocyte antigen.

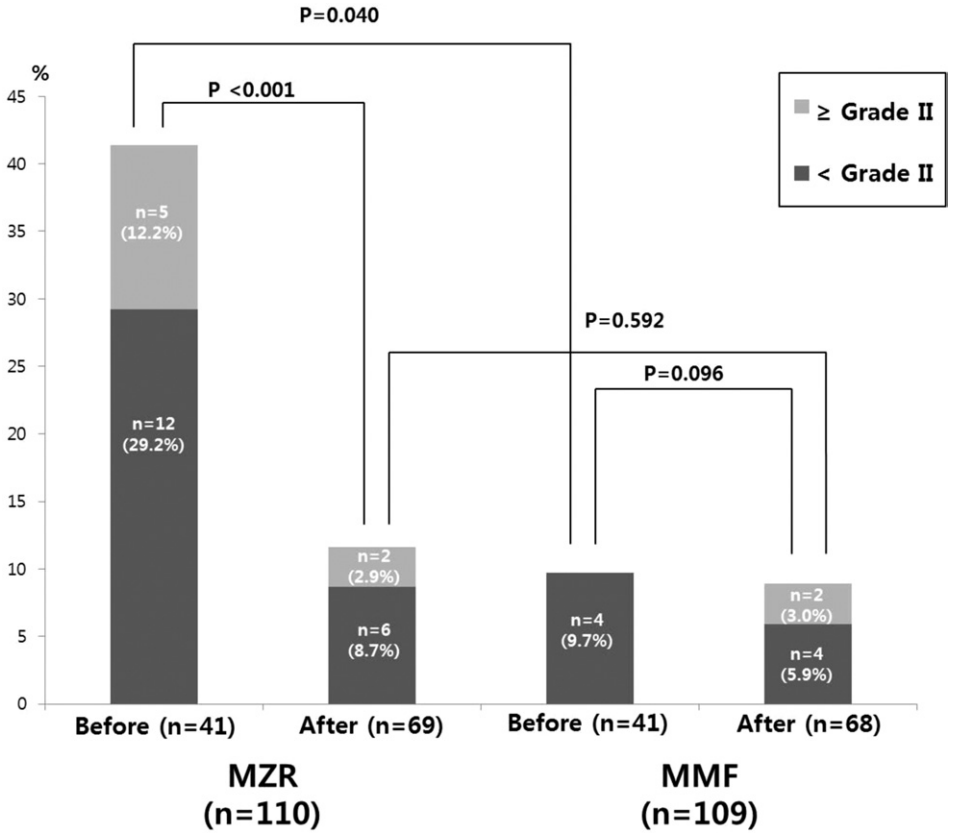

Fig 2. Incidence of biopsy-proven acute rejection in the mizoribine (MZR) and mycophenolate mofetil (MMF) groups. After change in dose, incidence of biopsy-proven acute rejection significantly decreased in the MZR group (17/41 [41.4%] vs 8/69 [11.6%]; $P < .0001$), but did not change significantly in the MMF group (4/41 [9.7%] vs 6/68 [8.9%]; $P = .096$).

dence of BPAR was similar between the MZR and MMF groups ($P = .592$; Fig 2). The MZR group was not inferior to the MMF group in terms of incidence of efficacy failure (95% confidence interval, −0.035–0.195 > noninferiority limit [−0.2]).

The GSRS did not change significantly in the MZR group after transplantation; 5.44 ± 5.59 to 4.94 ± 5.01 ($P = .493$). However, GSRS significantly decreased after transplantation in the MMF group: 5.45 ± 5.31 to 3.86 ± 4.15 ($P = 0.011$). The GIQLI increased significantly in both groups after transplantation and the prescription of the study drug ($P < .001$ and $P < .001$, respectively).

Safety Evaluation

Among 302 cases 190 (87.2%) patients experienced more than 1 adverse event, and 81 (37.2%), more than 1 serious

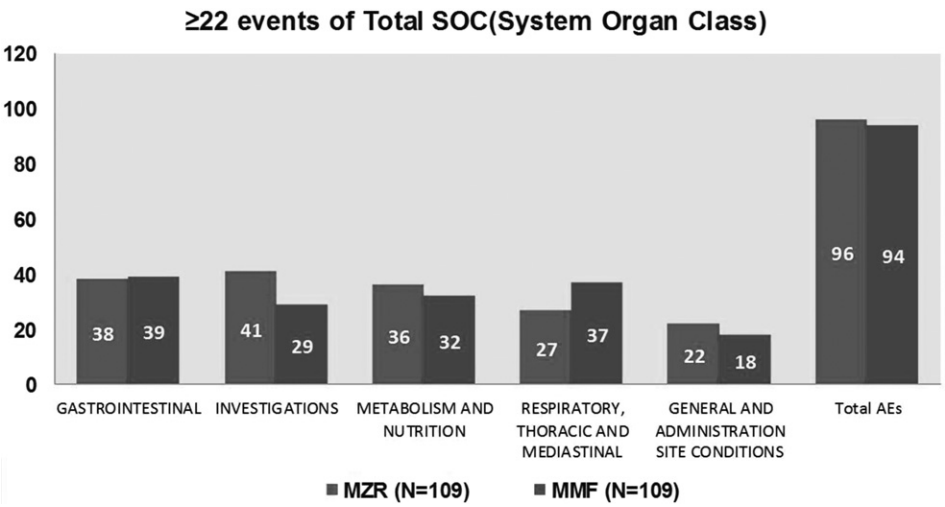

Fig 3. Gastrointestinal events (77 cases, 40.5% of patients) were the most common adverse events followed by events related to investigations and the metabolic and nutritional systems; developed more than 22 cases of adverse events. MZR, mizoribine; MMF, mycophenolate mofetil; AE, adverse event.

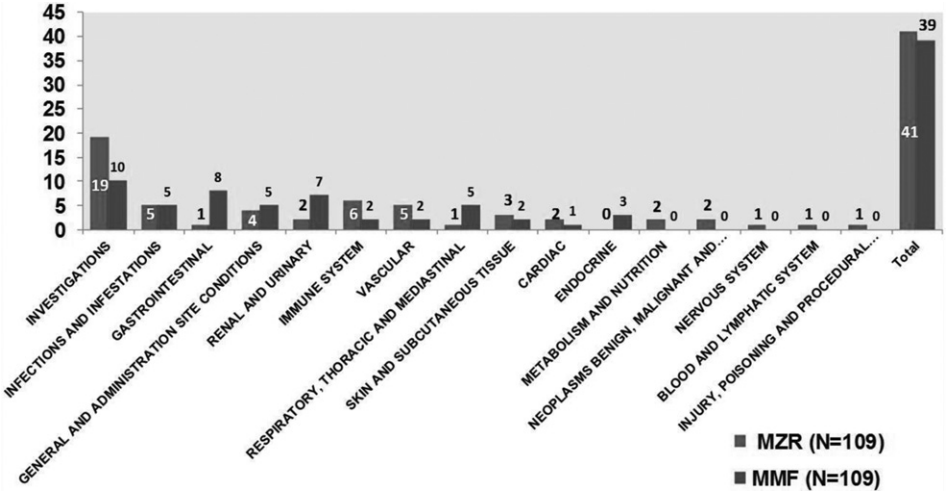

Fig 4. Incidence of serious adverse events. No significant differences were found between the mizoribine (MZR) and mycophenolate mofetil (MMF) groups ($P = 0.889$).

adverse event. The incidence of adverse events was significantly increased among both MZR and MMF groups after the maximal permissible dose change: 130 events in 40 patients vs 228 in 61 patients ($P = 0.027$) in the MZR group and 140 in 39 patients vs 215 in 58 patients ($P = 0.046$) in the MMF group. The MZR group included 96 patients (88.1%) who experienced 176 adverse events, and 41 (37.6%) who experienced 44 serious adverse events. In the MMF group, 94 patients (86.2%) experienced 188 adverse events, and 40 (36.7%), 44 serious adverse events ($P = .686$ and .889, respectively). Gastrointestinal events ($n = 77$, 40.5%) were the most common adverse event followed by events of the investigations, metabolic, and nutritional systems (Fig 3). Investigational serious adverse events were most common ($n = 29$, 35.8%, Fig 4), but not significantly different between the MZR and MMF groups ($P = .889$). Drug-related adverse events occurred in 23 cases in 22 patients, with infection as the most common one ($n = 4$, 18.2%). Two deaths (0.9%) occurred due to aspiration pneumonia and septic shock in the MMF group, but these events were not related apparently to the study drug.

Adverse events during the study period resulted in 9 (8.3%) temporary and 5 (4.6%) permanent study drug discontinuations in the MZR group and 8 (7.3%) temporary and 2 (1.8%) permanent study drug discontinuations in the MMF group. The causes of study drug discontinuation are summarized in Table 2. No significant differences were observed between the groups ($P = .653$).

Laboratory tests revealed no differences between the MZR and MMF groups during the study period except for blood uric acid level, which was significantly elevate at 6 months after surgery in the MZR group (43 vs 22 cases; $P = .002$). However, the mean uric acid levels of the 2 groups (6.12 mg/dL vs 5.33 mg/dL) remained within the normal range (3.5–8.0 mg/dL; Fig 5).

DISCUSSION

We have previously reported the efficacy and safety of TacroBell, a generic tacrolimus formulation.[8,9] An acute rejection rate of 10.6% was observed among renal transplant patients treated with TacroBell.[9] The acute rejection rate for MZR and MMF in combination with TacroBell was 13.7% in the current study; episodes greater than Banff 07 criteria grade II occurred among 4.1% of the total study population. These rates are comparable to the results of previous studies of Prograf.[10,11] Our results demonstrated that immunosuppressive therapy with generic tacrolimus

Table 2. Causes of Drug Discontinuation

	MZR Group ($n = 109$)		MMF Group ($n = 109$)	
	Temporary ($n = 9$; 8.3%)	Permanent ($n = 5$; 4.6%)	Temporary ($n = 8$; 7.3%)	Permanent ($n = 2$; 1.8%)
Infection	3 (2.8%)	2 (1.8%)	5 (4.6%)	
GI symptoms	1 (0.9%)		2 (1.8%)	
Rejection	4 (3.7%)			1 (0.9%)
Hyperglycemia	1 (0.9%)		1 (0.9%)	
Neutropenia		1 (0.9%)		
Asthenia		1 (0.9%)		
Pericarditis				1 (0.9%)
Lymphoma		1 (0.9%)		

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

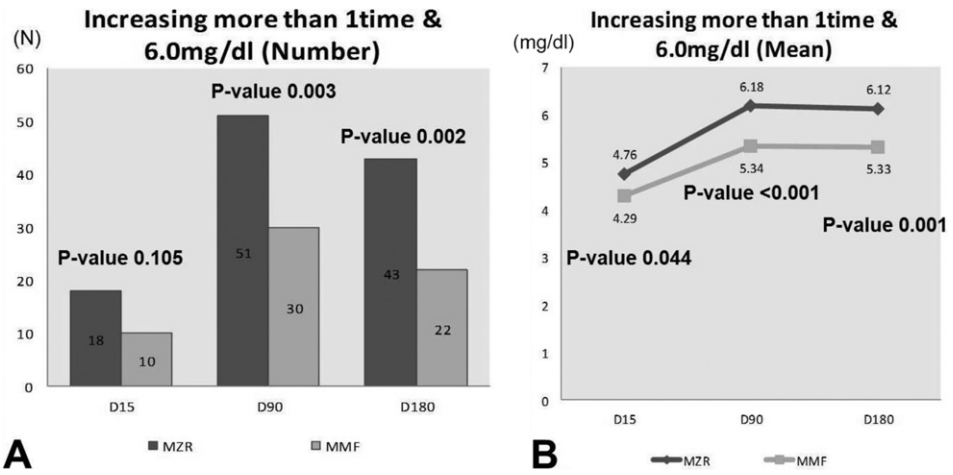

Fig 5. Abnormal uric acid levels were significantly more frequent in the mizoribine (MZR) group than in the mycophenolate mofetil (MMF) group at all visits **(A)**, and mean uric acid levels were significantly higher in the MZR group than in the MMF group **(B)**.

and MZR or MMF was well tolerated. Furthermore, this study attained its 26-week primary and secondary endpoints showing that the efficacy and safety outcomes of the MZR group were similar and statistically noninferior to those of the MMF group.

The optimal dose of MZR has not yet been established. More BPAR episodes occurred in the MZR than the MMF group before increasing the maximum permissible dose. In the MZR group, 17 (41.4%) BPARs were observed before the change, whereas 8 (11.6%) were observed thereafter. This decrease in BPAR among the MZR group after the dose change was significant ($P < .0001$), indicating that the initial target dose of MZR was too low to prevent acute rejection episodes. A multicenter trial in Japan[12] reported that a significantly higher rejection-free rate (85.0%) was observed at 3 months after transplantation among patients treated with a high dose of MZR (5 mg $\cdot$ kg^{-1} $\cdot$ day^{-1}) compared with <3 mg $\cdot$ kg^{-1} $\cdot$ day^{-1} (64.9%) or 3–5 mg $\cdot$ kg^{-1} $\cdot$ day^{-1} (65.1%). High-dose MZR (4–6 mg $\cdot$ kg^{-1} $\cdot$ day^{-1}) exhibited superior immunosuppressive effects with fewer adverse events and more cost-effectiveness.[13]

Recently, Nishimura et al reported that high-dose MZR (6 mg/kg) safely and effectively reduced the frequency of cytomegalovirus- and polyomavirus-related events in renal transplant recipients.[14] However, we did not observe a difference in the incidence of viral infections.

Hyperuricemia developed more frequently among patients who receive high-dose MZR (4–6 mg $\cdot$ kg^{-1} $\cdot$ day^{-1}) after kidney transplantation.[13,15] The uric acid level was significantly elevated in the MZR group in our study ($P <$ .001). Furthermore, gout medication was more frequently prescribed to the MZR group.

In conclusion, our study demonstrated that MZR in combination with tacrolimus exhibited a good safety profile and was noninferior to MMF in combination with tacrolimus.

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