Long-term Survival Analysis of Kidney Transplant Recipients Receiving Mizoribine as a Maintenance Immunosuppressant: A Single-Center Study

Dongyeol Lee, Hee Yeoun Kim, Jin Ho Lee, Yong Hun Sin, Joong Kyung Kim, and Joon Seok Oh*

Division of Nephrology, Department of Internal Medicine, Bong Seng Memorial Hospital, Busan, Korea

ABSTRACT

Background. Mizoribine (MZR) has been developed as an immunosuppressant and is widely used in Asia. However, most studies on MZR have been performed in Japan, and there remains a lack of reports on long-term use in other countries. The purpose of this study is to evaluate the efficacy and safety of MZR's use in Korean kidney transplant recipients by observing their clinical courses and analyzing their long-term patent and graft survival rates.

Methods. We studied 129 subjects who had received MZR as a maintenance immunosuppressant since January 2000. Our analysis was based on the patients' medical records from January 2000 to December 2017.

Results. The overall survival rates of the kidney transplant recipients were 100% at 1 year, 99.1% at 5 years, 96.8% at 10 years, and 92.5% at 15 years. The graft survival rates were 100% at 1 year, 98.3% at 5 years, 93.2% at 10 years, and 82.2% at 15 years. There were differences in the recipient survival and graft survival rates according to the kidney donor and the use of renal replace therapy before transplant. There were no differences in the survival rates according to the MZR dose, the type of underlying disease, or other clinical factors.

Conclusions. The use of low doses of MZR as a maintenance immunosuppressant could be an effective means of ensuring relatively good long-term patient and graft survival rates in cases of kidney transplant.

KIDNEY transplant is one of the most commonly performed solid organ transplants worldwide. The survival rates of kidney transplant patients have gradually improved according to the development of immunosuppressive agents. However, long-term use of these drugs can cause problems such as nephrotoxicity, infection, and malignant neoplasms. Therefore, many trials are underway for the long-term safety and effectiveness of immunosuppressant use. Mizoribine (MZR) is an immunosuppressant that has been isolated and purified from *Eupenicillium brefeldianum* M–2166 and used as a maintenance therapy for kidney transplantation since 1984. It has also been used as a therapeutic agent for lupus nephritis, rheumatoid arthritis, and nephrotic syndrome [1–3]. However, most of the research on MZR has been done in Japan, so there is a lack of reports on long-term use in other countries. This study investigated the effect and stability of MZR for Korean kidney transplant recipients.

PATIENTS AND METHODS

We screened 129 patients who had received MZR as a maintenance immunosuppressant for kidney transplant since January 2000 at Bong-Seng Memorial Hospital, Busan, Korea. We retrospectively analyzed the patients' January 2000 to December 2017 medical records, which included information on any underlying diseases and laboratory findings. Statistical analysis using SPSS version 13.0 for

*Address correspondence to Joon-Seok Oh, MD, PhD, Bongseng Memorial Hospital, 401 Jungang-daero, Dong-gu, Busan, Republic of Korea (48775); Tel: +82-51-664-4220; Fax: +82-51-664-4229. E-mail: midmro1@gmail.com

0041-1345/19
https://doi.org/10.1016/j.transproceed.2019.03.060

Windows (IBM, Armonk, NY, United States) was performed, and all data were expressed as means and standard deviations or as percentages. Survival curves were obtained using the Kaplan-Meier method and were tested by log-rank test.

RESULTS

A total of 129 kidney transplant recipients who had been receiving MZR had a mean age of 41.6 (SD, 11.7) years. The causes of end-stage kidney disease were glomerulonephritis in 46 patients (35.7%), diabetes mellitus in 18 patients (14.0%), polycystic kidney disease in 6 patients (4.7%), hypertension in 3 patients (2.3%), and unknown in 56 patients (43.4%). The duration of kidney replacement therapy before the transplant was 33.4 (SD, 44.6) months. There were 68 hemodialysis patients (52.7%), 23 peritoneal dialysis patients (17.8%), and 10 patients (7.8%) who had been undergoing both. Six patients (4.7%) underwent second kidney transplant because of decreased function of the first transplanted kidney, and 22 patients (17.1%) underwent preemptive transplant. First kidney transplant was performed in 113 patients (87.6%), and second kidney transplant was performed in 16 patients (12.4%). The mean age of the donors, including 74 men (57.4%) and 55 women (42.6%), was 39.3 (SD, 11.4) years. The following types and numbers of donation had been recorded: living related donation, 74 (57.4%); living unrelated donation, 40 (31.0%); and deceased donation, 15 (11.6%) (Table 1). The mean dosage of MZR used in this study was 2.2 (SD, 0.6) mg/kg/d, which amounted to 1.8 mg/kg/d at the 25th percentile, 2.3 mg/kg/d at the 50th percentile, and 2.7 mg/kg/d at the 75th percentile (Table 2). Calcineurin inhibitors were used in all patients, and 80 patients (63%) were treated with tacrolimus. In the tacrolimus group, average trough level of tacrolimus was 7.34 (SD, 2.58) ng/mL at 1 year, 5.82 (SD, 1.77) ng/mL at 5 years, and 5.09 (SD, 1.48) ng/mL at 10 years. Average trough level of cyclosporine in the cyclosporine treated group was 173.05 (SD, 60.78) ng/mL at 1 year, 117.33 (SD, 43.82) ng/mL at 5 years, and 93.86 (SD, 35.17) ng/mL at 10 years. The average dose of prednisolone was 3.23 (SD, 1.39) mg/d.

Post kidney transplant, 26 patients (20.2%) developed diabetes mellitus, and 5 (3%) developed malignant solid tumors. No patients experienced post-transplant lymphoproliferative disorder. Among 20 patients who had developed post-transplant infection, 11 patients (8.5%) had virus infection, 5 (3.9%) were infected with a mycobacterium, 2 (1.6%) were infected with a fungus, and 2 (1.6%) were infected with a bacterium (exceptions: mild urinary tract infections). A total of 32 patients (24.8%) underwent biopsy after kidney transplant (exceptions: cases of protocol biopsy). Among them, 18 patients (14.0%) experienced acute rejection, 8 experienced tubular atrophy (6.2%), 5 had recurrence of glomerulonephritis (3.9%), and 1 developed BK virus infection. Of the patients who experienced rejection, 15 had cellular rejection, accounting for 11.6% of all patients. Three patients (2.3%) experienced antibody-mediated rejection (Table 3).

Table 1. Characteristics of Study Participants

No.	129
Age, recipient, mean (SD), y	41.6 (11.7)
Sex, recipient, No. (%), M/F	63 /66 (48.8/51.2)
BMI at transplant, recipient, mean (SD)	21.3 (3.1)
Etiology, No. (%)	
Glomerulonephritis/nephropathy	46 (35.7)
Diabetes mellitus	18 (14.0)
Hypertension	3 (2.3)
Polycystic kidney disease	6 (4.7)
Unknown	56 (43.4)
Time for renal replacement therapy, mean (SD), mo	33.4 (44.6)
Mode of renal replacement therapy before transplant, No. (%)	
Preemptive	22 (17.1)
Hemodialysis	68 (52.7)
Peritoneal dialysis	23 (17.8)
Hemodialysis + peritoneal dialysis	10 (7.8)
Transplant	6 (4.7)
Transplant time, No. (%)	
First	113 (87.6)
Second	16 (12.4)
HLA mismatch, mean (SD)	3.2 (1.2)
0, No. (%)	4 (3.1)
1, No. (%)	4 (3.1)
2, No. (%)	24 (18.6)
3, No. (%)	44 (34.1)
4, No. (%)	38 (29.5)
5, No. (%)	13 (10.1)
6, No. (%)	2 (1.6)
Donor type, No. (%)	
Living related	74 (57.4)
Living unrelated	40 (31.0)
Deceased	15 (11.6)
Sex, donor, No. (%), M/F	74/55 (57.4/42.6)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); F, female; M, male.

The overall survival rates of the patients were 100% at 1 year, 99.1% at 5 years, 96.8% at 10 years, and 92.5% at 15 years. The graft survival rate was 100% at 1 year, 98.3% at 5 years, 93.2% at 10 years, and 82.2% at 15 years (Figs 1, 2).

The patient and graft survival rates were analyzed for each clinical factor. Graft survival was the best for living related donation, followed by living unrelated donation; deceased donation showed only low graft survival (Fig 3). Renal replacement therapy before transplant also affected the survival rate. Cases of preemptive kidney transplant had a higher survival rate than did cases of hemodialysis or peritoneal dialysis (Fig 4). However, there were no

Table 2. Dose of Mizoribine for Study Participants, mg/kg/d

Mean dose	2.2
Minimum	0.9
Maximum	3.9
25th percentiles	1.8
50th percentiles	2.3
75th percentiles	2.7

Table 3. Clinical Outcomes of Study Participants

NODAT, No. (%)	26 (20.2)
Malignant neoplasm, No. (%)	
Solid organ malignant neoplasm	5 (3.9)
PTLD	0 (0)
Infection cause, No. (%)	
Virus	11 (8.5)
Mycobacterium	5 (3.9)
Fungus	2 (1.6)
Bacteria	2 (1.6)
Graft kidney biopsy result, No. (%)	
Acute rejection	18 (14.0)
IF/TA	8 (6.2)
Recurred GN	5 (3.9)
BKVAN	1 (0.8)
Acute rejection type	
Acute cellular rejection	15 (11.6)
Antibody-mediated rejection	3 (2.3)

Abbreviations: BKVAN, BK virus–associated nephropathy; IF/TA, interstitial fibrosis/tubular atrophy; GN, glomerulonephritis; NODAT, new-onset diabetes after transplant; PTLD, post-transplant lymphoproliferative disease.

differences in the recipient survival and graft survival rates according to the MZR dose, the type of underlying disease, or other clinical factors.

DISCUSSION

Mizoribine inhibits inosine monophosphate dehydrogenase, a key enzyme in the formation of guanine ribonucleotides from inosine monophosphate [1]. In a cell cycle analysis, MZR suppressed the differentiation and proliferation of T lymphocytes and B lymphocytes by inhibiting the guanine nucleotide-dependent mechanism of lymphocyte migration from the G1 phase to the S phase [4]. Because of MZR's immunosuppressive effect, it is widely administered as a maintenance immunosuppressant after kidney transplant.

Mizoribine has been shown to have relatively lower pharmacologic efficacy than mycophenolate mofetil (MMF) or azathioprine, both of which inhibit purine synthesis as

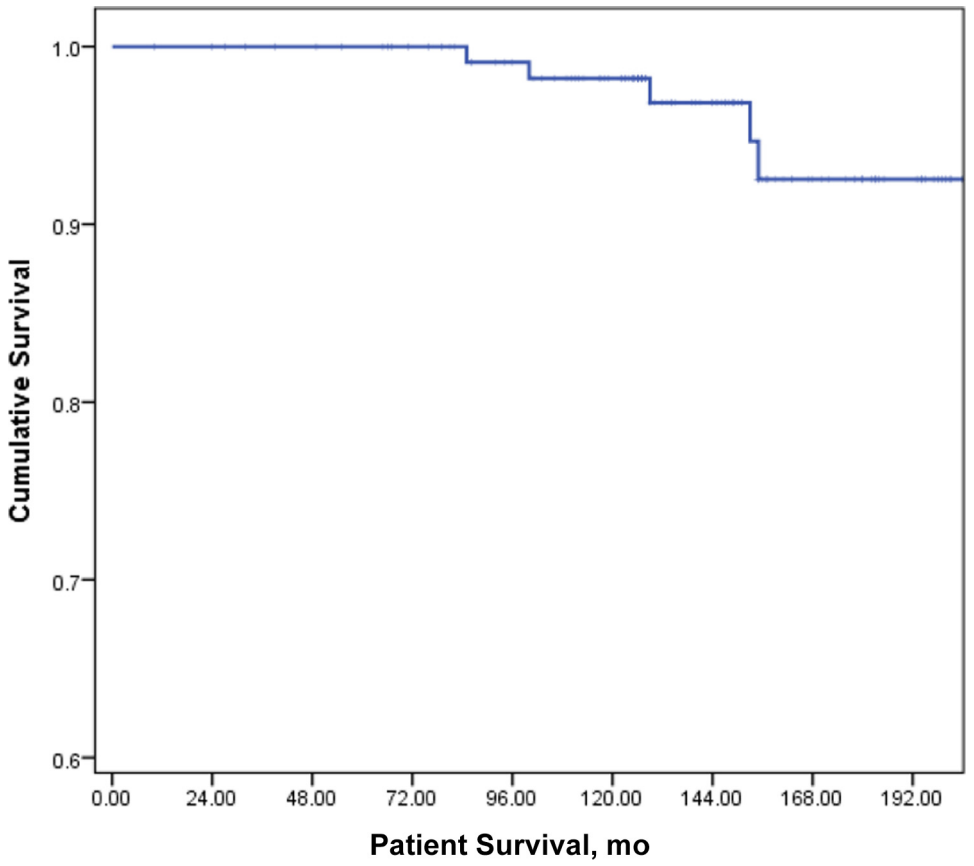

Fig 1. Kaplan-Meier survival curve of kidney transplant recipient who has received mizoribine as immunosuppressant.

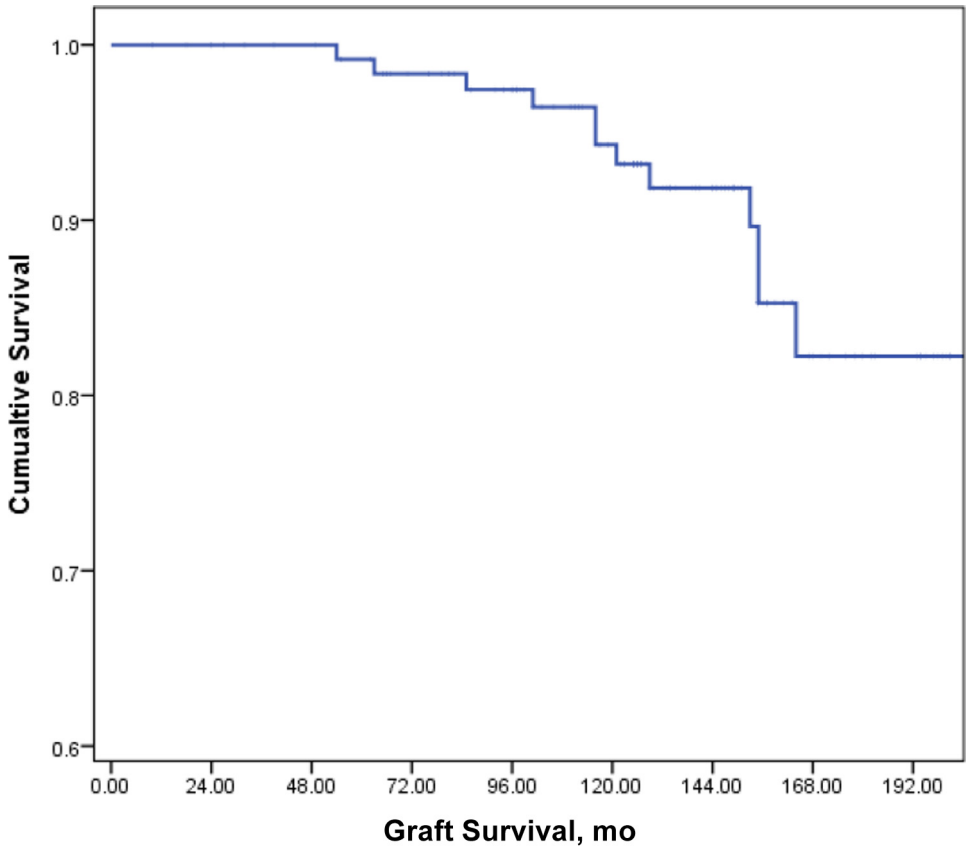

Fig 2. Kaplan-Meier survival curve of renal graft who has received mizoribine as immunosuppressant.

immunosuppressants [5]. Correspondingly, recent reports have shown that efficacy and safety in kidney transplant can be achieved when MZR is used above the recommended dose [6,7]. It was also reported that high-dose MZR can be effectively and safely used even in ABO-incompatible kidney transplant [8]. However, most of the reports published to date are on patients with end-stage renal disease in Japan; there remain few reports on the use of MZR in other regions. In Korea, there was only 1 report comparing MZR's efficacy and safety with MMF. However, the short study period of 26 weeks limited the information that could be obtained on long-term use of MZR [9].

For kidney transplant recipients administered MZR, in 1999 Tanabe et al reported overall survival rates of 98% at 1 year, 93% at 5 years, and 88% at 9 years along with graft survival rates of 98% at 1 year, 73% at 5 years, and 58% at 9 years [10]. Mizoribine has shown results similar to those of azathioprine, an immunosuppressant commonly used in the 1990s. According to data from the Korea Network for Organ Sharing for 2017, the survival rates of renal transplant recipients were 97.8% at 1 year, 94.8% at 5 years, and 91.4% at 9 years. In our study, the 1-, 5-, and 10-year survival rates of kidney transplant recipients were 100%, 99.1%, and 96.8%, respectively, and the graft survival rates were 100%, 98.3%, and 82.2%, respectively. Because of the change of immunosuppressant from cyclosporine to tacrolimus since 2000, our results might be considered superior to those of Tanabe's study.

In the meta-analysis reported by Xing et al, the patient survival rate and graft survival rate were similar in a group using MZR at more than 3.0 mg/kg/d compared with a group using MMF. Among patients taking MZR at less than 3.0 mg/kg/d, the survival rate was inferior to that for patients taking MMF [11]. However, in this meta-analysis, mainly high-dose MZR was used with tacrolimus. When low doses of MZR were used with tacrolimus, the

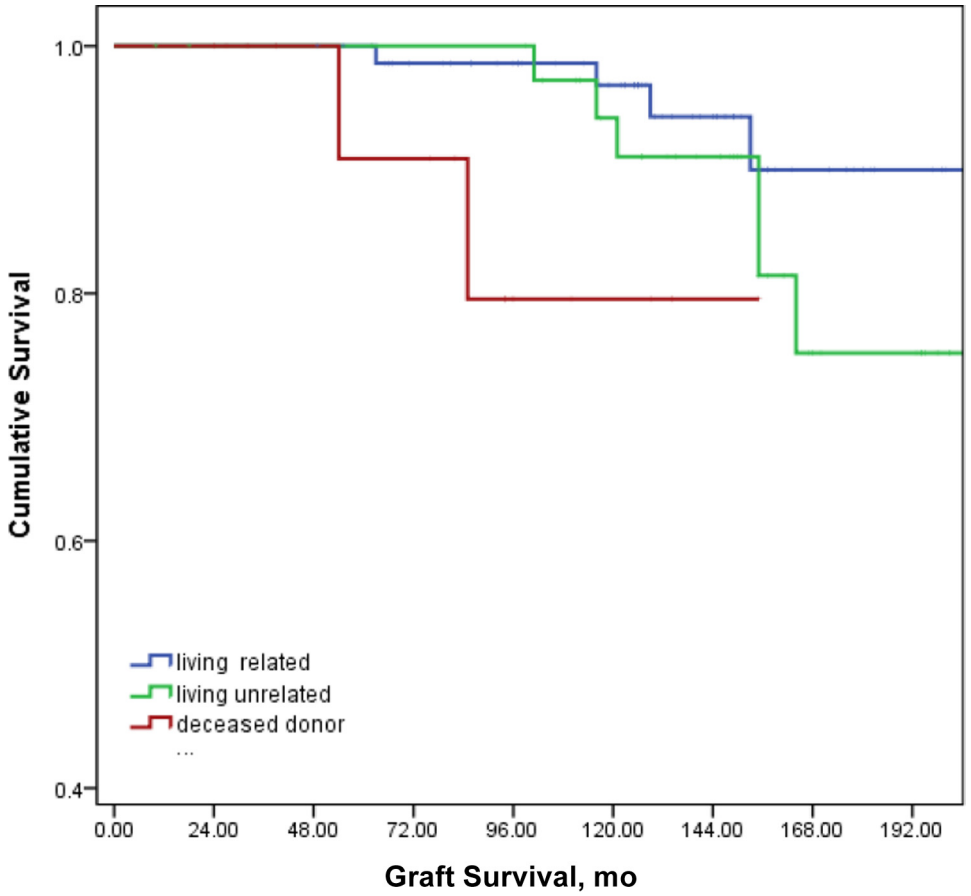

Fig 3. Graft survival according to donor relationship (log-rank test).

incidence of acute rejection episodes was similar between the MZR and MMF groups [9,12]. Our current study using MZR at 2.2 (SD, 0.6) mg/kg/d showed that long-term survival was not inferior to MMF. This might have been because 63% of the patients had been administered MZR and tacrolimus together.

In a study on Asian patients, MZR at low and high doses showed lower incidences of cytomegalovirus infection and BK infection than did MMF [13]. In our study, the incidence of infection was lower than in other high-dose MZR studies. Moreover, we did not find any cases of cytomegalovirus disease because of our relatively small doses of MZR. Our overall results suggest that the use of low-dose MZR might result in lower rates of infection.

Low doses of MZR based on tacrolimus, which is more potent than cyclosporine, might show a sufficient immunosuppressive effect. Furthermore, cytomegalovirus infection, BK virus infection, and other infections are less likely to occur than in cases where MMF is administered.

CONCLUSIONS

The use of a low dose of MZR as a maintenance immunosuppressant could be an effective means of ensuring good patient and graft survival. Additionally, it could also be a good way to reduce the probability of infection, which is a dangerous adverse effect of immunosuppressive drug administration.

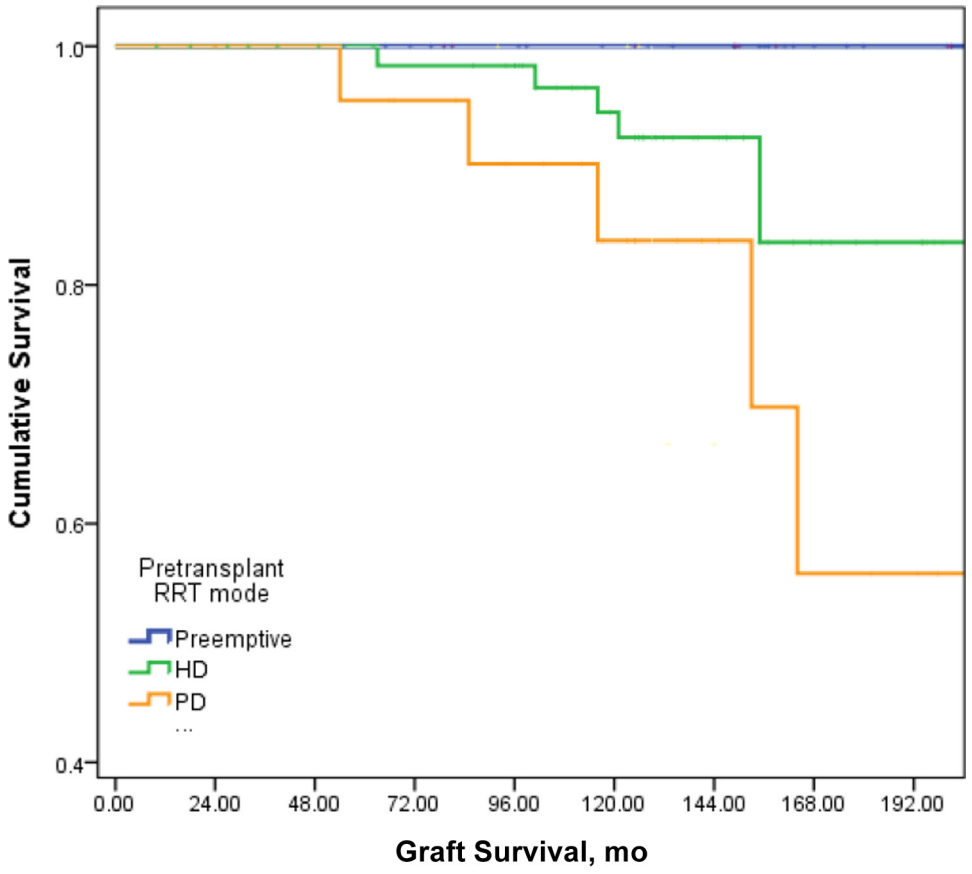

Fig 4. Graft survival according to renal replacement therapy before transplant (log-rank test). HD, hemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy.

REFERENCES

[1] Turka LA, Dayton J, Sinclair G, Thompson CB, Mitchell BS. Guanine ribonucleotide depletion inhibits T cell activation. Mechanism of action of the immunosuppressive drug mizoribine. J Clin Invest 1991;87:940–8.

[2] Tanaka H, Tsugawa K, Nakahata T, Kudo M, Onuma S, Kimura S, et al. Mizoribine pulse therapy for a pediatric patient with steroid-resistant nephrotic syndrome. The Tohoku J Exp Med 2005;205:87–91.

[3] Nozu K, Iijima K, Kamioka I, Fujita T, Yoshiya K, Tanaka R, et al. High-dose mizoribine treatment for adolescents with systemic lupus erythematosus. Pediatr Int 2006;48:152–7.

[4] Yokota S. Mizoribine: mode of action and effects in clinical use. Pediatr Int 2002;44:196–8.

[5] Sugiyama K, Satoh H, Saito K, Takahashi K, Saito N, Hirano T. Immunosuppressive efficacy of mycophenolate mofetil when compared with azathioprine and mizoribine against peripheral lymphocytes from renal transplant recipients. Transpl Int 2005;18:590–5.

[6] Nakamura N, Mikami H, Matsuoka H, Irie S, Abe Y, Sasatomi Y, et al. Experiences of high-dose mizoribine as antimetabolite immunosuppressants for kidney transplantation. Transplant Proc 2012;44:150–3.

[7] Oshiro Y, Nakagawa K, Hoshinaga K, Aikawa A, Shishido S, Yoshida K, et al. A Japanese multicenter study of high-dose mizoribine combined with cyclosporine, basiliximab, and corticosteroid in renal transplantation (the fourth report). Transplant Proc 2013;45:1476–80.

[8] Yoshimura N, Ushigome H, Matsuyama M, Nobori S, Suzuki T, Sakai K, et al. The efficacy and safety of high-dose mizoribine in ABO-incompatible kidney transplantation using anti-CD20 and anti-CD25 antibody without splenectomy treatment. Transplant Proc 2012;44:140–3.

[9] Ju MK, Huh KH, Park KT, Kim SJ, Cho BH, Kim CD, et al. Mizoribine versus mycophenolate mofetil in combination therapy with tacrolimus for de novo kidney transplantation: evaluation of efficacy and safety. Transplant Proc 2013;45:1481–6.

[10] Tanabe K, Tokumoto T, Ishikawa N, Kanematsu A, Oshima T, Harano M, et al. Long-term results in mizoribine-treated renal transplant recipients: a prospective, randomized trial of mizoribine and azathioprine under cyclosporine-based immunosuppression. Transplant Proc 1999;31:2877–9.

[11] Xing S, Yang J, Zhang X, Zhou P. Comparative efficacy and safety of mizoribine with mycophenolate mofetil for Asian renal transplantation—a meta-analysis. Clin Biochem 2014;47:663–9.

[12] Shi Y, Liu H, Chen XG, Shen ZY. Comparison of mizoribine and mycophenolate mofetil with a tacrolimus-based immunosuppressive regimen in living-donor kidney transplantation recipients: a retrospective study in China. Transplant Proc 2017;49:26–31.

[13] Yuan X, Chen C, Zheng Y, Wang C. Conversion from mycophenolates to mizoribine is associated with lower BK virus load in kidney transplant recipients: a prospective study. Transplant Proc 2018;50:3356–60.