Hyperuricemia in Living Donor Kidney Transplantation Patients During Mizoribine Administration Caused Mainly by Changes in Kidney Function

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ABSTRACT

Background. Although mizoribine (MZR) is used as an immunosuppressant after renal transplantation, the occurrence of hyperuricemia has been reported. The onset of hyperuricemia is often observed within the first several months after surgery. Since MZR is a renal excretion-type drug excreted as an unchanged drug from the kidneys, MZR blood concentrations may rise due to the influence of renal function. We investigated whether the onset of hyperuricemia after MZR administration was associated with the direct effect of a change in renal function.

Methods. Serum uric acid (serum UA), serum creatinine (sCr), serum β2-microglobulin (serum β2-MG), and serum cystatin C (serum Cys-C) were measured for about 3 months in 22 subjects. Correlation coefficients were calculated using the change rates of serum UA and sCr (Δ serum UA, Δ sCr), serum UA and serum β2-MG (Δ serum UA, Δ serum β2-MG), and serum UA and serum Cys-C (Δ serum UA, Δ serum Cys-C) at the onset of hyperuricemia.

Results. The correlation coefficients between Δ serum UA and Δ sCr, Δ serum UA and Δ serum β2-MG, and Δ serum UA and Δ serum Cys-C were 0.723 ($P < .001$), 0.863 ($P < .001$) and 0.548 ($P < .001$), respectively. Further, serum UA and sCr level reached their highest peak on the same day after MZR administration, and the behavior was mostly consistent.

Conclusion. It was suggested that hyperuricemia occurred about 3 months after MZR administration due mainly to temporary changes in kidney function.

MIZORIBINE (MZR) is used in Japan, China, and Korea as an antirejection drug after renal transplantation in combination with steroids and a calcineurin inhibitor. MZR is reported to have fewer side effects of bone marrow depression, infections, and diarrhea compared to other immunosuppressants [1–6]. MZR exert their immunosuppressive effect by selectively inhibiting inosine monophosphate dehydrogenase in the de novo pathway of purine synthesis in lymphocytes, thereby inhibiting the proliferation of T and B lymphocytes [7–9].

Although mycophenolate mofetil also has the same pharmacological action as MZR [10,11], the incidence of hyperuricemia with MZR has been reported to be higher compared to mycophenolate mofetil [2,5,6]. However, there are some reports that the incidence of hyperuricemia is similar between the drugs [12–14], but many points remain unidentified. Since approximately two-thirds of uric acids are eliminated via the kidneys, blood uric acid concentrations are largely influenced by renal function. The onset of hyperuricemia after initiation of MZR administration is often observed within the first several months after surgery [15], and we have also frequently experienced elevation of uric acid level within 2 to 3 months postsurgery. On the other hand, MZR is a renal excretion-type drug excreted as

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Table 1. Clinical and Demographic Data for the Recipients and Donors

	MZR (n = 22)
Cause of uremia (%)	
Chronic glomerulonephritis	10 (45.5%)
IgA	7 (31.8)
NS	1 (4.5%)
Diabetic nephropathy	1 (4.5%)
Membranoproliferative glomerulonephritis	2 (9.1%)
Others	1 (4.5%)
Recipient sex (%)	
Male	20 (90.1%)
Female	2 (9.9%)
Recipient age, mean ± SD, years	30.4 ± 7.7
Recipient weight, mean ± SD, kg	67.0 ± 21.8
Pretransplant dialysis	22 (100%)
Duration of dialysis before transplantation, mean ± SD, months	18.3 ± 32.8
Donor sex (%)	
Male	8 (36.4%)
Female	14 (63.6%)
Donor age, mean ± SD, years	51.6 ± 6.5
Donor type (%)	
Father	7 (31.8%)
Mother	10 (45.5%)
Sibling	4 (18.2%)
Others	1 (4.5%)
HLA-AB mismatches (%)	
0	3 (13.6%)
1	6 (27.3%)
2	10 (45.5%)
3	3 (13.6%)
4	0 (0%)
HLA-DR mismatches (%)	
0	3 (13.6%)
1	19 (86.4%)
2	0 (0%)
ABO blood type (%)	
Identical	20 (90.9%)
Compatible	2 (9.1%)

Abbreviations: MZR, mizoribine; NS, nephric syndrome; SD, standard deviation.

an unchanged drug from the kidneys, and a change in renal function may cause an increase in MZR blood concentrations. Therefore, we examined whether the onset of hyperuricemia after administration of MZR was associated with the direct effect of a change in renal function or due to increased MZR blood concentrations. To find the answer to this question, we investigated whether MZR was related to increases in uric acid level by measuring uric acid level and several other renal function markers for as many days as possible for about 3 months after surgery.

MATERIALS AND METHODS

Subjects

This is a retrospective study of patients who underwent renal transplantation from January 2012 to March 2014 at the Institute of Liver Transplantation of General Hospital of Chinese People's Armed Police Force, received mizoribine (MZR, n = 22), and were able to be followed for 12 months or more. All patients were ABO-compatible living donor renal transplantation recipients and received tacrolimus as a calcineurin inhibitor. This study was conducted according to the Declaration of Helsinki. A review of the protocol was conducted by the hospital institutional review board (2016 General Hospital of Chinese People's Armed Police Force Institutional Review Board Approval No. 2016002), and written informed consent was obtained from all patients who participated in this study.

Immunosuppressive Protocol

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

Measurement of Renal Function Markers and Selection Criteria

We asked patients to visit the hospital as often as possible to collect numerous laboratory values for about 3 months after surgery once their uric acid level returned to nearly normal (observation period) and then measured serum uric acid (serum UA), serum creatinine (sCr), serum β2-microglobulin (serum β2-MG), and serum cystatin C (serum Cys C). Hyperuricemia is defined as a uric acid level greater than 417 μmol/L (7.0 mg/dL), which is the upper limit of normal at our institution.

The patient's inclusion selection criteria adapted to calculate the correlation coefficient was a subject who had uric acid level increased to 417 μmol/L or more after the uric acid level returned to nearly normal after surgery (for approximately 3 months; observation period). The exclusion criteria were 1. subjects whose uric acid level did not increase to 417 μmol/L or more during the observation period, 2. subjects whose uric acid level remained high at 417 μmol/L or more for 15 days or more after surgery (subjects with persistently abnormal renal function), and 3. subjects who had acute transplant rejection and were affected by the condition.

The Measurement Range When Calculating the Correlation Coefficient

The calculation range of the calculation of the correlation coefficient is the peak (measurement day after surgery) in which the uric acid level has risen to 417 μmol/L (7.0 mg/dL) or more and the peaks before and after (uric acid level was 417 μmol/L or less). At least 3 ranges were taken. Also, we used the measurement day included within that range as much as possible. For example, when A to D exist in the measurement range of a certain patient meeting the selection criteria A: The level just before the uric acid value rises to 417 μmol/L or more (serum UA is 417 μmol/L or less); B: The serum uric acid peak value is 417 μmol/L or more; C: A level of serum uric acid lower than B but still a serum UA level of 417

μmol/L or more; and D: Uric acid value reduced to less than 417 μmol/L, the rate of change for serum UA at points A to D were calculated. The equation is shown below.

$$\text{A:}\frac{A}{(A+D)/2}\times 100 \quad \text{B:}\frac{B}{(A+D)/2}\times 100$$

$$\text{C:}\frac{C}{(A+D)/2}\times 100 \quad \text{D:}\frac{D}{(A+D)/2}\times 100$$

Using the same time interval used to calculate Δ serum UA, the change rates in other renal function (Δ sCr, Δ serum β2-MG, and Δ serum Cys-C) were also calculated. From these change rates, the correlation coefficients of Δ serum UA with Δ sCr, Δ serum β2-MG, and Δ serum Cys-C were calculated.

Subjects in Which the Behavior of Uric Acid and sCr Values Were Consistent With Each Other

Patients with a positive correlation between the change rate of the uric acid level and sCr level at the same measurement date in the calculation range of these correlation coefficients and having correlation coefficients of 0.7 or more obtained from the ratio of the change rates of both (the rate of change of serum UA/change rate of sCr on the same measurement day) were defined as subject where the behavior of uric acid level and sCr level coincided with each other.

Statistical Analyses

The data are presented as means ± standard deviations or percentages. Statistical analyses were performed with IBM SPSS Statistics (Version 19.0, Armonk, NY, United States). Correlation was tested using Pearson's correlation coefficient. All tests were 2-sided, and a P value of $<.05$ was considered statistically significant.

RESULTS

Baseline characteristics of the subjects who received mizoribine (MZR, n = 22) are shown in Table 1. The number of subjects included in the calculation of correlation coefficients was 11 out of 22. Some subjects developed hyperuricemia at 2 places points during the observation period (2 subjects). Among the subjects excluded, 6, 3, and 2 subjects, respectively, met exclusion criteria 1, 2, and 3. The change rates at 13 places points (11 subjects) were calculated by the method described in "The measurement range when calculating the correlation coefficient and correlation coefficient" in the Materials and Methods section. Since a normal distribution was confirmed based on all the change rates in each renal function markers including serum UA, Pearson's correlation coefficient was used to calculate the correlation coefficients.

The correlation coefficients between Δ serum UA and Δ sCr, Δ serum UA and Δ serum β2-MG, and Δ serum UA and

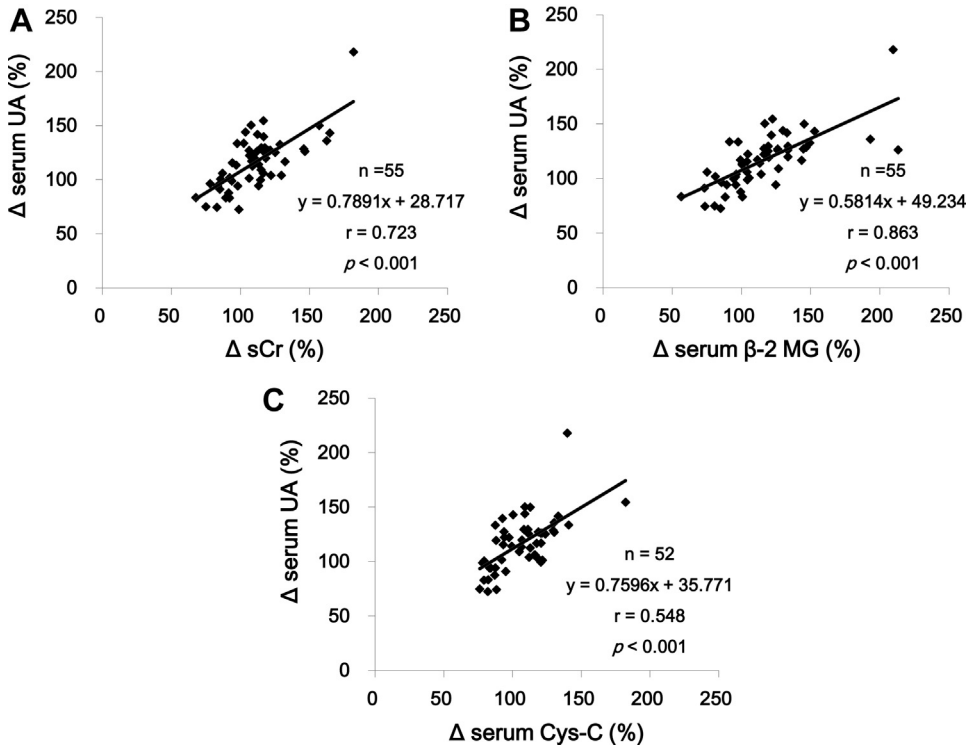

Fig 1. Correlations of serum uric acid with serum creatinine, serum β2-microglobulin, and serum cystatin C. Change rates in serum uric acid, serum creatinine, serum β2-microglobulin, and serum cystatin C (Δ serum UA, Δ sCr, Δ serum β2-MG, and Δ serum Cys-C) were calculated. Then, correlation coefficients of Δ serum UA with Δ sCr **(A)**, Δ serum β2-MG **(B)**, and Δ serum Cys-C **(C)** were calculated based on the change rates above. Change rates and the calculation method: see "Observation time points used to calculate correlation coefficients" in the Materials and Methods section. Abbreviation: MZR, mizoribine.

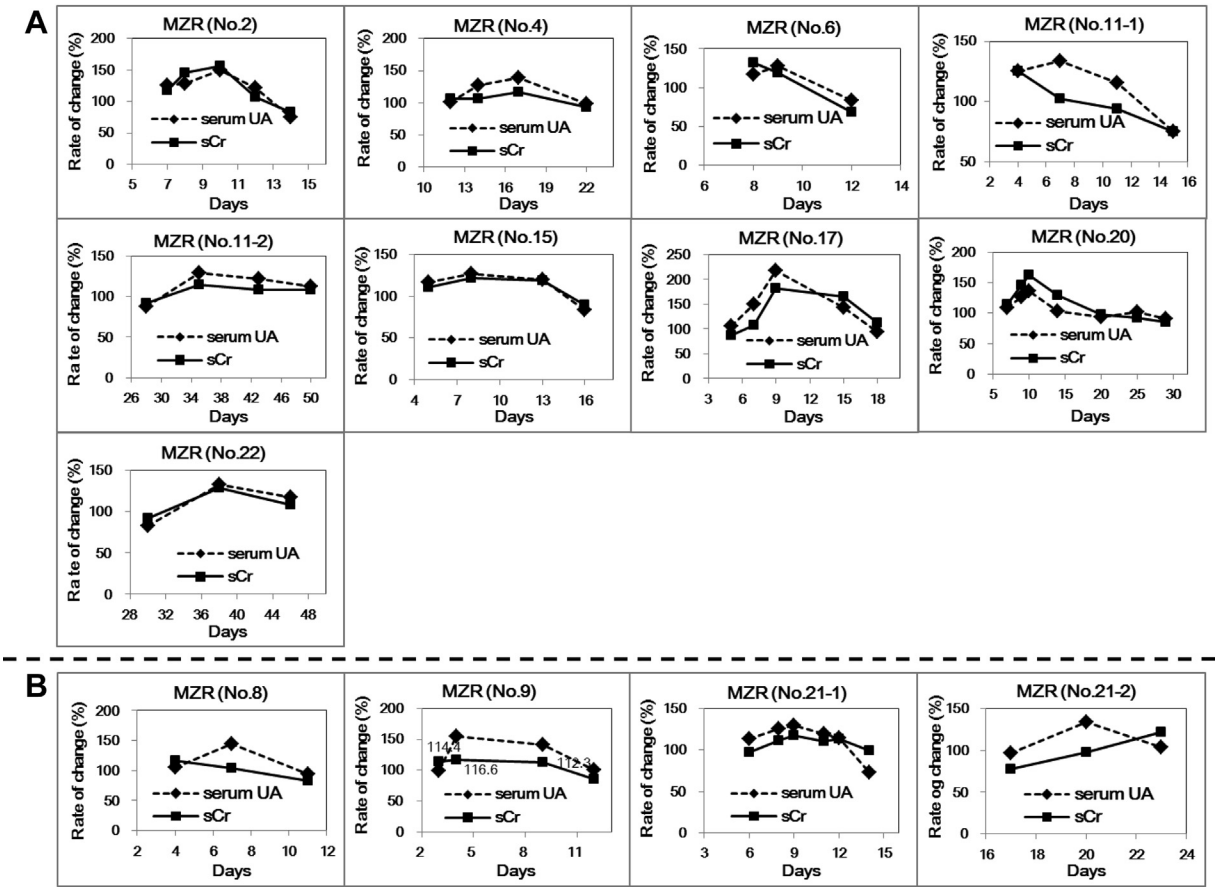

Fig 2. Subjects in which behavior of uric acid and sCr level were consistent **(A)** and those in which behavior of uric acid and sCr level were inconsistent **(B)**. Abbreviations: MZR, mizoribine; sCr, serum creatinine; serum UA, serum uric acid.

Δ serum Cys-C were 0.723 ($P < .001$), 0.863 ($P < .001$) and 0.548 ($P < .001$), respectively, indicating a correlation between serum UA and other renal function markers (Fig 1).

T_{sCrmax} (the day when sCr reached the maximum level) and T_{UAmax} (the day when serum UA reached the maximum level) were also examined for the time points used for the calculation of the correlation coefficients. They were consistent with each other at 9 out of 13 places points (Fig 2).

DISCUSSION

A positive linear correlation was found between Δ serum UA and Δ sCr. In addition, positive linear relationships were observed for correlation coefficients between Δ serum UA and Δ serum β2-MG and between Δ serum UA and Δ serum Cys-C. These results suggest that changes in serum UA during the observation period (about 3 months after surgery) may be primarily related to transient changes in renal function. The sCr and uric acid level of many subjects exhibited consistent behavior in that those laboratory values reached a peak on the same day and the behavior of the measurement values before and after a peak were comparable. Consequently, most of the increases in uric acid level were presumed to be due to changes in the ability of uric acid excretion with fluctuations in renal function.

On the other hand, MZR is a renal excretion-type drug excreted as an unchanged drug from the kidneys; therefore, the elevation of uric acid level may be caused by the effect of renal function which leads to increases in MZR blood concentrations. However, when MZR was administered to patients who underwent kidney transplantation, an approximately 2-fold difference in the volume of distribution values measured in the same patient were observed in 2 out of 6 patients (volume of distribution may reflect the absorption rate) [16]. This suggests that day-to-day fluctuation of absorption in intraindividual measurements is not necessarily small and the time-dependent fluctuation rate of renal function may not always reflect MZR blood concentrations directly. Also, when uric acid production increases due to an elevated blood concentration of MZR, sCr rise occurs beforehand, the blood concentration of MZR rises, followed by an increase in uric acid level. Therefore, lag time may occur between sCr and uric acid level (MZR exerts its immunosuppressive effect by selectively inhibiting inosine monophosphate dehydrogenase in the de novo pathway of purine synthesis) [7–9]. Therefore, lag time may

appear between sCr and uric acid values. However, since the behavior of the sCr and uric acid values were consistent in most subjects, it was considered that the change in MZR blood concentrations was unlikely to be associated with increases in uric acid level.

Furthermore, MZR blood concentrations may increase with the elevation of the dose of MZR. When MZR was administered to healthy volunteers at a dose of 12 mg/kg, slight increases in uric acid level were observed. Uric acid level was not increased in the MZR 6 mg/kg group compared to the placebo group [17]. Since MZR was administered at a dose of 3 mg/kg in this study, it was considered that the uric acid level was unlikely to be increased depending on the dose. However, when the renal function is extremely low, there is a possibility that serum UA elevation may be related to similarly to that observed at 12 mg/kg of healthy subjects due to extremely high blood concentration of MZR.

One of the limitations in this study was a potential bias in the subject characteristics because only patients in Beijing were included in the study. Kidney transplant patients usually visit the hospital once a month after hospitalization (approximately 15 days). By including only patients living in Beijing, subjects were more likely to make themselves available more frequently for follow-up study visits at our institution. Another limitation was a potential bias due to the small sample size as the study was performed in a single center.

In conclusion, it was suggested that, among elevated uric acid level observed after MZR administration as an antirejection therapy for renal transplantation, if administered at the standard dose, the hyperuricemia occurring up to about 3 months after surgery once the sCr level returned to nearly normal was not caused mainly by MZR administration but by changes in uric acid excretion capacity in the temporary kidney.

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