Hyperuricemia and Acute Renal Failure in Renal Transplant Recipients Treated With High-Dose Mizoribine

K. Akioka*, T. Ishikawa, M. Osaka, Y. Kadotani, K. Okugawa, K. Nakano, Y. Osaka, K. Tsuchiya, and H. Sako

Surgery, Omihachiman Community Medical Center, Omihachiman, Japan

ABSTRACT

Background. Hyperuricemia is a common adverse event frequently found in renal transplant recipients with mizoribine (MZ). Hyperuricemia itself will be a cause of renal dysfunction, and renal dysfunction also will be a cause of hyperuricemia simultaneously. This study investigates frequency of hyperuricemia and renal failure in renal transplant recipients treated with high-dose MZ.

Patients and Methods. From December 2007 to October 2015, there was a total of 32 living related renal transplant recipients treated with high-dose MZ. Of the 32 patients, 28 were treated with urate-lowering medications.

Results. One patient received allopurinol (AP) and 13 patients received benzbromarone (BB). For 6 of them, their urate-lowering medications were converted to febuxostat (FX) form AP or BB. In the remaining 14 patients, FX was administered from the beginning. In 2 cases of ABO-incompatible living related renal transplant recipients who were maintained with high-dose MZ and BB, severe hyperuricemia and acute renal failure occurred. One patient was a 48-year-old man, and his creatinine (Cr) level increased to 8.14 mg/dL and his serum uric acid (UA) was 24.6 mg/dL. Another patient was a 57-year-old man, and his Cr level increased to 3.59 mg/dL and his UA was 13.2 mg/dL. In both cases Cr and UA were improved, and no finding of acute rejection and drug toxicity was observed in graft biopsy specimens. BB was switched to FX and discontinuance or reduction of MZ was done.

Conclusion. Combination of MZ and BB has the risk of acute renal dysfunction after renal transplantation. Latent renal dysfunction should be watched for in renal transplant recipients receiving high-dose MZ.

MIZORIBINE (MZ), which was developed and used in Japan, is one of the anti-metabolite agents for immunosuppression. The mechanism of immunosuppression of MZ and mycophenolate mofetil (MMF) are the same, however, the effect of MZ, which is administered at 2–3 mg/kg as the normal dose, might be insufficient. To obtain the efficacy of MZ similar to MMF, high-dose MZ (6 mg/kg) was administered. High-dose MZ is as effective as MMF for induction and maintenance of immunosuppression of renal transplants. Hyperuricemia is a common adverse event frequently found in renal transplant recipients with MZ. Hyperuricemia itself can be a cause of renal dysfunction or renal failure, and renal dysfunction also can be a cause of hyperuricemia simultaneously. This study investigates the frequency of hyperuricemia and renal failure in renal transplant recipients treated with high-dose MZ.

PATIENTS AND METHODS

From December 2007 to October 2015, a total of 32 renal transplant recipients treated with high-dose MZ were enrolled in this study. Morphological characteristics of the recipients were as follows: age, 24 ~ 68 years (47.6 ± 13.0); male:female, 21:11; observation period,

*Address correspondence to Kiyokazu Akioka, Omihachiman Community Medical Center, 1379 Tsuchida-cho, 523-0082 Omihachiman, Japan. E-mail: kakioka@koto.kpu-m.ac.jp

0041-1345/16
http://dx.doi.org/10.1016/j.transproceed.2016.11.015

Table 1. Summary of Age, Gender, and Relationship of 32 Recipients and Donors and Pretransplantation and Post-transplantation Urate Level and Urate-Lowering Medication

Case No.	Recipient Age/Sex	Disease	Donor Age/Sex/Relation	Pre Transplant UA	Pre Transplant Anti-UA Medication	Post Transplant UA	Post Transplant Anti-UA Medication
1*	43 F	Nephrosis	49 F, sister	6.9	0	6.6	0
3	61 M	CGN	32M, son	7.3	0	11	BB-FX
4	65 F	CGN	67 M, husband	5.5	0	9.1	BB
6	68 M	CGN	59 F, wife	5.4	AP	8.8	BB
7	45 F	NIDDM	42 F, sister	6.9	0	9.2	BB
8	48 F	NIDDM	44M, brother	8	0	8	BB-FX
9	63 M	CGN	61F, wife	8	0	8	BB
10	35 M	CGN	65 F, mother	10.2	0	8.3	BB
12	65 M	NIDDM	27 M, nephew	5.6	AP	11.4	BB-FX
14	31 M	CGN	56F, mother	8.2	0	12.3	BB-FX
15	47 F	CGN	50 F, sister	9.3	0	8.2	BB
18	57 M	CAN	58 F, wife	8.7	0	9.8	BB-FX
19	48 M	intN	76 M, father	10.3	0	9.5	BB-FX
20	50 F	CGN	52 M, husband	5.4	0	7.4	BB
21	46 M	NIDDM	69 F, mother	6.7	0	9.3	AP-FX
23	34 M	CAN	64 M, father	9.1	0	11.4	FX
24	24 M	RefluxN	57 M, father	4.5	0	9.3	FX
25	26 M	IgA	49 M, father	8.4	0	9.4	FX
26	65 F	CGN	62 M, husband	5.3	0	10.2	FX
28	31 F	RPGN	59 F, mother	7	0	8.1	FX
30	44 M	NIDDM	69 F, mother	8.1	0	7.1	FX
31*	54 F	RPGN	59 F, sister	4.2	0	4.7	0
32	34 M	NS	37 F, sister	5.1	0	8.1	FX
34*	61 F	IgA	70 F, sister	7.9	0	7	0
35	41 M	CGN	42 F, sister	6.7	FX	8.4	FX
37*	29 M	CGN	57 F, mother	4.5	FX	5.7	0
40	50 F	intN	52 M, husband	4.8	FX	8.4	FX
41	27 M	intN	60 F, mother	5.8	AP	7.3	FX
44	49 M	PKD	49 F, wife	5.6	FX	9.2	FX
46	63 M	CGN	58 F, wife	5.7	AP	9.3	FX
48	44 M	NIDDM	46 F, sister	10.7	0	8.9	FX
49	67 M	NIDDM	58 F, wife	7.1	FX	7.3	FX

Abbreviations: F, female; M, male; CGN, chronic glomerular nephritis; NIDDM, non–insulin-dependant diabetes mellitus; CAN, chronic allograft nephropathy; intN, interstitial nephritis.
*Patients with asterisk, Case No. 1, 31, 34 and 37 were non-post transplant hyperuricemic recipients.

6.6–100.1 months (48.8 ± 25.2); donor types, spouses 10, parents 11, siblings 9, and others 2; ABO compatibility, compatible 19, different 5, and incompatible 8; immunosuppression regimens, cyclosporine (CsA) + MZ + prednisolone (PSL) + basiliximab (Anti-CD25Ab 14), tacrolimus (Tac) + MZ + PSL + Anti-CD25Ab 5, CsA + MZ + everolimus (EVR) + PSL + Anti-CD25Ab 2, Tac + MZ + EVR + PSL + Anti-CD25Ab 3, CsA + MZ + PSL + Anti-CD25 Ab + Anti-CD20 Ab + double filtration plasma pheresis (DFPP), plasma exchange (PE) 6, Tac + MZ + PSL + Anti-CD25 Ab + Anti-CD20 Ab + DFPP, PE 2. All patients had living related renal transplants. Two of them had second renal transplants.

Urate-lowering drugs were administered when uric acid (UA) level was ≥7.0 mg/dL. Twenty-eight of the 32 patients were treated with urate-lowering medications, namely, allopurinol (AP), benzbromarone (BB), or febuxostat (FX). Frequency of hyperuricemia and renal failure, treatment of hyperuricemia, and post-transplantation course were observed.

RESULTS

Hyperuricemia was observed in 28 of 32 patients, at the rate of 87.5%. Medications for hyperuricemia were varied. One patient was treated with AP and 13 patients were treated with BB. Six of them had their urate-lowering medications converted to FX form AP or BB. In the remaining 14

Table 2. Morphological Status of Recipients With Post-transplantation Hyperuricemia Group and Non-hyperuricemia Group and Incidence of Pretransplantation Hyperuricemia in Both Groups

Post Transplant UA ≥7.0 mg/dl and/or Post Transplant Anti-UA Drug (+) n = 28		
Recipient age	24 ~ 68 yo (47.6 ± 13.1)	Sex, M:F 20:8
Donor age	60 ~ 76 yo (53.6 ± 11.7)	Sex, M:F 7:21
Relationship of Donor spouses 10, parents 10, siblings 6, others 2		
Pre-transplant urate lowering medicine or UA ≥7.0 mg/dl n = 22 78.6%		
Post Transplant UA <7.0 mg/dl and Post Transplat Anti-UA Drug (–) n = 4		
Recipient age	29 ~ 61 yo (46.8 ± 12.1)	Sex, M:F 1:3
Donor age	57 ~ 70 yo (58.8 ± 8.7)	Sex, M:F 0:4
Relationship of Donor spouses 0, parents 1, siblings 3, others 0		
Pre-transplant urate lowering medicine and/or UA ≥7.0 mg/dl n = 1 25.0%		

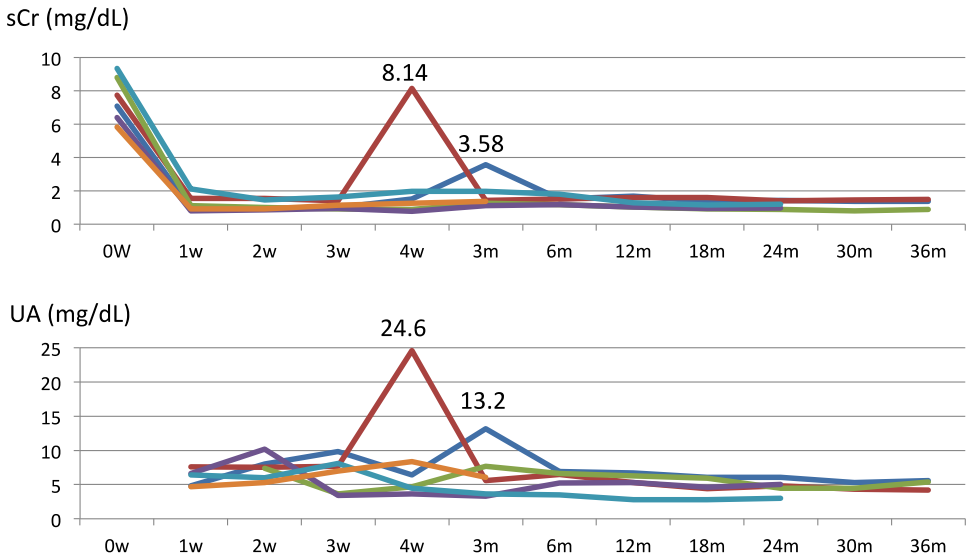

Fig 1. Serum creatine (sCr) and UA of ABO-incompatible renal transplant recipients are shown. Two of 6 recipients showed transient hyperuricemia and increase of sCr levels at postoperative 4 weeks and postoperative 3 months, respectively. Both patients received BB for the treatment of hyperuricemia, resulting in the concomitant elevation of UA and sCr levels. Their symptoms were improved after switching BB to FX. The increase in UA and sCr was reversible.

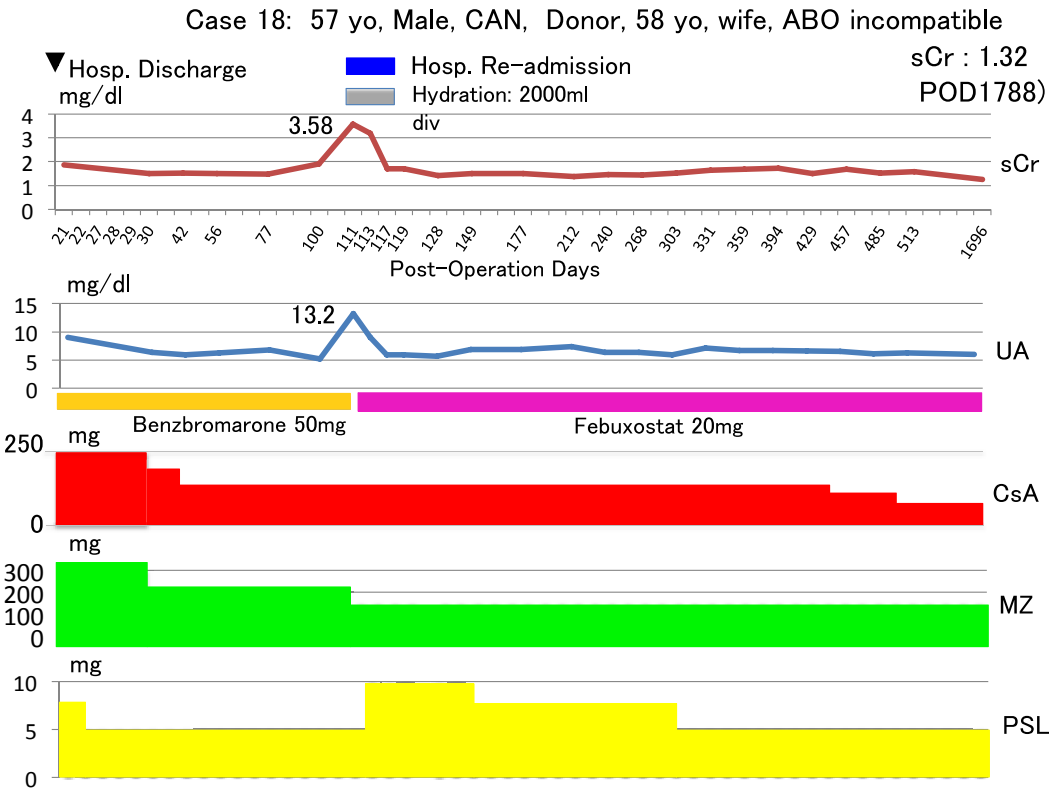

Fig 2. A 57-year-old man received an ABO-incompatible renal transplant from his 58-year-old wife. He had acute renal dysfunction, his sCr level was 3.58 mg/dL, and his UA was 13.2 mg/dL at 3 months after the transplantation.

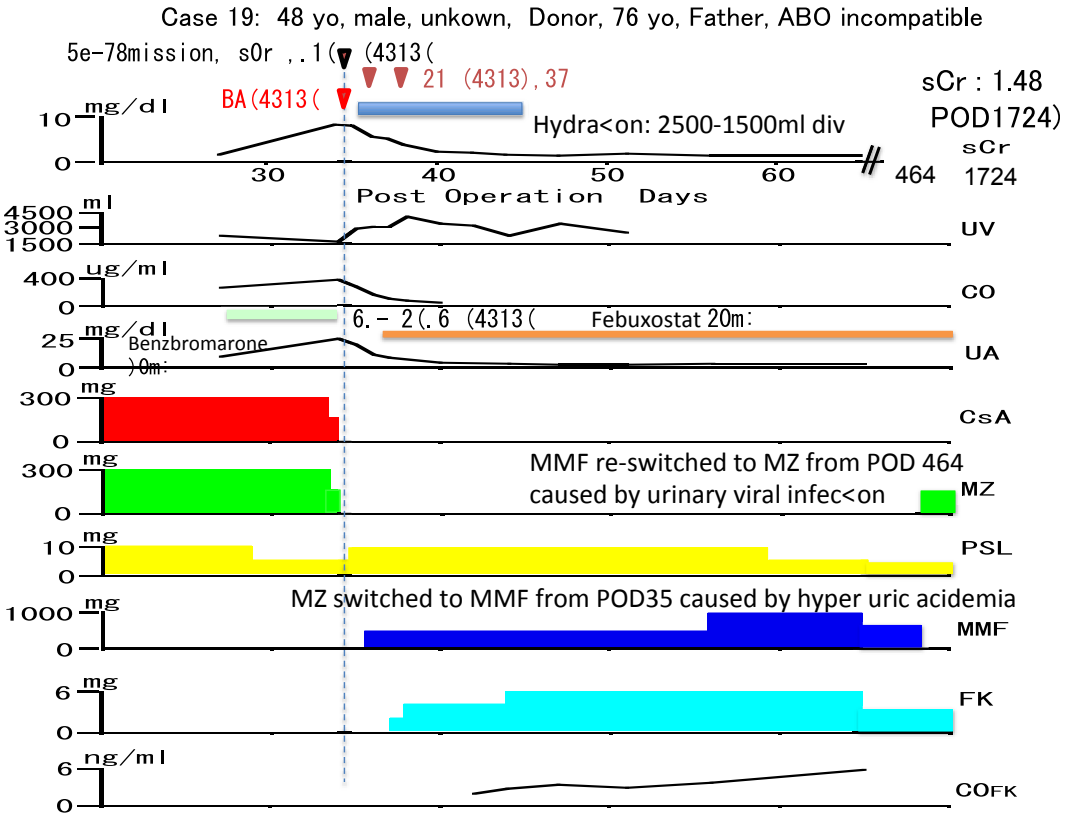

Fig 3. A 48-year-old man received an ABO-incompatible renal transplant from his 76-year-old father. He had acute renal dysfunction, his sCr level was 8.14 mg/dL, and his UA was 24.3 mg/dL on day 34 after transplantation. Switching of MZ to MMF and BB to FX was done, and his sCr level and UA recovered.

patients, FX was administered from the beginning without a history of other medications. Twenty-two of 28 post-transplantation hyprerurice mic recipients had past histories of pretransplantation hyperuricemia and/or UA-lowering medicine. Only 1 of 4 non–post-transplantation hyperuricemic recipients had a history of pretransplantation hyperuricemia. In Tables 1 and 2, characteristics of all 32 cases are summarized; pretransplantation and post-transplantation urate levels of recipients and urate-lowering medications are also summarized.

Especially in 2 ABO-incompatible living related renal transplant recipients maintained with high-dose MZ and BB, they had severe hyperuricemia and acute renal failure (Fig 1). Two recipients showed a transient severe hyperuricemia and an increase of serum creatinine (sCr) levels at 1 month or 3 months after transplantation, respectively. One patient was a 48-year-old man, and his Cr level increased to 8.14 mg/dL and his serum uric acid (UA) was 24.6 mg/dL. Hemodialysis was done for reduction of UA (Fig 2). Another patient was a 57-year-old man, and his Cr level increased to 3.59 mg/dL and his UA was 13.2 mg/dL (Fig 3). In both cases, no finding of acute rejection or drug toxicity was observed in graft biopsy specimens. BB was switched to FX and discontinuance or reduction of MZ was done. FX was effective enough to treat severe hyperuricemia.

DISCUSSION

It is reported that high-dose MZ is effective for maintenance of immunosuppression for ABO-compatible, different, and -incompatible kidney transplants [1–3]. Multi-center studies of high-dose MZ for kidney transplantations have been done, and hyperuricemia was a common adverse event frequently observed. Frequencies of hyperuricemia in those studies were 32.0%–61.1% [4]. In our center, 28 of 32 recipients were treated with UA- lowering medication after transplantation, and the rate of hyperuricemia after high-dose MZ was 87.5%. There was no difference in morphological status between recipients with hyperuricemia and without hyperuricemia as shown in Tables 1 and 2.

Pretransplantation hyperuricemia and/or medication for hyperuricemia had severely affected the incidence of post-transplantation hyperuricemia.

We previously reported a case of hyperuricemia and acute renal failure in an ABO-incompatible kidney transplant recipient treated with high-dose MZ [5]. In that case,

the donor was a marginally appropriately aged donor, therefore, the graft function might be relatively so poor that it might be a cause of elevations of UA and sCr in simultaneous ways. In another new case, the donor was a normally appropriate donor who did not have a risk of hypo-renal function such as an aged donor. However, even in a normally appropriate donor, transient deterioration of renal function would lead to a decrease in UA excretion, which would be a cause of hyperuricemia. In renal transplant recipients, tiny events, such as dehydration and hypotension, would be a cause of a transient decrease of renal function. The second case had a history of a dehydration episode, which would be a cause of the series of hyperuricemia and increase of Cr in simultaneous way. Some reports mentioned that hyperuricemia contributes to deterioration of the glomerular filtration rate in renal transplantation [6,7]. Mechanism of BB is accelerating for excretion of UA in the patients with appropriate renal function, and the excretion of UA might be poor in the patients with relatively hypo graft function. High-dose MZ would induce hyperuricemia at a very high rate, so it would lead to a relatively hypo graft function. The combination of high-dose MZ and BB was a relative risk factor for hyperuricemia and acute renal failure after renal transplantation. It was important for post–renal transplantation patients to choose the combination of anti-metabolite agents and urate-lowering agents. Treatment with FX was effective enough to recover their renal functions. It is reported that FX sufficiently lowered UA levels without severe adverse effects in transplant recipients with post-transplantation hyperuricemia [8].

In conclusion, hyperuricemia was observed in more than 80% of renal transplant recipients treated with high-dose MZ. The combination of high-dose MZ and BB was a risk factor for acute renal dysfunction after renal transplantation. Renal dysfunction might be a cause of hyperuricemia, following an aggravation of renal dysfunction. Latent renal dysfunction should be watched for in renal transplant recipients with high-dose MZ.

REFERENCES

[1] Nishimura K, Uchida K, Yuzawa K, et al. Excellent results with high-dose mizoribine combined with cyclosporine, corticosteroid, and basiliximab in renal transplant recipients: multicenter study in Japan. Transplant Proc 2012;44:147.

[2] Yoshimura N, Ushigome H, Matsuyama M, 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] Yoshimura N, Nakao T, Nakamura T, et al. Effectiveness of the combination of everolimus and tacrolimus with high dosage of mizoribine for living donor-related kidney transplantation. Transplant Proc 2016;48:786.

[4] Ushigome H, Uchida K, Nishimura K, et al. Efficacy and safety of high-dose mizoribine combined with cyclosporine, basiliximab, and corticosteroids in renal transplantation: a Japanese multicenter study. Transplant Proc 2016;48:794.

[5] Akioka K, Masuda K, Harada S, et al. Acute renal failure caused by hyperuremic acidemia in ABO-incompatible kidney transplant maintained with cyclosporine and high-dose mizoribine: a case report. Transplant Proc 2013;45:2815.

[6] Kim KM, Kim SS, Yun S, et al. Uric acid contributes to glomerular filtration rate deterioration in renal transplantation. Nephron Clin Pract 2011;118:136.

[7] Huang Y, Li YL, Huang H, et al. Effects of hyperuricemia on renal function of renal transplant recipients: a systematic review and meta-analysis of cohort studies. PLoS One 2012;7:e39457.

[8] Sofue T, Inui M, Hara T, et al. Efficacy and safety of febuxostat in the treatment of hyperuricemia in stable kidney transplant recipients. Drug Des Devel Ther 2012;8:245.