Conversion From Mycophenolates to Mizoribine Is Associated With Lower BK Virus Load in Kidney Transplant Recipients: A Prospective Study

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ABSTRACT

Background. BK virus allograft nephropathy (BKVAN) is a graft-threatening complication after kidney transplantation. Current consensus regarding the prevention of BKVAN is to screen for BK viremia and to treat sustained BK viremia through reducing immunosuppression. This study assessed the effect of conversion from mycophenolates to mizoribine (MZR) on the prevention of BK viremia in kidney transplant recipients.

Methods. De novo kidney transplant recipients were screened for BK viruria. Sustained high levels of BK viruria ($>10^7$ copies/mL) were treated by switching from mycophenolates to MZR. The reduction and clearance of BK viruria and viremia were evaluated.

Results. Fifty kidney transplant recipients with high levels BK viruria were enrolled, including 11 recipients with BK viremia. After 6 months of MZR therapy, only 3 recipients still had high levels of BK viruria. The clearance rate of BK viremia was 100%. One episode of acute rejection occurred (2.0%) and was reversed by steroid administration. The serum uric acid level of the recipients was similar before and after switching to MZR, but the proportion of recipients receiving uric acid–reducing drugs increased significantly after 3 months of MZR therapy (19/50 vs 31/50; $P = .02$). No new cases of BK viremia were observed after conversion to MZR.

Conclusion. Conversion from mycophenolates to MZR in kidney transplant recipients with sustained high levels of BK viruria was associated with reduction of BK viruria and clearance of BK viremia. This may be an effective approach to prevent BK viremia and BKVAN.

BK VIRUS (BKV) allograft nephropathy (BKVAN) is a graft-threatening complication after kidney transplantation [1]. Reactivation of the BKV in the transplanted kidney can lead to BKVAN in up to 10% of kidney transplant recipients [2]. The BKV may reactivate under intense immunosuppressive conditions after kidney transplantation and produce progressive disease through 3 stages: viruria, viremia, and BKVAN. Sustained viremia has been reported to correlate with BKVAN, and once BKVAN develops, graft loss has been estimated to occur in 50% of transplant recipients [3,4]. The current consensus regarding prevention of BKVAN is to screen for BK viremia and to treat sustained BKV plasma loads through reducing immunosuppression [1]. However, screening for BK viremia reduces but does not eliminate the risk of BKVAN [5]. Even with successful management of BKVAN, the treatment is associated with an increased allograft loss rate [6]. Although BK viremia is more predictive of BKVAN development compared with BK viruria, several studies have demonstrated that BK viruria is correlated with BK viremia [7,8] and allograft dysfunction [9,10]. Therefore, methods to prevent BK viremia are needed [5]. It has not been

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determined whether or not pre-emptive treatment of BK viruria can prevent viremia.

Mizoribine (MZR), an imidazole nucleoside analog isolated from the mold *Eupenicillium brefeldianum*, is an immunosuppressive agent used for kidney transplantation, autoimmune diseases, and steroid-resistant nephrotic syndrome in Japan, China, and South Korea [11–14]. MZR blocks inosine 5-monophosphate dehydrogenase in the same manner as mycophenolate. The chemical structure of MZR is similar to that of ribavirin, a well-known antiviral agent [15]. It was also reported that MZR can inhibit the replication of some DNA and RNA viruses, including cytomegalovirus (CMV), hepatitis C virus, respiratory syncytial virus, bovine viral diarrhea virus, and influenza virus types A and B [15–19]. In addition, a previous study suggested an inhibitory effect of MZR on BKV [20]. Therefore, the aim of the current study was to determine the effect of conversion from mycophenolates to MZR in kidney transplant recipients with high levels of BK viruria for the prevention of BK viremia.

PATIENTS AND METHODS

Patients and Conversion Protocol

From July 2014 to October 2016, 216 kidney transplants were performed at our center (Organ Transplant Center, First Affiliated Hospital of Sun Yat-sen University). Fifty recipients were enrolled for switching from mycophenolate mofetil (MMF) or mycophenolate sodium (MPS) to MZR. Inclusion criteria were ≥18 years old; maintenance immunosuppression consisted of tacrolimus, MMF or MPS, and prednisone; serum creatinine level <150 μmol/L; and sustained high-level BK viruria (defined as the occurrence of 2 or more consecutive positive urine samples with BKV DNA > 10^7 copies/mL). Recipients who experienced an episode of acute rejection were excluded. The study was approved by our local institution ethnics committee and was conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent before entering the study.

Conversion Protocol

MMF or MPS was discontinued. The initial dosage of MZR was 5 mg/kg/d (≤3 months posttransplant) or 3 mg/kg/d (>3 months posttransplant), divided into 2 daily doses, with a goal to maintain a target 12-hour trough level >1000 ng/mL for the first 3 months and 500 to 1000 ng/mL after 3 months.

Baseline Immunosuppressive Regimen

All patients received induction therapy with 3 methylprednisolone pulses (3 × 500 mg). The majority of the recipients received rabbit antithymocyte globulin (Thymoglobulin), 1.5 mg/kg/d up to 7 days (range, 3–7 days). The first dose of rabbit antithymocyte globulin (Thymoglobulin) was given intraoperatively. Subsequent maintenance immunosuppression consisted of prednisone 20 mg/d with a taper to 5 mg/d by 1 month posttransplant, MMF 1000 mg twice daily with a taper to 500 mg twice daily by 3 months, and tacrolimus to maintain a target 12-hour trough level of 7 to 10 ng/mL for the first 3 months, 6 to 8 ng/mL for months 3 to 6, and 5 to 7 ng/mL after 6 months. When the enteric-coated formulation of MPS was used, the dose was 720 mg twice daily, with a taper to 360 mg twice daily by 3 months.

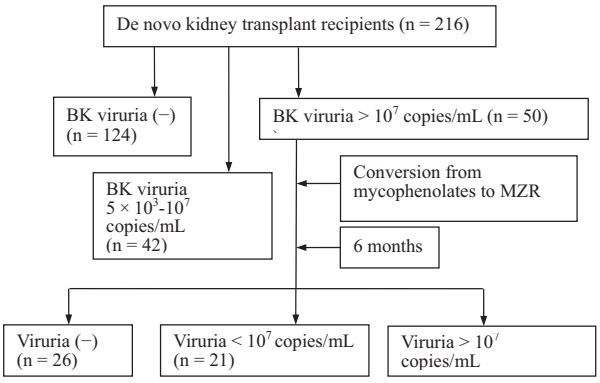

Fig 1. Flow diagram of BKV therapy with mizoribine (MZR).

BKV Quantitative Measurement and Screening Protocol

Quantification of the urine or serum BKV load was performed by quantitative PCR (MJ Research, Waltham, Mass, United States) according to the method we previously described [21,22]. The urine or serum BKV load was expressed in BKV genome copies/mL of urine or serum. The lower limit of quantitation was 1000 copies/mL. High-level viruria was defined as urine BKV DNA > 10^7 copies/mL, and high level viremia was defined as plasma BKV DNA > 10^4 copies/mL [1]. Patients were screened for BKV replication in urine biweekly for the first 3 months, then monthly until month 12, then every 3 months until 2 years posttransplant. Monthly plasma testing for BKV viremia was performed for the first 12 months, then every 3 months until 2 years posttransplant [23].

Measurement of MZR Trough Level

MZR trough level was measured by high-performance liquid chromatography as we have previously described [24].

Diagnosis of BKVAN

BKVAN was defined by the typical viral cytopathic changes and confirmed by positive immunohistochemical nuclear staining with the anti-BKV large T antigen monoclonal antibody as previously described [25]. Histologic patterns of BKVAN were defined according to the consensus conference on BKVAN [1]. Acute rejection was defined by the Banff criteria [26].

Statistical Analysis

Results were expressed as numerical values and percentages for categorical variables and as mean (SD) deviation for continuous variables. Statistical analyses were performed with IBM SPSS software, version 19.0 (Armonk, NY, United States). Comparisons were based on the χ^2 test for categorical data and the t test for paired continuous data. All statistical analyses were 2-sided. A P value < .05 was considered statistically significant.

RESULTS

Characteristics of Donors and Patients

As shown in Fig 1, 216 patients were screened for BKV in urine and serum before study enrollment. Fifty patients fulfilled the inclusion criteria. The mean (SD) time from kidney transplantation to enrollment was 3.4 (2.2) months (range, 1–7 months; median, 3.0 months). Before switching,

Table 1. Donor, Recipient, and Transplantation Data

Recipients (n = 50)	
Sex (male/female), n	33/17
Age, mean (SD), y	41.5 (9.7)
Diabetes mellitus, n (%)	6 (12)
Retransplant, n (%)	4 (8)
PRA > 10%, n (%)	6 (12)
Donors	
Sex (male/female), n	43/7
Age, mean (SD), y	28.0 (14.5)
Donor type (%) (DBD/DCD)	42/8
Transplantation	
HLA mismatch, mean (SD), n	2.7 (1.3)
Cold ischemia time, mean (SD), h	12.5 (3.4)
Delayed graft function, n (%)	6 (12)
Double J stent	50 (100)
Induction therapy	
Rabbit antithymocyte globulin (Thymoglobulin), n (%)	48 (96)
Basiliximab, n (%)	2 (4)
Immunosuppression at discharge	
Tacrolimus, MMF, prednisone, n (%)	32 (64)
Tacrolimus, MPS, prednisone, n (%)	18 (36)

Abbreviations: DBD, donation after brain death; DCD, donation after cardiac death; MMF, mycophenolate mofetil; MPS, mycophenolic sodium; PRA, panel-reactive antibodies.

all patients received triple immunosuppression with tacrolimus, mycophenolates (MMF, n = 32; MPS, n = 18), and prednisone. The majority of the patients received induction therapy with rabbit antithymocyte globulin (Thymoglobulin) (Table 1).

Virus Loads

As shown in Table 2, 47 patients (94%) showed reduction of BK viruria to a level of $< 10^7$ copies/mL after 6 months of MZR. The percentage of patients showing high levels of BK viruria at 1, 3, and 6 months after conversion was 64%, 18%, and 6%, respectively. The rate of BK viruria clearance at 1, 3, and 6 months after conversion was 6%, 52%, and 52%, respectively.

Eleven patients showed sustained positive BK viremia (defined as the occurrence of 2 or more consecutive positive serum samples), 7 patients (64%) exhibited high level viremia (5.3×10^7 [9.9×10^7] copies/mL), and the other 4 patients exhibited low level viremia (6.2×10^3 [2.7×10^3] copies/mL). Ten (91%) patients showed viremia clearance at 1 month after conversion. The rate of BK viremia clearance reached 100% at 3 months after conversion and continued to 6 months (Table 2).

Clinical Outcomes

As shown in Table 3, the serum creatinine and the estimated glomerular filtration rate of the patients were similar before and after conversion. There were no statistical differences in uric acid (UA) levels before and after conversion. However, the proportion of patients receiving UA-lowering medications increased from 38% (19/50) before conversion to 52% (26/50; $P = .23$ compared with baseline) at 1 month and 62% (31/50; $P = .02$ compared with baseline) at 3 months, and remained at 62% at 6 months. The tacrolimus trough level at 6 months after conversion was lower than the baseline level ($P = .002$) (Table 3).

One patient experienced an episode of acute rejection (Banff Type IA), which was reversed by steroid administration followed by increasing the MZR dosage from 3 mg/kg/d to 5 mg/kg/d. No new case of BK viremia was observed after conversion to MZR. Biopsy results showed no BKVAN in 3 patients with high-level BK viruria at 6 months after conversion (Table 2).

DISCUSSION

In this study, we found that most kidney transplant recipients with high levels of BK viruria showed a reduction of virus load in the urine after switching from MMF or MPS to MZR for 6 months. In 11 recipients with simultaneous BK viremia, the clearance rate of BK viremia was 100% at 6 months. No patients had a recurrence of BK viremia, and no BKVAN was identified clinically or by biopsy.

There were several disadvantages of urine BKV testing and pre-emptive treatment for BK viruria, including a low positive predictive value for BKVAN, delayed decline of urine BKV loads, and lack of clearance compared with BK viremia in response to reduced immunosuppression. Overall, this may increase the risk of overreduction of immunosuppression and subsequent rejection [1]. In this study, we also found the delayed decline of BK viruria and lack of clearance in response to conversion from mycophenolates to MZR; however, the rate of acute rejection after conversion was rather low (2%) compared with rates of 8% to 12% seen with protocols for reducing immunosuppression for BK viremia [27,28].

Table 2. Change of BK Virus Loads After Conversion From Mycophenolates to Mizoribine

	Baseline	1 Month	3 Months	6 Months
BK viruria (n = 50)				
High-level viruria (>10^7 copies/mL), n (%)	50 (100.0)	32 (64.0)	9 (18.0)	3 (6.0)
Other viruria (10^3–10^7 log copies/mL), n (%)	0	12 (24.0)	15 (30.0)	21 (42.0)
Rate of BK viruria clearance, n (%)	-	6 (12.0)	26 (52.0)	26 (52.0)
BK viremia (n = 11)				
High-level viremia (>10^4 copies/mL), n (%)	7 (63.6)	1	0	0
Other viremia (10^3–10^4 copies/mL), n (%)	4 (36.4)	0	0	0
Rate of BK viremia clearance, n (%)	-	10 (90.9)	11 (100.0)	11 (100.0)

Table 3. Changes in Biochemical Parameters After Conversion to Mizoribine

Time, mo	0	1	3	6
Serum creatinine, mean (SD), μmol/L	100.7 (21.6)	98.7 (22.8)	98.9 (21.9)	100.3 (21.7)
eGFR, mean (SD), mL/min/1.73 m^2	73.2 (20.0)	74.6 (18.9)	74.5 (17.9)	73.6 (20.4)
Uric acid, mean (SD), μmol/L	352.0 (58.9)	371.7 (85.9)	363.6 (60.5)	340.4 (58.6)
Tacrolimus trough level, mean (SD), ng/mL	7.3 (1.5)	6.8 (1.4)	6.9 (0.9)	6.5 (0.9)*
Mizoribine trough level, mean (SD), ng/mL	-	583 (440)	533 (275)	597 (237)

Abbreviation: eGFR, estimated glomerular filtration rate.
*Comparison vs baseline value, $P = .002$.

There are only a few reports in the literature regarding pre-emptive treatment for BK viruria. Funahashi et al reported that conversion from MMF to MZR in patients with positive BK viruria reduced the virus load, but all the patients in the study had low baseline virus loads ($<10^7$ copies/mL) [20]. Broeders et al suggested that high-level BK viruria may be used as a marker of overimmunosuppression, and that pre-emptive reduction of immunosuppression improved patient survival but did not affect graft survival or graft function [29].

Several risk factors for the development of BKVAN have been identified in previous studies. Of the various risk factors, MMF use was associated with a high risk of BKV infection [30,31]. The treatment of BKVAN is based on reducing immunosuppression, and treatment protocols are center specific. In general, reducing the dosage by 50% or discontinuing MMF or MPS is common and is usually combined with reducing the dosage of calcineurin inhibitors by 25% to 50% [32,33]. The effect of MZR on the reduction of BKV loads in this study may be because of its less potent immunosuppressive effect at dosages up to 3 mg/kg/d. A meta-analysis showed that high-dosage (5–6 mg/kg/d) MZR has the same immunosuppressive efficacy as MMF in kidney transplantation recipients [12]. Moreover, MZR per se may have an inhibitory effect on the BKV, as suggested by Funahashi et al [20]. It has been reported that MZR suppresses CMV replication in vitro [34] and that it has a strong synergistic effect with ganciclovir in anti-CMV activity [15]. Studies have also shown that CMV infections were significantly lower in renal transplant recipients treated with MZR compared with MMF [13,35].

There were no significant changes in graft function after conversion to MZR. Although we did not reduce the dose of tacrolimus intentionally, the tacrolimus trough level of the recipients at 6 months after conversion was lower than the baseline level; this can be explained by the natural tendency of minimization of the immunosuppressive agents over time. Hyperuricemia is the primary adverse effect of MZR [36,37]. Hyperuricemia associated with MZR was easily controlled by UA-reducing drugs such as allopurinol, benzbromarone, or febuxostat, as shown by the similar serum UA levels before and after treatment with MZR. In this study, the proportion of recipients receiving UA-reducing drugs increased significantly after 3 months of MZR.

There are some limitations of this study. First, this study is not randomized and there is no control group; it is unclear whether clearance rates seen here are similar to what would have been seen without any intervention beyond the standard reductions in immunosuppression that would have occurred at 3 months and later. In this study tacrolimus levels were statistically significantly lower at 6 months. Second, although it is tempting to speculate that the antiviral properties of MZR were responsible for the reduction in viruria and viremia, this may also have been because of mycophenolate discontinuation and substitution with low-dose MZR rather than standard-dose MZR. Third, the follow-up time is too short. Nevertheless, this study provided direct evidence suggesting that conversion from MMF or MPS is associated with a reduction in the BKV load in urine and plasma in patients with high levels of BK viruria or viremia.

CONCLUSION

Early conversion from MMF or MPS to MZR in renal transplant recipients with sustained high levels of BK viruria was associated with reduction of BK viruria and clearance of BK viremia. Randomized controlled clinical studies are necessary to verify that MZR therapy reduces BK viral load in urine and plasma.

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