ELSEVIER

Conversion From Mycophenolate Mofetil to Mizoribine for Patients With Positive Polyomavirus Type BK in Urine

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ABSTRACT

It is known that administration of mycophenolate mofetile (MMF) is associated with BK virus (BKV) nephropathy in renal transplant recipients. To determine any inhibitory effect of mizoribine for BKV, seven patients with positive BKV in their urine who took MMF as immunosuppressive therapy were evaluated after MMF was changed to mizoribine. Baseline BKV DNA in urine, which ranged from 2.2×10^2 to 5.5×10^6 copies per milliliter, decreased in all cases (mean = 1.9×10^{-1} times; median 2.8×10^{-3} times). Four cases turned negative within 6 months and one within 12 months. No acute rejection or deterioration of graft function occurred during the administration of mizoribine. An inhibitory effect of mizoribine on BKV was suggested.

ALTHOUGH IMMUNOLOGICAL REJECTION of a transplanted kidney has recently decreased due to strong immunosuppressive regimens, nephropathy associated with polyomavirus type BK (BKV) has emerged as a clinical problem. To treat BKV nephropathy, clinicians have reduced immunosuppression or used antiviral agents. However, reduction in immunosuppression sometimes causes immunological rejection; no BKV-specific antiviral therapy is available. These treatment failures have led to the loss of the transplanted kidney.

Mycophenolate mofetile (MMF) is used widely because of its stronger effects than mizoribine. However, mizoribine has been reported to display antiviral as well as immunosuppressive effects. In this study, we changed MMF to mizoribine for patients with positive urinary BKV.

PATIENTS AND METHODS

From April 2005 to April 2007, 26 renal transplant recipients who took a calcineurin inhibitor, MMF, and steroid as maintenance immunosuppressive therapy were evaluated for BKV DNA in their urine. A positive result was defined when quantitative BKV DNA was greater than 1.0×10^2 copies per milliliter in real-time polymerase chain reaction. For patients with positive BKV in their urine, MMF was changed to 200 mg mizoribine per day and continued at 0.5 to 1.0 μg per milliliter as a serum trough level. Urinary BKV DNA was measured repeatedly every 2 to 3 months after drug conversion.

RESULTS

BKV DNA was detected in the urine of 7/26 patients at 4 to 42 months after transplantation (mean = 21.6 months). In all cases, BKV DNA was negative in the blood. The patients' characteristics are shown in Table 1. Two cases showed episodes of acute rejection treated with steroid pulses. Decoy cells were seen in two cases whose BKV DNA in the urine was over 10^6 copies per milliliter. The serum creatinine level was 1.4 ± 0.9 mg/dL (mean ± standard deviation) at the start of this prospective study. The mean follow-up period was 11.0 months (range = 4–21 months).

Baseline BKV DNA in urine, which ranged from 2.0×10^2 to 4.3×10^6 copies per milliliter decreased in all cases (mean = 8.1×10^{-2} times; median = 2.9×10^{-3} times; Fig 1). The Mann-Whitney *U* test revealed statistical significance ($P < .001$). Four cases turned negative within 6 months. In addition, one case who turned negative at 12 months was again positive 3 months later, but the DNA level was still low. No acute rejection occurred during the administration of mizoribine and the mean serum creatinine level 6 months after drug conversion was 1.3 ± 0.7 mg/dL.

Patient 2 stopped taking mizoribine at 9 months after conversion from MMF. This 35-year-old woman, who took tacrolimus, MMF, and prednisone as maintenance immu-

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Table 1. Patient Characteristics

No.	Age (y)	Immunosuppressive Regimen	AR	Decoy Cell	After Transplantation (mo)	Follow-up (mo)	BKV DNA in Urine (copies/mL)		Serum Cr (mg/dL)	
							Baseline	Current	Baseline	Current
1	33	CyA + MMF + Pred	+	−	28	9	2.0×10^2	$1.0 \times 10^2>$	0.77	0.76
2	35	Tac + MMF + Pred	−	+	26	9	4.3×10^6	5.5×10^2	1.07	1.01
3	33	CyA + MMF + Pred	−	+	42	20	3.3×10^6	2.1×10^3	1.60	1.89
4	60	CyA + MMF + Pred	−	−	37	21	7.8×10^3	3.1×10^2	0.80	0.72
5	58	CyA + MMF + Pred	−	−	6	9	3.4×10^4	$1.0 \times 10^2>$	3.30	2.50
6	25	Tac + MMF + Pred	+	−	8	5	3.9×10^4	$1.0 \times 10^2>$	1.33	1.13
7	34	Tac + MMF + Pred	−	−	4	4	4.7×10^3	$1.0 \times 10^2>$	1.23	1.16

CyA, cyclosporine; MMF, mycophenolate mofetil; Tac, tacrolimus; Pred, prednisone; AR, acute rejection; Cr, creatinine.

nosuppression had BKV detected in her urine at 26 months after renal transplantation. MMF was converted to mizoribine, and 9 months later the BKV DNA in her urine had decreased from 4.3×10^6 to 5.5×10^2 copies per milliliter. Mizoribine was changed to azathioprine because she hoped for a pregnancy, but the BKV DNA increased to 2.3×10^4 copies per milliliter within 6 months. The antimetabolite was returned to mizoribine, and the BKV DNA decreased again to 1.1×10^2 copies per milliliter or almost negative (Fig 2).

DISCUSSION

Since Purighalla et al first reported it in 1995,[1] BKV nephropathy has been increasingly recognized as an important cause of renal transplant dysfunction, which it linked to recent strong immunosuppressive regimens containing tacrolimus or MMF. BKV nephropathy has been reported to develop in 1% to 9% of renal transplant recipients, which often leads to loss of allograft function.[2–4] BKV-specific antiviral therapy has not yet been developed. To control BKV replication, several treatments have been tried; intravenous immunoglobulin,[5] cidofovir,[6,7] or fluorochinolone,[8] though they are not efficacious. At present, reducing the level of maintenance immunosuppression seems to be the most common and effective treatment for BKV;[4,9] however, this change may lead to subsequent allograft rejection. This situation makes it difficult to treat BKV infection.

Mizoribine, an imidazole nucleoside analog isolated from the mold *Eupenicillium brefeldianum,* is an immunosuppressive agent used for renal transplantation, autoimmune diseases, and steroid-resistant nephrotic syndrome in Japan. Furthermore, mizoribine has been reported to possess inhibitory effects on the replication of some DNA and RNA viruses, such as cytomegalovirus,[10] respiratory syncytial virus,[11] influenza virus types A and B,[12] and bovine viral diarrhea virus.[13] The antiviral mechanism of mizoribine may relate to its similar chemical structure to ribavirin, a well-known broad-spectrum antiviral agent. Both drugs are known to act as inosine monophosphate dehydrogenase inhibitors.

In the present study, BKV DNA in urine decreased in all cases after converting MMF to mizoribine. This result can be explained by three possible reasons: an immunological reaction upon converting the antimetabolite inhibits viral replication; an inhibitory effect on BKV; and BKV disappeared as a natural part of its course regardless of the drug change. However, patient 2's case indicated that BKV only

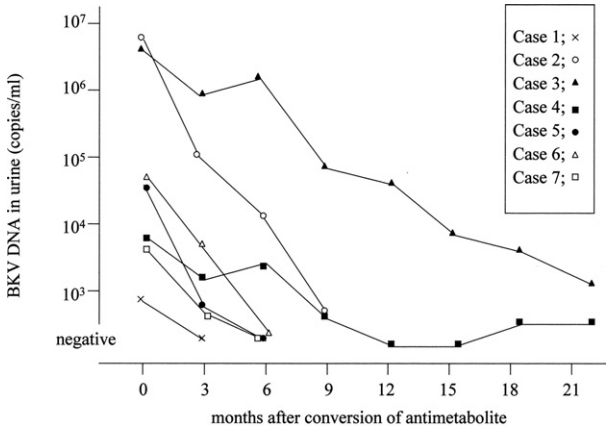

Fig 1. BKV virus DNA in seven positive patients' urine. After conversion from mycophenolate mofetil to mizoribine, four cases turned negative within 6 months and one additional case turned negative at 12 months.

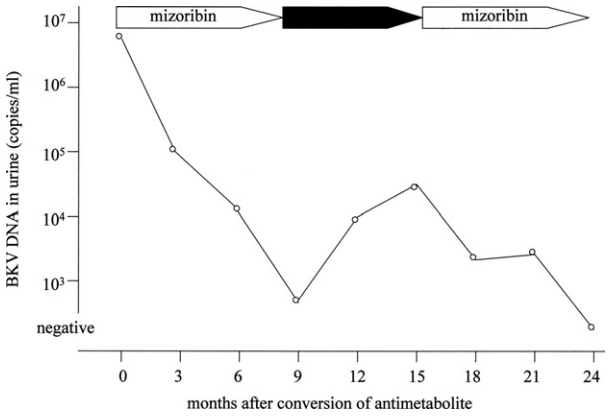

Fig 2. BKV virus (BKV) DNA in urine of case 2. During administration of mizoribine, BKV DNA in urine decreased, and in contrast, when immunosuppression was changed to azathioprine, BKV DNA increased.

decreased administration of mizoribine. This case suggested the possibility that mizoribine possesses anti-BKV effect.

To clarify whether there is a difference in viral decrease between MMF abandonment and conversion to mizoribine, a control population including just MMF abandon is required. However, detection of BKV DNA in urine does not always mean a tubulointerstitial disorder because BKV lies concealed in the urothelial cells even of normal populations, which means the need for treatment of just positive BKV in urine is poor. Therefore, there is an ethical problem to withdraw MMF for such patients, because it increases the risk of immunological rejection. To precisely assess the inhibitory effect of mizoribine for BKV, in vitro experiments should be performed.

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