Do Antithymocyte Globulin-Free Acute Rejection Therapies Increase the Risk of Polyoma Nephropathy in Renal Transplant Recipients?

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ABSTRACT

Introduction. BK virus nephropathy is a serious complication that can lead to allograft kidney loss. Excessive immunosuppression increases the risk. We aimed to evaluate whether there is an increased risk of BK viremia and nephropathy in patients who underwent high-dose immunosuppression because of the development of acute rejection in the early period after kidney transplantation.

Methods. This retrospective cohort study was performed between April 2015 and March 2016. Twenty-nine patients who had biopsy-proven acute rejection in the first 3 months were evaluated for BK viremia and nephropathy. Thirty patients who had transplantations at the same period were the control group. Plasma BK-DNA values were examined at 1, 2, 3, 6, 9, and 12 months after the rejection treatment and at 3, 6, 9, and 12 months in the control group. Presence of polyoma nephropathy was examined with surveillance biopsies at the 6 and 12 months.

Results. Acute rejection treatment was started on the 12th day after transplantation (2–37 days). Seventeen cellular rejections and 12 humoral rejections were reported by biopsy. Two of the 12 humoral rejections were suspicious. Only pulse steroid (PS) (n = 18); PS, plasmapheresis, and intravenous immunoglobulin (n = 8); PS and intravenous immunoglobulin (n = 2); and PS and plasmapheresis (n = 1) treatments were performed. In 21 patients in the rejection group and 25 patients in the control group, BK-DNA was not positive at all. Two patients had graft loss at 11 and 36 months in the rejection group. Graft losses were secondary to rejection.

Conclusions. Treatment with antithymocyte globulin-free regimens after acute rejection episodes did not lead to an increase in BK viremia.

BK nephropathy (BKN) is one of the most feared infectious complications because of graft loss in kidney transplant patients. The estimated prevalence reported after transplantation is between 1% and 10% [1–6]. It may lead to tubulointerstitial nephritis and less frequently to ureter stenosis and hemorrhagic and nonhemorrhagic cystitis in the transplanted kidney [7–11]. BK virus (BKV) infection is often seen in the first year after transplantation [12]. BK viremia can be seen before renal dysfunction. The degree of immunosuppression is an important risk factor for the development of BKN. BKV replication may be indicative of immunosuppression excess [13]. There are studies reporting that tacrolimus increases BKV replication and that sirolimus decreases it [14]. Advanced age, male sex, white race, diabetes mellitus, delayed graft function, use of antithymocyte globulin (ATG), and acute rejection treatments have been reported to increase BKV replication [5,15]. We aimed to evaluate whether there is an increase in the risk of

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Table 1. Patient Characteristics and Plasma BK-DNA Results

	Rejection Group (n = 29)	Control Group (n = 30)
Age, y	40.2 (22–57)	42.4 (19–72)
Male, %	44.8	66.7
3-month BK-DNA, copies/mL	0 (n = 26) 270 (n = 1) 731 (n = 1) 13,000 (n = 1)	0 (n = 28) 4210 (n = 1) 5700 (n = 1)
6-month BK-DNA, copies/mL	0 (n = 25) 140 (n = 1) 145 (n = 1) 262 (n = 1) 26,800 (n = 1)	0 (n = 26) 260 (n = 1) 10,000 (n = 1) 10,400 (n = 1) not measured (n = 1)
9-month BK-DNA, copies/mL	0 (n = 25) 161 (n = 1) 7249 (n = 1) not measured (n = 2)	0 (n = 27) 128 (n = 1) 231 (n = 1) 668 (n = 1)
12-month BK-DNA, copies/mL	0 (n = 28) 6728 (n = 1)	0 (n = 28) 115 (n = 1) 123 (n = 1)
Serum creatinine at 12 months, mean (minimum-maximum), mg/dL	1.55 (0.85–2.65) n = 28	1.18 (0.7–2.18) n = 30
eGFR at 12 months, median (minimum-maximum), mL/dk/1.73 m^2	59 (29–115) n = 28	74 (28–112) n = 30
Graft loss	n = 2 (11 months, 36 months)	0

Abbreviation: eGFR, estimated glomerular filtration rate.

BK viremia and nephropathy by high-dose immunosuppression for treatment in patients with acute rejection in the early period after kidney transplantation.

MATERIALS AND METHODS

This retrospective cohort study was performed between April 2015 and March 2016 at our institution. Twenty-nine patients who had biopsy-proven acute rejection and got high-dose immunosuppressive treatment in the first 3 months were evaluated for BK viremia and nephropathy. The control group consisted of 30 patients who were transplanted at the same period and had no rejection. Plasma BK-DNA values were examined at 1, 2, 3, 6, 9, and 12 months after the rejection treatment and at 3, 6, 9, and 12 months in the control group. The presence of polyoma nephropathy was examined with surveillance biopsies at the 6 and 12 months. SPSS version 16.0 (SPSS, Inc, Chicago, Ill, United States) was used for statistical analysis and P values less than 5% were considered significant ($P < .05$).

RESULTS

Calcineurin inhibitors (CNIs) were preferred in all of the 59 patients. Tacrolimus was used in 47 patients and cyclosporine in 12 patients. Prednisolone, CNI, and everolimus were used in 2 patients. The remaining patients were given prednisolone, CNI, mycophenolate mofetil or mycophenolate sodium. One patient in the control group received no induction agent and the remaining 58 patients received ATG as the induction agent.

Acute rejection treatment was started on the 12th day after transplantation (2–37 days). Seventeen cellular rejections and 12 humoral rejections were reported by biopsy. Two of the 12 humoral rejections were suspicious. Only pulse steroid (PS) (n = 18); PS, plasmapheresis, and intravenous immunoglobulin (n = 8); PS and intravenous immunoglobulin (n = 2); and PS and plasmapheresis (n = 1) treatments were performed. In 21 patients in the rejection group and 25 patients in the control group, BK-DNA was not positive at all. The highest BK-DNA values were seen in the rejection group at 2 months and in the control group at 6 months (45,100 copies/mL, 10,400 copies/mL, respectively). Subsequent BK-DNA results of these 2 patients were negative. BK-DNA was negative in 28 patients in both groups at 12 months (Table 1). Polyoma nephropathy was seen on biopsy of a patient with rejection group whose BK-DNA was 13,000 copies/mL at 3 month. BK-DNA became negative in 2 months. Polyoma nephropathy was not seen in the biopsy performed in the seventh month, antibody mediated rejection (AMR) was reported. That patient lost the allograft kidney at 11 months. In the control group, no graft loss was observed. Two patients in the rejection group lost graft kidneys at 11 months and 36 months. Graft losses were secondary to rejection. In the patient who had graft loss at 36 months, BK-DNA was not positive at all. The number of patients with BK-DNA $\geq$ 10,000 copies/mL was 3 in the rejection group and 2 in the control group (Table 2). When we look at the relationship between CNI type and BK-DNA > 1000 copies/mL, no significant relationship was found ($P = .67$).

DISCUSSION

By using more potent immunosuppressive regimens, rejection rates were improved, but infectious problems that can

Table 2. Patients With Plasma BK-DNA > 1000 Copies/mL

BK-DNA, copies/mL (mo)	Rejection	Calcineurin Inhibitor	Serum Creatinine/eGFR at the Final Control, mg/dL/mL/dk/1.73 m^2	Follow-up Period, mo
10,400 (6)	No	Tacrolimus	0.98/> 60	35
5700 (3) → 10,000 (6)	No	Tacrolimus	1.11/56	38
4210 (3)	No	Tacrolimus	0.81/> 60	33
45,100 (2)	Yes	Cyclosporine	2.17/36	38
2660 (2)	Yes	Tacrolimus	1.48/56	37
13,000 (3)	Yes	Tacrolimus	Graft loss	11
26,800 (6) → 7249 (9) → 6728 (12)	Yes	Tacrolimus	1.11/> 60	33

cause graft loss such as BKN are increasing. In a patient with graft dysfunction, it may not be easy to differentiate acute rejection with BKN on biopsy. Tubulointerstitial nephritis occurs in both cases. Acute rejection can also be seen together with BKN [16,17].

Awadalla et al [18] compared 40 patients with BKN to 404-patient control group. The control group was using a tacrolimus-based immunosuppressive regimen and no induction was performed. They found a significant relationship between increased HLA mismatching and BKN. They also reported that increased numbers of rejection episodes and ATG-requiring steroid unresponsive rejections were associated with BKN. Increased HLA mismatching may be associated with increased induction, increased maintenance immunosuppression, and immunosuppressive therapy that is intensified secondary to increased rejection episodes. In a single-center prospective study involving 78 patients, Hirsch et al [1] reported that antirejection therapy, including corticosteroids, increased BKV replication and BKN. Demey et al [19] reported that acute rejection episodes and use of tacrolimus increased BKN and BKV replication in a systematic review and meta-analysis of 34 studies with a prospective design. However, the relationship between antirejection therapy and BKV was not mentioned [19]. Moura et al [20] examined 553 patients in a retrospective study. In 41 patients, BK replication was present. The only factor that increased the risk of BKV replication was the use of mycophenolate sodium. However, the lack of information about induction and antirejection therapies were the limitations of the study [20].

In our study, we investigated the presence of BK viremia and BKN after rejection treatment in patients with acute rejection in the early postoperative days. The use of tacrolimus was higher in the rejection group vs the control group (93.1% vs 66.6%, respectively). Mycophenolate-based antimetabolite treatment was similar in both groups. Intensive immunosuppressive therapy for acute rejection did not lead to an increase in BK viremia and nephropathy. As an important detail, pulse steroids were used in all of the rejection episodes, but ATG was not used in any of them. BKV replication was markedly decreased after the sixth month. In the follow up of the patient with BKN, BK viremia and biopsy findings of BKN were improved, but there was a graft loss due to AAR. Although BKN did not directly lead to graft loss, decreased immunosuppression may have led to AAR. In conclusion, we found that treatment with ATG-free regimens after acute rejection episodes did not lead to an increase in BK viremia. The limitations of our study are that it had a retrospective design, was single-centered, and had a low number of patients. It is clear that multicentered, prospective studies with more patients are needed.

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