Treatment of BK Polyomavirus-Associated Nephropathy in Paediatric Kidney Transplant Recipients: Leflunomide Versus Cidofovir

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Abstract

Objectives: **BK polyomavirus-associated nephropathy is a clinicopathological entity that negatively affects graft function in kidney transplant recipients. We compared the efficacy of leflunomide and cidofovir to treat BK polyomavirus-associated nephropathy in pediatric kidney transplant recipients.**

Material and Methods: **Medical records of pediatric recipients with BK viremia for the period 2004 through 2019 were reviewed retrospectively, and patients diagnosed with BK polyomavirus-associated nephro-pathy were included in the study. A serum BK virus level above 104 copies/mL was accepted as BK viremia. We defined BK polyomavirus-associated nephropathy as detection of BK virus SV40 antigen on immunochemistry staining of renal graft tissue accompanied by signs of tubulointerstitial nephritis or elevated serum creatinine in addition to BK viremia.**

Results: **Of 304 kidney transplant recipients, 53 had persistent BK viremia; 36 of these patients (61.1% male) were included in the study with the diagnosis of BK polyomavirus-associated nephropathy. Twelve patients (33.3%) received cidofovir, and 14 (38.8%) received leflunomide. Results were similar between the cidofovir and leflunomide groups for serum creatinine level at last follow-up (0.91 ± 0.29 vs 0.94 ± 0.37 mg/dL, respectively; *P* = .843) and graft failure rate (8.3% vs 14.2%, respectively; *P* = .632). Graft failure was observed in 8.3% of patients with BK polyomavirus-associated nephropathy.**

Conclusions: **Leflunomide and cidofovir showed similar efficacy for treatment of BK polyomavirus-associated nephropathy.**

Key words: *Acute rejection, Anti-inflammatory agent, Antiviral agent, Graft function, Virus latency and reactivation*

Introduction

The BK virus is a nonenveloped DNA virus in the polyomavirus family, which is ubiquitous. Approximately 60% to 90% of the adult population is seropositive for BK virus. The virus remains latent in the urinary system epithelium and can be reactivated in cases where the immune system is suppressed.[1-3] BK polyomavirus-associated nephropathy (BKPyVAN) occurs with cytopathic damage and secondary inflammation in the graft caused by increased BK virus replication due to primary infection or reactivation. The incidence of BKPyVAN in pediatric kidney transplant recipients has been reported to be 4% to 5%.[4] The incidence is highest in the first 3 to 6 months after kidney transplant.[3]

Although the main step of BKPyVAN treatment is to reduce immunosuppression, there are no clear data on proper parameters for reduction of immunosuppression.[5] Reduction of immunosuppression increases the risk of acute rejection after BKPyVAN. In patients with a diagnosis of BKPyVAN accompanied by acute rejection, rate of graft loss is as high as 67%.[6,7] As a result of its immunomo-dulatory effect, intravenous immunoglobulin (IVIG) has been used to treat BKPyVAN; however, its clinical effect has only been supported by small case series.[8-10] Cidofovir, a nucleoside analog, exerts its effect by irreversibly binding to viral DNA polymerase. Studies have shown that cidofovir in the treatment of BKPyVAN, in addition to reducing immunosuppression, is beneficial

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or, on the contrary, ineffective.[11-13] Leflunomide is known for its immunomodulatory and immunosuppressant effects; however, it also interrupts BK virus DNA synthesis.[14] Leflunomide is used as an alternative agent to mycophenolate mofetil (MMF) in the treatment of BKPyVAN. For these reasons, leflunomide was trialed in kidney transplant recipients with BKPyVAN who did not respond to immunosuppression dose reduction.[5,11,15-18]

The aim of this study was to determine the prevalence of BKPyVAN in pediatric renal transplant recipients, to compare the efficacy of leflunomide and cidofovir in cases unresponsive to reduction of immunosuppression, and to determine the rate of graft loss associated with BKPyVAN.

Materials and Methods

The medical records of kidney transplant recipients with BK viremia from the period 2004 through 2019 were reviewed retrospectively, and those diagnosed with BKPyVAN were included in the study. The inclusion criteria were as follows: (1) age <18 years at the time of kidney transplant; (2) follow-up period >12 months after transplant; and (3) patients whose medical records were not missing. Patients with isolated BK viruria or transient BK viremia were excluded from the study. Ethics committee approval for the study was obtained from Akdeniz University Medical Faculty Ethics Committee (decision No. 802/10.11.2021). The study was conducted in accordance with the Helsinki Declaration.

The demographic characteristics, kidney donor sources, immunosuppressive agents used in induction and maintenance therapy, and the presence of acute rejection therapy were recorded. A quantitative real-time polymerase chain reaction was used to detect and quantify BK virus DNA copies. A serum BK virus level above 10^4 copies/mL was accepted as BK viremia. Persistent viremia was defined as plasma BK level >10^4 copies/mL for longer than 3 weeks.[19] Diagnosis of BKPyVAN was defined as detection of BK virus SV40 antigen in renal graft tissue by immunochemistry staining accompanied by signs of tubulointerstitial nephritis or persistent BK viremia with graft dysfunction. In patients without histopathological findings of BKPyVAN, other pathologies that may cause graft dysfunction (such as rejection, infection, vascular problems) were excluded for the diagnosis of BKPyVAN. Graft dysfunction was defined as an increase in serum creatinine of 0.3 mg/dL from baseline.

In patients with BK viremia, the first aspect of our treatment approach was dose reduction of immunosuppressive drugs paired with initiation of ciprofloxacin therapy. After detection of BK viremia, the graft functions were checked biweekly, and BK plasma levels were checked monthly. Patients with a diagnosis of BKPyVAN who did not respond to the first-line treatments mentioned above were started on cidofovir or leflunomide. Leflunomide was given as an oral loading dose of 100 mg/day followed by 10 mg/day in patients <40 kg or 20 mg/day in patients >40 kg, respectively.[20] The MMF was discontinued when leflunomide treatment started. Cidofovir was given intravenously as a dose of 0.25 to 1 mg/kg at intervals of 3 to 4 weeks.[21] The cidofovir infusion was repeated 2 to 4 times. Before 2013, the use of leflunomide in the treatment of BKPyVAN was not widespread; at that time in our center, cidofovir was given priority in the treatment of patients unresponsive to immunosuppression dose reduction. On the other hand, the first leflunomide treatment was started in 2010, and its use has increased over time. The patients in the study group were divided into 2 groups according to the use of cidofovir or leflunomide.

Statistical analyses

Descriptive statistics were presented as frequency (with percentage), mean ± SD, and median (with IQR) values, where appropriate. The Shapiro-Wilk test, histograms, and Q-Q plots were used for evaluation of normality of distribution. The Fisher exact test was used to analyze relationships between categorical variables. For the comparison of continuous variables, the Student t test was used when variables showed normal distribution, whereas the Mann-Whitney U test was used in the contrary case. For the evaluation of pretreatment and posttreatment responses, a paired sample *t* test was used for variables with normal distribution and the Wilcoxon test was used for variables without normal distribution. Statistical analyses were performed by using the SPSS program for Windows (version 21.0). $P < .05$ was significant.

Results

Of 304 kidney transplant recipients, 53 (17.4%) had persistent BK viremia, and 36 (11.8%) of these

patients (61.1% male) were included in the study with the diagnosis of BKPyVAN (Figure 1). At the time of transplant, the median age of patients with BKPyVAN was 12.23 years (IQR 4.06-15.41 years) and the mean follow-up period was 8.32 ± 3.79 years. The ratio of deceased and living donors was similar (47.2% vs 52.8%). The distribution of living donors was 11 mothers, 7 fathers, and 1 grandmother. We observed that congenital anomalies of the kidney and urinary tract were the most common primary kidney diseases (41.6%) (Table 1). Twelve patients (33.3%) had a human leukocyte antigen mismatch >3. Anti-thymocyte globulin was administered in 52.8% of patients for induction therapy, and tacrolimus was used in 80.6% of patients.

The median time between kidney transplant to the occurrence of BK viremia was 3.02 months (IQR 1.88-6.46 months). At the time of BKPyVAN diagnosis, the mean plasma BK virus load was $387 \pm 145 \times 10^4$ copies/mL. Twelve recipients (33.3%) had acute graft dysfunction at the time of diagnosis, and BK virus load was found to be similar in patients with and without graft dysfunction (P = .432). Pathological evidence to support BKPyVAN diagnosis was observed in 55.6% of the patients, and the diagnosis of BKPyVAN was made with the persistence of BK viremia accompanied by graft dysfunction in the remaining 16 patients (44.4%) (Table 1).

As a first-line treatment, MMF dose was reduced in 34 patients (94.4%), MMF was switched to azathioprine in 9 patients (25.0%), and calcineurin inhibitor dose was reduced in 29 patients (80.5%). Ciprofloxacin was given to all patients (Figure 1). The median ciprofloxacin administration period was 4 weeks (1.3-6 weeks, minimum-maximum). Although the BK virus load decreased partially after ciprofloxacin, the difference was not significant (P = .123). After immunosuppression dose reduction and ciprofloxacin treatment, BK viremia disappeared in 10 patients within a median of 14 weeks (IQR 9-19 weeks); graft loss was not observed in these patients.

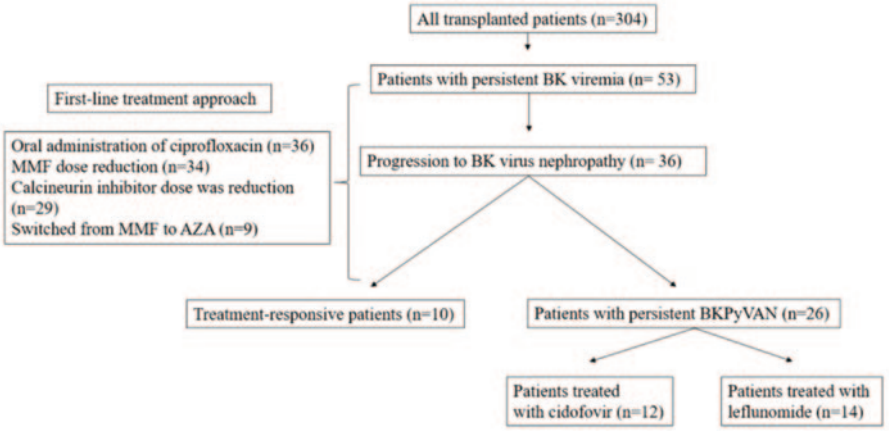
Table 1. Clinical Features of Patients Diagnosed With BK Virus Nephropathy (n = 36)

Variable	Value
Age at transplant, y	12.23 (4.06-15.41)
Posttransplant follow-up time, y	8.32 ± 3.79
Primary kidney disease diagnosis	
CAKUT	15 (41.6%)
FSGS	6 (16.7%)
Congenital nephrotic syndrome	4 (11.1%)
Cystic kidney diseases	5 (13.9%)
Other glomerulonephritis	2 (5.5%)
Tubulopathies	1 (2.8%)
Unknown etiology	3 (8.3%)
Deceased donor transplant	17 (47.2%)
Mean HLA mismatches	2.88 ± 1.28
Patients with HLA mismatch >3	12 (33.3%)
Preemptive kidney transplant	12 (33.3%)
Induction therapy	
ATG + prednisolone	19 (52.8%)
Basiliximab + prednisolone	4 (11.1%)
Only prednisolone	13 (36.1%)
Calcineurin inhibitor	
Tacrolimus	29 (80.6%)
Cyclosporine	7 (19.6%)
Acute graft dysfunction at time of diagnosis	12 (33.3%)
BKPyVAN with pathology-based diagnosis	20 (55.6%)
Acute rejection after BKPyVAN diagnosis	5 (13.9%)
Serum creatinine at last follow-up, mg/dL	0.95 ± 0.36
Graft failure	3 (8.3%

Abbreviations: ATG, anti-thymocyte globulin; BKPyVAN, BK polyomavirus-associated nephropathy; CAKUT, congenital anomalies of the kidney and urinary tract; FSGS, focal segmental glomerulosclerosis; HLA, human leukocyte antigen

Values are median values (IQR), mean values ± SD, or number (%) of patients.

Figure 1. Flowchart of Study Patients



Abbreviations: AZA, azathioprine; BKPyVAN, BK polyomavirus-associated nephropathy; MMF, mycophenolate mofetil

After the first-line approach for BKPyVAN, 12 patients (33.3%) received cidofovir and 14 (38.8%) received leflunomide. The clinical and laboratory characteristics of patients treated with cidofovir and leflunomide are shown on Table 2. Age at transplant (P = .762), donor source (P = .512), diagnosis of primary kidney disease (P = .187), and content of induction therapy (P = .731) were found to be similar between the cidofovir group and the leflunomide group. However, the mean posttransplant follow-up period was longer in the cidofovir group versus the leflunomide group (10.37 ± 2.58 vs 6.21 ± 2.87 years; P = .001). The median duration of leflunomide use was 11.95 months (7.42-34.71 months). The median number of cidofovir repetitions was 4 (range, 2-8), and the cumulative cidofovir dose was 3.38 mg/kg (2.20-5.85 mg/kg). There were no adverse side effects associated with leflunomide and cidofovir, so there was no need to discontinue treatment for any of the participants.

Before start of cidofovir and leflunomide treatment, the BK virus load, graft functions, and the rate of patients diagnosed with pathology were similar between groups (Table 2). Although the median viremia clearance time after treatment was shorter in the leflunomide group, this difference was not significant (13.14 vs 17.35 weeks; P = .123). Acute rejection episodes after the diagnosis of BKPyVAN were observed in 3 (21.4%) patients with leflunomide and 2 (16.6%) patients with cidofovir (P = .768). Four patients with acute rejection were given IVIG treatment, and 2 of them had plasmapheresis before IVIG. High-dose prednisolone treatment was also given in 2 patients with acute rejection because BK viremia had disappeared at the time of diagnosis. Graft loss due to rejection occurred in a patient in the leflunomide group whose BK viremia and rejection episode were not controlled despite plasmapheresis and IVIG therapy.

Results at last follow-up were similar between the cidofovir and leflunomide groups for serum creatinine (0.91 ± 0.29 vs 0.94 ± 0.37 mg/dL, respectively; P = .843) and glomerular filtration rate (61.23 ± 16.95 vs 59.31 ± 20.42 mL/min/1.73 m^2, respectively; P = .745). Graft failure occurred in 1 of 12 patients (8.3%) treated with cidofovir and 2 of 14 patients (14.2%) treated with leflunomide (P = .632). In the leflunomide group, graft loss was associated with progressive BKPyVAN in 2 patients and accom-panied by acute humoral rejection in 1 patient. Graft failure ratio was 8.3% in recipients with BKPyVAN and 5.6% in recipients with BK viremia. Among all kidney transplants, the rate of graft failure due to BKPyVAN was 0.9%.

Table 2. Comparison of Clinical and Laboratory Characteristics of Patients Treated With Leflunomide or Cidofovir

Variable	Leflunomide (n = 14)	Cidofovir (n = 12)	*P*
Age at transplant, y	8.89 ± 3.88	9.59 ± 5.76	.762
Posttransplant follow-up time, y	6.21 ± 2.87	10.37 ± 2.58	.001
Deceased donor transplant	8 (57.1%)	6 (50.0%)	.512
Mean HLA mismatches	3.42 ± 1.39	2.33 ± 1.23	.067
Preemptive kidney transplant	5 (35.7%)	4 (33.3%)	.480
Induction therapy			
ATG + prednisolone	8 (57.1%)	6 (50.0%)	.731
Basiliximab + prednisolone	1 (7.1%)	1 (8.3%)	
Only prednisolone	5 (35.7%)	5 (41.6%)	
Calcineurin inhibitor			
Tacrolimus	11 (78.6%)	11 (91.6%)	.359
Cyclosporine	3 (21.4%)	1 (8.4%)	
Plasma BK virus load before treatment, ×10^4 copies/mL	846 ± 92	783 ± 25	.365
Acute graft dysfunction at time of diagnosis	3 (21.4%)	5 (41.6%)	.210
BKPyVAN with pathology-based diagnosis	7 (50.0%)	10 (83.3%)	.081
Viremia clearance time after treatment, wk	13.14 (6.14-68.10)	17.35 (3.86-67.14)	.123
Acute rejection after BKPyVAN diagnosis	3 (21.4%)	2 (16.6%)	.768
Serum creatinine at last follow-up, mg/dL	0.91 ± 0.29	0.94 ± 0.37	.843
GFR at last follow-up, mL/min/1.73 m^2	61.23 ± 16.95	59.31 ± 20.42	.745
Graft failure	2 (14.3%)	1 (8.3%)	.632

Abbreviations: ATG, anti-thymocyte globulin; BKPyVAN, BK polyomavirus-associated nephropathy; GFR, glomerular filtration rate; HLA, human leukocyte antigen

Values are median values (IQR), mean values ± SD, or number (%) of patients.

Discussion

We observed that BK viral clearance can be achieved with both leflunomide or cidofovir in patients with BKPyVAN unresponsive to immunosuppression reduction. The BK viremia clearance was achieved in 12 of 14 patients (86%) treated with leflunomide, with a median of 13 weeks. Leflunomide was used to treat BK viremia (without nephropathy) in 7 pediatric kidney transplant recipients with a mean age of 12.1 years; complete BK virus clearance was detected in 67% of the patients.[15] No graft loss was observed in any patient in this group.[15] Canivet and colleagues evaluated the efficacy of leflunomide in adult patients with BKPyVAN; BK virus DNAemia clearance was achieved in 41% of patients within 6 months.[16] In a retrospective study that evaluated the experiences of 3 centers in France, the success rate of viral clearance with leflunomide was 76%, and

the time to viral clearance was 10.1 months.[17] In a meta-analysis of 9 retrospective case series and 3 prospective observational studies, BK viremia clearance success with leflunomide ranged from 33.3% to 92.3%.[18] A prospective open-labeled study evaluated the efficacy of immunosuppression dose reduction and leflunomide in 12 patients with biopsy-proven BKPyVAN; improvement in graft function was observed in 66%, and BK virus clearance was observed in 42% of patients.[22] In our study, the rate of the functional graft was higher and the time to achieve viral clearance was shorter with leflunomide treatment compared with previous studies.

In our single-center experience, we observed that cidofovir use was more common before 2013 in patients diagnosed with BKPyVAN. Graft function was preserved in 11 of the 12 treated patients, with a viral clearance time of approximately 17 weeks. The experiences of 90 physicians from 27 countries were compiled in a study from 2015 and showed that 32% of the participants preferred cidofovir as an adjuvant treatment.[23] Although studies have shown that cidofovir prevents graft loss in patients with BKPyVAN, case series have shown that cidofovir is not more beneficial than immunosuppression dose reduction.[11-13,24,25] Muhlbacher and colleagues used low-dose (0.25 mg/kg) cidofovir therapy in 23 adult renal transplant recipients with BKPyVAN; BK virus clearance was achieved in 77.8%, and graft function in 61% of patients remained stable.[26] An 18-year-old patient who underwent kidney transplant with a diagnosis of Schimke immuno-osseous dysplasia developed BKPyVAN and BK virus-associated pneumonia during follow-up; cidofovir was administered in addition to immunosuppression therapy change, and virus elimination was achieved.[27] The cumulative dose of cidofovir administered in our study was 3.38 mg/kg (median of 4 repetitions), and cidofovir-induced nephrotoxicity was not observed.

In our study, the frequency of BK viremia was 17.4%, and the frequency of BKPyVAN was 11.8%. Graft failure was observed in 8% of pediatric kidney transplant recipients with BKPyVAN, whereas 0.9% of pediatric kidney transplant recipients lost their graft due to BKPyVAN. In the study of Avci and colleagues from our country, the frequency of BK viremia and BKPyVAN in pediatric kidney transplant recipients was 5.5% and 2.8%, respectively.[28] Among 106 pediatric kidney transplant recipients retrospectively analyzed for the period from 2009 to 2019, 30.2% of recipients developed BK viremia and 6.6% had BKPyVAN.[29] The Cooperative European Pediatric Renal Transplant Initiative Registry reported the frequency of presumptive and biopsy-proven BKPyVAN as 15.8% and 4.5%, respectively.[19] In the database supported by the United Network for Organ Sharing and the Organ Procurement and Transplantation Network, graft loss due to BKPyVAN was reported as 0.47% in pediatric kidney transplant recipients.[30] In an article published by the North American Pediatric Renal Trials and Collaborative Studies registry in 2007, graft failure was reported in 24% of recipients with BKPyVAN.[4] We suggest that the low incidence of BKPyVAN compared with the literature may be due to the stepwise treatment and close monitoring of BK virus load at our center.

Our study had some limitations. First, this was a single-center experience with relatively limited kidney transplant recipient data. Because of the study's retrospective nature, we could not compare the treatments applied under equal conditions. Treatment responses were evaluated only with plasma BK virus count and graft functions; the BK virus-specific immune response was not covered in the study. However, despite these limitations, our study contributes to the literature regarding treatment responses of pediatric kidney transplant recipients with BKPyVAN.

Conclusions

Leflunomide is as effective as cidofovir with regard to viral clearance and preservation of graft functions in patients with BKPyVAN who do not respond to dose reduction of immunosuppression therapy. Multicenter and large-scale prospective studies are needed to regulate treatment protocols.

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