Biopsy proven BK virus nephropathy in kidney transplant recepients: A multi-central study from Turkey (BK-TURK STUDY)

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Abstract

Background: Polyomavirus BK virus infection is a significant complication of renal transplantation and is an important cause of allograft loss. Today, despite the innovations in the pharmaceutical industry, a curative treatment against the BK virus has not been developed. The management is not standardized and is generally based on reported experience from transplantation centers. However, the literature on the subject with large samples is limited. Therefore, we designed a study to present our countrywide experience with BK virus nephropathy (BKVN) in renal transplant recipients. **Methods:** Our study was conducted with thirty kidney transplant centers from all provinces of Turkey. Only cases with BKVN proven by allograft biopsy were included in our study. Demographic characteristics and laboratory values of the patients were obtained from the archives and electronic databases of the centers. **Results:** A total of 13.857 patients from 30 transplantation centers were screened. 207 BKVN cases proven by allograft biopsy were identified and included in the study. The mean age was 46.4±13.1, and 146 (70.5%) patients were male. Twenty-six patients did not receive any induction therapy, 144 patients received anti-T lymphocyte globulin (ATLG), and 37 patients received basiliximab after transplantation. 23.6% of the patients had acute rejection history in the first six months of renal transplantation. all were treated with pulse steroids, and 46 were also treated with ATLG. The mean time to diagnosis of BKVN was 15.8±22.2 months after transplantation. At the time of diagnosis, the patients' mean creatinine level was 1.8±0.7 mg/dl, and the mean estimated glomerular filtration rate was 45.8±19.6 ml/min. While BKVN was solely reported in 181 cases, there were cellular rejection findings in 21 biopsy specimens and humoral rejection in 4 biopsy specimens. In addition of dose reduction or discontinuation of immunosuppressive drugs, eighteen patients were treated with cidofovir, 11 patients with leflunomide, 17 patients with quinolones, 15 patients with intravenous immunoglobulin (IVIG), five patients with cidofovir+IVIG, and 12 patients with leflunomide+IVIG. None of the patients who received leflunomide and leflunomide+IVIG had allograft loss. Allograft loss was observed in 12 (15%) of 78 patients treated with antivirals or immunomodulators. Allograft loss occurred in 32 patients (15%) during follow-up out of 207 patients with BKVN. Five patients were retransplanted, and none developed BKVN during the follow-up. **Conclusions:** BKVN is still a significant cause of allograft loss in kidney transplantation, which has not been fully elucidated. Leflunomide appears to be an effective treatment in these patients.

INTRODUCTION

BK virus (BKV) was first described by Gardner et al. in 1971, isolated in the urine and urinary epithelium of a renal transplant recipient with renal failure and ureteral stenosis[1]. BKV is a non-enveloped, 42 nm virus with a double-stranded circular DNA containing 5000 bases and an icosahedral capsid from the Papoavirus group in the Polyomaviridae family[2]. Primary infection is frequently seen in early childhood, sometimes with clinical signs of upper respiratory tract infection, and is usually asymptomatic[2]. After the primary infection, the virus exists in a latent state in the urogenital tract[2].

BKV seroprevalence is 80% in adults worldwide, and BKV infection is seen in 10-60% after renal transplantation. 5% (1-10) of these infections progress as BKV nephropathy (BKVN), and it is still a significant problem affecting allograft survival in the post-transplant period[3]. Alterations in immunosuppressive (IS) treatments and diagnostic approaches lead to epidemiological differences. The incidence of BKVN is higher in the first two years after transplantation and risk is increased in patients over 50 years of age, male gender, cases with high HLA incompatibility, with multiple allograft rejection episodes, and those who receive intensive triple IS therapy[3]. Patients may not show any symptoms other than impaired renal function. BKVN may present with interstitial nephritis, ureteral stenosis, hydronephrosis, and signs of a urinary tract infection. Progressive renal failure is approximately 30-60% in affected cases[2,3].

Early diagnosis of BKVN is essential. Since the disease is mostly silent, it is recommended to regularly monitor BKV DNA in blood and/or urine samples after transplantation[4]. It is recommended to reduce IS therapy in cases with BKV DNA levels above the critical threshold and to confirm both BKVN and the presence of concomitant rejection by performing a biopsy in patients with allograft dysfunction[4]. The crucial point in the treatment of BKVN is to reduce immunosuppression. In addition, cidofovir, intravenous immunoglobulin (IVIG), quinolones, and leflunomide therapy may be applied, but none of these treatments have strong evidence to be recommended[3].

The current knowledge of BKVN is mainly based on cross-sectional patient series with small numbers of cases. The studies reporting disease outcomes with large samples are rare in the literature. With this retrospective study, we aimed to contribute to the literature by analyzing our BKVN experience with the participation of transplantation centers in all provinces of our country.

PATIENTS-METHOD

This retrospective, multicenter study was conducted with the participation of 30 active renal transplant centers in Turkey. Inclusion criteria were having a renal transplant, allograft biopsy-proven BKVN in patients with blood and/or urine BKV DNA positivity, and complete access to patient data. Cases without an allograft biopsy or missing data were excluded from the study. Ethics committee approval was obtained from Sakarya University Hospital, (approval date:16.12.2021; decision number: E-71522473-050.01.04-92626-539).

Demographic data of patients, primary kidney diseases, donor information, number of mismatches, immunosuppression status before transplantation, induction IS regimens, baseline serum creatinine levels and estimated glomerular filtration rates (eGFR), delayed graft function (DGF) status, blood and/or urine BKV-DNA work-ups of the first 2 years after transplantation, the maintenance IS treatments, the time of BKVN diagnosis after transplantation, serum BKV DNA levels at the time of diagnosis, the creatinine, eGFR and urine protein levels at the time of diagnosis, the change in IS after diagnosis, the specific treatment for BKVN (IVIG, quinolone, cidofovir, leflunomide), if any, allograft biopsy findings, concomitant rejection status, additional treatments in cases with rejection, the creatinine, eGFR and urine protein levels 3-6 months after diagnosis of BKVN, and treatment, time elapsed between diagnosis and last clinic visit, allografts' and patient's final outcomes, retransplantation status, and recurrence rates after retransplantation were analyzed.

Diagnosis of BKVN, It was diagnosed in the presence of SV40 positivity and tubulointerstitial changes in kidney biopsy.

Statistical Analysis

The numeric values are shown with the mean, standard deviation, medians with ranges according to the distributions and categorical data, frequencies, and percentages. We compared the categorical variables with Chi-Square Test where applicable. We used the Student's T-Test to compare normally distributed data and the Mann-Whitney U test for non-normally distributed data. A p-value lower than 0.05 (5% of type-I error level) was considered statistically significant in the analyses. All statistical analyses were performed using the Statistical Package for Social Science (SPSS, Chicago, IL, USA) for personal computers, version 21.0.

RESULTS

A total of 13857 patients from 30 transplantation centers were screened. There were 248 cases (1.7%) with BKVN diagnosed in allograft biopsy. Of these cases, the pathologic diagnosis of 20 biopsy samples was uncertain, and 21 patients' blood BKV-DNA levels or clinical data were missing and excluded from the analysis. 207 (1.4%) patients were included in the study (**Flow diagram**).

The mean age was 46.4±13.1 and 146 (70.5%) cases were male. The most common primary kidney diseases were chronic glomerulonephritis [n=43 (21%)], hypertension [n=32 (15.6%)], and diabetic nephropathy [n=28 (13.7%)]. Baseline characteristics and laboratory data of the patients are given in **Table 1.**

Sixteen patients had fully matched HLA profiles with the donors, 34 patients had 1 HLA mismatch, 31 patients had 2 HLA mismatches, 50 patients had 3 HLA mismatches, 33 patients had 4 HLA mismatches, 31 patients had 5 HLA mismatches, and 12 patients had 6 HLA mismatches with their donors.

At the time of renal transplantation, 26 patients did not receive induction IS treatment, 144 patients had induction IS treatment with anti-T lymphocyte globulin (ATLG), and 37 patients had basiliximab. Thirty-six patients had delayed graft function (DGF).

The maintenance IS treatments at the time of discharge after transplantation were cyclosporine-A (CSA) + mycophenolate mofetil/mycophenolic acid (MMF/MFA) + steroid in 18 patients, tacrolimus (Tac) + MMF/MFA + steroid in 164 patients, Tac + MMF in 18 patients, a CSA + a mammalian target of rapamycin inhibitors (mTORi) in 4 patients, mTORi inhibitör + MMF/MFA + steroid in 2 patients, and a CSA + Azathioprine (AZA) + steroid in 1 patient.

While any acute rejection episodes did not develop in 158 patients, 49 patients were diagnosed with acute rejection within the first six months after transplantation.

BKV-DNA was screened monthly for nine months, then every three months from the serum samples in 110 patients and the urine samples in 25 patients.

The mean time to diagnosis of BKVN was 15.8±22.2 months after transplantation. At the time of diagnosis, the mean creatinine of the patients was 1.8±0.7 mg/dl (0.5-5.6), the mean eGFR was 45.8±19.6 ml/min (8-111), and the mean amount of daily urine protein excretion was 0,6±1,6 (0,01-19) g. The mean creatinine, eGFR, and proteinuria amounts in the first and six months are shown in the **Table 2.**

In the allograft biopsy specimens, 181 cases had only BKVN with typical basophilic nuclear bodies [SV40 (+) in the epithelial cells (renal tubular and Bowman's capsule) and fibrosis with varying degrees of inflammatory infiltration], and 21 cases had BKVN + cellular rejection, and four patients had BKVN + humoral rejection findings.

After the diagnosis of BKVN, the antimetabolite dose was reduced in 18 patients; the antimetabolite treatment was discontinued in 45 patients; the antimetabolite was discontinued, and the CNI dose was reduced in 47 patients; the antimetabolite was discontinued and switched to AZA in 30 patients; the antimetabolite was discontinued, CNI dose was reduced, and AZA was added in 11 patients; CNI was discontinued and switched to mTORi in 56 patients (**Table 3**).

Pulse steroid was given to 10 patients with concomitant rejection, and steroid + IVIG treatment was given to 10 of the patients, while no additional treatment was given to the others.

For BKVN, 18 patients were treated with cidofovir, 11 patients with leflunomide, 17 patients with quinolones, 15 patients with intravenous immunoglobulin (IVIG), 5 patients with cidofovir + IVIG, and 12 patients with leflunomide+IVIG.

Allograft loss occurred in 7 (38%) of the patients receiving cidofovir, 1 (5%) of the patients receiving quinolones, 2 (13%) of the patients receiving IVIG, and 2 (40%) the patients receiving cidofovir + IVIG. No allograft loss was observed in any patients who received leflunomide and leflunomide+IVIG. Allograft loss was observed in 12 (15%) of 78 patients given antiviral or immunomodulatory therapy (**Table 4**).

When BKVN recovered, and non-recovered groups were compared, the patients in the recovered group were younger, the BKV diagnosis was earlier after transplantation, leflunomide usage, lower acute humoral rejection rate and the serum creatinine values were lower at the time of diagnosis (**Table 5**). No difference was found in other parameters (gender, proteinuri levels, BKV-DNA copy, etc).

Allograft loss occurred in 32 patients (15%) during mean 49.5±40.8 mo follow-up out of 207 patients. 5 patients had retransplantation, and none developed BK virus nephropathy during the follow-up.

DISCUSSION

In this retrospective cross-sectional study, we analyzed the renal transplantation recipients with allograft biopsy-proven BKVN followed-up in 30 transplantation centers all over our country and presented the BKVN data with the largest patient sample in the literature.

BKV infection is a significant complication of renal transplantation. First described and isolated in a renal transplant recipient in 1971, BKV is recognized as a cause of allograft failure in renal transplant recipients[1]. BKV is classified into at least four major genotypes (I, II, III, and IV) and several subgroups (including Ia, Ib1, Ib2, Ic, IVa1, IVa2, IVb1, IVb2, IVc1, and IVc2) based on deoxyribonucleic acid sequence variations[5]. BKV genotype I is the most common subtype worldwide, followed by genotype IV[6].

The incidence of BKV infection after renal transplantation varies between 30-and 60% in the first four weeks[7]. In the following four weeks, the frequency of viremia is 12-13%. The incidence of viremia in the first three months is around 50%. BKVN develops in the following 4-8 weeks. BKVN occurs in 95% of viremic patients within the first two years after transplantation[7] . The incidence of BKVN varies between 1-and 10% in different studies[8]. In our study, approximately 14 thousand patients were screened, and BKVN was detected in 248 patients (1.7%) after an average of 15.8±22.2 (1-156) months after transplantation, and our results are consistent with the literature.

BKV replication usually occurs immediately after transplantation and after rejection therapy, in which cellular immunity is most suppressed[9]. Induction with T-cell depleting agents and polyclonal antibodies is associated with the development of BKV infection after transplantation[9]. Some studies have shown that exposure to triple immunosuppression with Tac, MMF/MFA, and steroids is associated with a higher risk of BKV infection. In our study, 144 (69%) of the patients had induction IS treatment with ATLG, and 164 (79%) of the patients with BKVN were receiving prednisolone/MMF-MFA/tacrolimus maintenance treatment after transplantation. Acute rejection was detected in 49 patients in the first six months, pulse steroid treatment was given to all patients, and ATLG was given to 46 patients. Both the triple maintenance IS protocol and the acute rejection treatment with ATLG may have facilitated the development of BKVN in these patients.

BKVN can have an insidious course after renal transplantation. The most common findings in patients were elevated serum creatinine and the development of proteinuria. The mean creatinine of our patients at the time of diagnosis was 1.8±0.7 mg/dl, eGFR was 45.8±19.6 ml/min, and the amount of proteinuria at the time of diagnosis was 0.6±1.6 g. The earlier the diagnosis is made in these patients, the less allograft dysfunction occurs. The American Society of Transplantation Infectious Diseases Community of Practice guideline (AST-IDCOP) suggests screening for BK viremia by quantitative testing (RT-PCR) monthly until month 9, then every three months until two years post-transplant[10]. On the other hand, the Kidney Disease Improving Global Outcomes (KDIGO) guideline suggests that quantitative testing should be performed every month

for the first 3–6 months after transplantation and then every three months until the end of the first post-transplant year[11]. In addition, it was emphasized that the BKV DNA levels of the patients should be checked if the serum creatinine rises and cannot be explained otherwise and after each acute rejection treatment. Screening can be done via sampling serum and urine for BKV DNA or examining the urine cytology[12]. The presence of BKV-infected cells (DECOY) in the urine sample is the clue for BKV infection. The positive predictive value is 20% with high sensitivity, and the negative predictive value is 100% (12). The positive predictive value of urine BKV DNA follow-up is 40%, and its negative predictive value is 100%. If urine BKV DNA is $>10^7$ copies/mL, it is interpreted as a positive result[13]. There is no need to look for BKV DNA in the blood of patients with negative BKV DNA in the urine. The positive predictive value of BKV DNA follow-up in serum is 60%, and its negative predictive value is high[12,13]. A result of BKV DNA is $>10^4$ copies/mL in plasma sampling is considered positive. In our sample, plasma BKV-DNA was screened monthly for the first nine months after transplantation and then every three months in 110 patients, and urine BKV-DNA was screened in 25 patients. Although our study is retrospective, currently, we think that plasma BKV DNA monitoring after transplantation is higher in our centers.

Allograft biopsy is the gold standard in the diagnosis of BKVN. The diagnosis is made by detecting typical basophilic nuclear bodies, inflammatory infiltration, and fibrosis in epithelial cells[14]. In addition, three patterns are seen in histopathology: Model A; cytopathic changes, normal renal parenchyma, interstitial fibrosis, and inflammatory infiltration are observed, and tubular atrophy is absent. Model B; cytopathic changes include focal, multifocal areas with tubular atrophy, interstitial fibrosis, and inflammation. Model C; may include diffuse renal tissue involvement and extensive tubular atrophy, with cytopathic change, ischemic glomerulopathy, transplant glomerulopathy, crescentic appearance, plasma cell infiltration, interstitial fibrosis, and inflammation[14, 15]. In our study, BKVN was proven by biopsy in all patients. The main findings in biopsies were the fibrosis with typical basophilic nuclear bodies [SV40 (+)] and varying degrees of inflammatory infiltration in epithelial cells. However, the staging was not performed in our biopsies, so we cannot give information about the pathological stage of the patients. The most important differential diagnosis is acute rejection. In the presence of diffuse tubulitis in areas far from viral cytopathic changes, acute cellular rejection with BKVN should also be considered[16]. Co-occurrence of endarteritis, fibrinoid vascular necrosis, glomerulitis, and C4d accumulation in peritubular capillaries is evidence of humoral rejection[16]. There were BK virus nephropathy + cellular rejection in 21 study patients and BK virus nephropathy + humoral rejection findings in 4 patients. Although the association of BKVN and rejection has been reported at rates of up to 50% in the literature [16], this rate was 12% in our study. The main question is the choice of treatment in the presence of rejection because steroid or ATLG treatment may exacerbate BKVN and contribute to the risk of allograft loss. Steroid plus IVIG treatment is considered a more innocent modality and is recommended. In our study, ten patients received pulse steroid treatment, ten received steroid + IVIG treatment, and five were not treated with additional IS therapy. While allograft loss developed in 12 patients (48%) with concomitant rejection, this rate was 10% in patients without rejection. Therefore, concomitant rejection in these patients negatively affects allograft survival.

The leading cause of the development of BKVN is excess immunosuppression. Therefore, the first intervention in patients with BKVN should be evaluation and reduction of the current IS therapy. The interventions to be considered are discontinuation of the antimetabolites, dose reduction of the CNIs, or switching the CNI to a mTORi[17]. Therefore, it is recommended to keep tacrolimus level $<$ 6 ng/ml, daily MMF dose [?] 1 g/day, and blood CSA around 100-150 mg/ml[17]. It takes 4-10 weeks for the viremia to start decreasing and 7-20 weeks for the viremia to disappear. If there is no decrease in viral load within four weeks, the dose of IS drugs should be reduced or discontinued, or antiviral treatment should be planned. In our study, the antimetabolite dose alone was reduced in 18 patients, antimetabolite treatment alone was discontinued in 45 patients, the antimetabolite was discontinued plus the CNI dose was reduced in 47 patients, the antimetabolite was switched to AZA in 30 patients, antimetabolites were switched to AZA plus CNI dose was reduced to 50% in 11 patients, and CNI was switched to mTORi in 56 patients. In the literature review, it is seen that the IS intervention approaches of different centers are pretty similar to our centers.

Although some agents have been suggested to be effective in treating BKVN, there are no randomized

controlled studies in the literature to make a recommendation. Cidofovir, leflunomide, quinolones, and IVIG are the most preferred agents worldwide. There is no randomized prospective controlled studies of cidofovir. Since the doses of the IS drugs are also reduced in reported cases where the viral load is decreased, there is no definite evidence of its independent effect. Cidofovir is an expensive drug applied at 0.25-1 mg/kg doses for 1-3 weeks. Anterior uveitis has been reported in 12-35% of cases[18]. In the cidofovir study with the largest number of patients, it was observed that while GFR was stable in the short term follow-up in 75 patients, GFR decreased in the long term observations. In our study, graft loss developed in 7 (38%) of 18 patients who received cidofovir. Leflunomide is developed for the treatment of rheumatoid arthritis and psoriatic arthritis. It was found to be effective against CMV and polyomavirus in vitro. In BKVN, leflunomide dose is 20-40 mg/day. A series of 26 patients followed up for 15 months; Tac was maintained within serum levels of 4-6 ng/ml, MMF discontinued, leflunomide initiated as 50-100 mg/ml, and 9 of the patients were also given cidofovir. Stable kidney function was achieved in 23 of 26 patients, and leflunomide was suggested to be an effective option[19]. There was no graft loss in our study in 11 patients receiving leflunomide and 12 patients receiving leflunomide + IVIG. Thus leflunomide seems to be the most effective treatment compared to other treatments. There is limited information about the efficacy of IVIG in BKVN. In a series of 8 patients, IS medications were reduced by 50%, and IVIG 2g/kg was given for 2-5 days. The follow-up period was 15 months, and graft function was preserved in 7 patients (88%)[20]. In our study, graft loss occurred in only 2 of 15 patients given IVIG, and IVIG can also be considered an effective treatment. Quinolones may be effective against BKV. There is a limited number of studies examining its effectiveness in BKVN treatment. A meta-analysis showed that fluoroquinolones did not prevent the development of BKVN after transplantation[21]. Fluoroquinolones may reduce the rate of the BK virus to some extent but may not have sufficient clinical effects[22]. In our study, graft loss developed in only 1 (5%) of 17 patients treated with quinolones, and quinolones were both cost and clinically effective.

There are also reports about patients who underwent retransplantation after allograft loss due to BKVN. In a series of 126 patients, graft survival at 1 and 3 years after retransplantation was 99% and 94%, and BKVN recurred in 17.5%[22]. In our study, five patients were retransplanted, and none developed BKVN in the follow-up.

Our study has the largest number of patients in the literature so far. However, there are some limitations, such as its retrospective design. On the other hand, it is a multicenter study, and the centers' IS reduction or discontinuation policies are different. However, there is a lack of information about the rationale for the treatment choices for patients.

In conclusion, BKVN is still an important and unclarified problem in renal transplantation. There are no randomized controlled studies, so the optimal treatment is not standardized. Therefore, randomized controlled studies and studies with larger samples are needed.

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