



Current Status, Prevention and Treatment of BK Virus Nephropathy

Ester Kurašová^{1,*}, Jakub Štěpán¹, Karel Krejčí¹, František Mrázek², Pavel Sauer⁴, Jana Janečková⁵, Tomáš Tichý³

ABSTRACT

All renal transplant recipients should undergo a regular screening for BK viral (BKV) viremia. Gradual reduction of immunosuppression is recommended in patients with persistent plasma BKV viremia for 3 weeks after the first detection, reflecting the presence of probable or suspected BKV-associated nephropathy. Reduction of immunosuppression is also a primary intervention in biopsy proven nephropathy associated with BKV (BKVN). Thus, allograft biopsy is not required to treat patients with BKV viremia with stabilized graft function. There is a lack of proper randomised clinical trials recommending treatment in the form of switching from tacrolimus to cyclosporin-A, from mycophenolate to mTOR inhibitors or leflunomide, or the additive use of intravenous immunoglobulins, leflunomide or cidofovir. Fluoroquinolones are not recommended for prophylaxis or therapy. There are on-going studies to evaluate the possibility of using a multi-epitope anti-BKV vaccine, administration of BKV-specific T cell immunotherapy, BKV-specific human monoclonal antibody and RNA antisense oligonucleotides. Retransplantation after allograft loss due to BKVN can be successful if BKV viremia is definitively removed, regardless of allograft nephrectomy.

KEYWORDS

BK virus nephropathy; BK virus-specific T-cell immunotherapy; monoclonal anti-BK virus antibodies; BK virus vaccine; immunosuppressive therapy; RNA antisense oligonucleotides; kidney transplantation

AUTHOR AFFILIATIONS

¹ University Hospital Olomouc and Palacký University Olomouc, Faculty of Medicine and Dentistry, Department of Internal Medicine III – Nephrology, Rheumatology and Endocrinology, Olomouc, Czech Republic

² University Hospital Olomouc and Palacký University Olomouc, Faculty of Medicine and Dentistry, Department of Immunology, Olomouc, Czech Republic

³ University Hospital Olomouc and Palacký University Olomouc, Faculty of Medicine and Dentistry, Department of Clinical and Molecular Pathology, Olomouc, Czech Republic

⁴ University Hospital Olomouc and Palacký University Olomouc, Faculty of Medicine and Dentistry, Department of Microbiology, Olomouc, Czech Republic

⁵ University Hospital Olomouc and Palacký University Olomouc, Faculty of Medicine and Dentistry, Department of Surgery II, Olomouc, Czech Republic

* Corresponding author: University Hospital Olomouc and Palacký University Olomouc, Faculty of Medicine and Dentistry, Department of Internal Medicine III – Nephrology, Rheumatology and Endocrinology, Zdravotníků 248/7, 779 00, Olomouc, Czech Republic; e-mail: ester.kurasova@fnol.cz

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INTRODUCTION

BKVN represents a severe infection, threatening function of the kidney graft, particularly during the first year after transplantation. Its occurrence is closely related to the level of attenuation of the recipient's immune system. In the absence of BK specific treatment options for advanced BKVN, active screening for BKV replication and subsequent immunosuppression adjustment represent essential measures in preventing the development of BKVN. Management during modification of immunosuppressive protocols as well as addressing the initial stages of replication associated with significant urinary BKV excretion remain not completely clear.

EPIDEMIOLOGY AND PATHOGENESIS OF BKVN

BKV is a polyomavirus, which traditionally causes nephropathy in renal allografts as a result of reactivation of latent BKV in renal tubular epithelium (1). Based on the amino acid sequence of the large T-antigen, polyomaviruses are divided into 4 genera with >70 species. BKV is an omnipresent, small (40–45 nm) DNA virus, consists of a capsid and a DNA double helix but lacks a lipid envelope. The large T-antigen is important for BKV replication, recognition by the cellular immunity components and virus oncogenicity. Genotype I and its subgroup I/b-2 (60–80%) are predominant, followed by the genotype IVa (10–20%) (2, 3). BKV was first reported in the 1970s (4). In the first months of life, maternal antibodies protect infants from BKV infection, and after their disappearance, BKV infection starts to occur, as demonstrated by 10% to 30% seropositivity in infants and 65% to >90% between 5 and 10 years of age (5). Primary BKV infection in immunocompetent patients is usually a subclinical event or associated with mild nonspecific symptoms, after which BKV persists in the kidney, peripheral-blood leukocytes and possibly the brain. Transmission is ongoing from person-to-person, faecal-oral transmission via wastewater is also possible. Furthermore, leukocyte-containing blood transfusion and transplacental transmission has been also reported (4, 6). BKV replicates itself in the nucleus of renal tubular proximal epithelial cells that are also the natural host cells (6). Daughter viruses are delivered to other cells to spread infection (7), which is followed by necrosis, inflammation and local tissue damage which enables the virus to penetrate into the intertubular space, peritubular capillaries and adjacent cells (8). About 5–15% of renal transplant recipients become viremic, and 20–40% become BK viruric, ureteral stenosis is rarer (9, 10). Only viremia has been related to BKVN (11). Graft failure has been observed in 50–80% of recipients who developed BKVN within 24 months from virus detection (12). Potential risk factors associated with BKVN development are the age of both the donor and the recipient, male gender, obesity, diabetes duration, delayed graft function (13), degree of HLA mismatches, ABO-discordance, the condition of retransplant, higher variability in mean tacrolimus levels, kidneys received from BKV seropositive donors and transplanted to BKV seronegative recipients

as well as donors and recipients positivity in the serum of both BKV and cytomegalovirus (CMV) (14).

CLINICAL MANIFESTATIONS OF BKVN

BKV replication can be detected as early as 1 month after kidney transplantation and its overall accumulative rate increases steadily with time after transplantation, most frequently occurs during the first year after transplantation (in a range of six days to five years) when immunosuppression is at its most intense (11, 15). BKV has been associated with several clinical manifestations amongst them most prominently BKVN, ureteral stenosis and late-onset haemorrhagic cystitis, particularly in patients after bone marrow transplantation (16). Most frequently, we may observe only asymptomatic, acute or gradual creatinine elevation, the urinalysis corresponds to interstitial nephritis. However, the urine examination may be even completely normal (17). Early donor-specific antibody (DSA) formation in case of BKV viraemia has been reported in African-American graft recipients more commonly in the first 24 months after transplantation (18). Association between persistent BKV viraemia (≥ 140 days) and significant class II DSA de-novo formation has also been pointed out by Sawinski et al. (2015) (19). Collapsing glomerulopathy in regressing BKVN after immunosuppressive therapy reduction has also been documented, as well as co-occurrence of BKVN with cytomegalovirus glomerulitis in the first weeks after kidney transplantation (20, 21). Also, the association with malignancies remains a topic of ongoing discussion (16). Cases of BKV-positive urothelial bladder carcinoma developing 15 months after transplantation have been reported, as well as BKV-positive urothelial carcinoma of the graft 5 years after clinically successful BKVN therapy (22, 23). Unusual manifestations may include vasculopathy, retinitis, hepatitis, systemic lupus erythematosus, Guillain-Barré syndrome, cases of meningoencephalitis and interstitial pneumonitis (24). Metastatic clonal BKV spread from kidneys to other organs was not detected (25).

BKVN DIAGNOSTICS

Regular screening of BKV reactivation in asymptomatic patients is of paramount importance to prevent graft dysfunction. Prospective screening may be based on monitoring of decoy cells in urine; quantitative polymerase chain reaction (PCR)-BKV analysis of urine and peripheral blood is rather currently used (26).

PCR

The presence of viruria usually precedes BKV viraemia by 4 weeks and the development of BKVN with graft dysfunction by 8 weeks in average (27). PCR method analysing is the most sensitive marker of BKV reactivation, occurring in 23–73% of recipients. More than 95% of viral load in urine comes from BKV replication in uroepithelium and only less than 5% from tubular cell BKV replication (28).

Recently, high levels of BKV viruria ($\geq 2.5 \times 10^7$ copies/ml) have been documented as a possible early marker of the BKV viraemia and BKVN development risk (29). The influence of persistent nephrotoxicity of calcineurin inhibitors (CI) on the higher incidence of significant BKV viruria ($> 10^7$ copies/ml) with more frequent transition to BKV viraemia and BKVN in the first year after transplantation has also been reported (30). Frequent PCR screening of viruria is currently a common method for early detection of BKV replication (31). Its importance is highest during the first year after transplantation, or within 2 years from the procedure (32). BKV viraemia affects 8–62% of kidney recipients with a maximum incidence of 3–6 months after transplantation (33). BKVN incidence during the first year is reported in a range of 1–10% (34). Plasma viraemia $> 10^4$ copies/ml has a stronger positive predictive value for BKVN than viruria (35). However, less than 10^4 /ml plasma copies have been demonstrated in up to 35% of BKVN patients (36). Today, higher BKV prevalence is noted based on standardized detection. In one recent study, PCR testing for viraemia or viruria indicated BKV positivity in 62% of patients (37). In the current study urinary cell mRNA profiling showed 86% sensitivity and 100% specificity (38). PCR negative cases have been reported sporadically (39).

ALTERNATIVE METHODS OF BKV REPLICATION DETECTION

PCR from saliva and oral cavity flush has similar efficacy in detection of BKV and John Cunningham virus (JCV) as the blood and urine analysis (40). The uptake of cylinder-like three-dimensional aggregates of polyomaviruses in urine in the electronmicroscopic examination, so-called Haufen bodies (HB), is accompanied by substantial BKV viraemia and provided 100% sensitivity and 99% specificity for detection of biopsy proven BKVN. Quantitative determination of HB and BKVN has also demonstrated very good correlation (41). Determination of BKV mRNA levels in urine using a cut-off limit of 6.5×10^5 BKV VP1 mRNAs/ng of RNA in urinary cells has shown 99% sensitivity and specificity for BKVN detection (42). Elevation in urinary exosomal BKV-micro RNA-B1-5p throughout the first 12 months post-transplantation precedes the development of PCR-BKV viraemia and subsequent manifestation of BKVN (43). Serology examination aimed at demonstration of BKV antibodies is not beneficial for detection of BKVN. In case of primary infection after transplantation they increase in the IgG class in at least 6 weeks after contact with the virus, but even in the intervals of up to 2 years (44).

CURRENT GUIDELINES FOR PRE-TRANSPLANT SCREENING OF BKV REPLICATION

Due to the absence of valid studies, pre-transplant donor screening of BKV viruria, virus genotyping or examination of VLP/VP1 specific antibodies is not recommended. Similarly, recipient testing for VLP/VP1 specific antibodies, neutralizing BKV antibodies (BKV subtypes), and the presence and function of BKV-specific T cells is not suggested within pre-transplant screening (45).

CURRENT GUIDELINES FOR POST-TRANSPLANT SCREENING OF BKV REPLICATION

BKV-DNA viraemia PCR monitoring is recommended in the post-transplant period to initiate preemptive therapy early and prevent the development of BKVN. Alternatively, urinary DC evaluation may be used when the urine finding of > 3 DC/HPF or BKV viruria $> 10^7$ copies/ml may be considered positive (45, 46). Testing should be performed monthly during the first year after transplantation for the first 9 months; afterwards, every 3 months up to 2 years after transplantation (47). Then, it is appropriate to test at an annual frequency for 5 years. Potential BKV replication should also be evaluated at any per-protocol or diagnostic biopsy, particularly in case of unclear dysfunction. Detection of BKV-DNA viraemia should be confirmed within the next 3 weeks by a repeated examination. In case of viraemia persistence and stable graft function compared to the previous examination, where the patient is not at a higher risk of acute rejection (AR), immunosuppressive therapy may be reduced without biopsy (45).

CURRENT GUIDELINES FOR GRAFT BIOPSY IN CASE OF SUSPECTED BKVN

Biopsy should be performed before reduction of immunosuppressive therapy in case of a high immunological risk or progressive graft dysfunction (48). Biopsy procedure should include collection of 2 samples of the renal tissue to capture the medullary part of the parenchyma. 10–30% of biopsy samples may be falsely negative in case of focal distribution of changes and predominance of medullary involvement within BKVN (45, 49). BKVN should be considered in cytopathic changes in tubular epithelial cells and confirmed with immunohistochemistry (SV40+). Histological findings in demonstrated BKVN should be evaluated based on the AST-IDCOP 2013 guidelines together with the guidelines of Banff 2018 Study group (45, 48). The Banff 2018 kidney allograft biopsy classification schema applies a semiquantitative scoring system of 0, 1, 2, or 3 for scoring acute and chronic histological lesions within the kidney allograft (50, 51). In 2019 a consensus panel including viral infections associated with transplantation was established (51). However, a well-designed study failed to show clear relationship between any of the morphological histological features or categories and graft prognosis (49). Furthermore, another large study has demonstrated that graft loss in BKVN correlates with 3 clinical parameters only – transplant from a deceased donor, level of BKV viraemia, and the incidence of late AR (52). Multicenter retrospective study of 124 patients with BKVN found no correlation between Banff 2018 classification classes and risk of graft loss (53).

CURRENT GUIDELINES IN CASE OF BKVN AND AR COINCIDENCE

If AR and BKVN co-occurrence is suspected, we should search for the presence of rejection endarteritis, fibrinoid

vascular necrosis, glomerulitis or C4d deposition around the peritubular capillaries. Tubulitis and peritubular inflammation are not AR-specific and are also present in BKVN. Moreover, they may occur outside the region where BKVN was detected (54). C4d+ positivity may be detected in tubular basement membranes in isolated BKVN, but not in peritubular capillaries. Alloreactive and virus-reactive T cells co-occurrence is also common (55). Thus, anti-rejection therapy should be initiated in patients with biopsy proven AR, with persistent BKV viraemia (with or without histological verification of BKVN) as the first step. Only if there is a clinical and laboratory response to anti-rejection therapy after approximately 2 weeks, the second step should follow with reduction in immunosuppressive therapy (45).

CURRENT GUIDELINES FOR BKV VIRAEMIA AND BKVN THERAPY

Therapy of significant BKV viraemia and BKVN is based on reduction of immunosuppressive therapy. The diagnosis of BKVN is probable in case of demonstration of $> 10^3$ copies/ml of blood (2 measurements over 3 weeks) and presumptive in case of demonstration of $> 10^4$ copies/ml of blood (at least 1 measurement out of 2). BKV viraemia resolution may be expected in 80–100% of patients after reduction of immunosuppressive therapy, BKV viraemia recurrence in 10% of patients. Further reduction of immunosuppression is recommended in such a case (56, 57). If immunosuppressive therapy is reduced in already developed BKVN (biopsy proven), the effect on viraemia is usually substantially worse and further intervention is often required; function restitution may take longer and definitive failure of graft function is more frequent as well (45, 58). Immunosuppressant level targets should be < 6 ng/ml for tacrolimus, < 150 ng/ml for cyclosporine, < 6 ng/ml for sirolimus; mycophenolate should be administered in a half or lower dose. Complementary therapy based on conversion of tacrolimus to low-dose cyclosporine, CI to sirolimus or mycophenolate replacement with leflunomide may be considered. There are practically two options for immunosuppressive therapy reduction. In the first case, we initiate therapy with reduction of the CI dose by 25–50%; in the next step, MMF is reduced by 50% or then completely withdrawn. This approach could be particularly advantageous in the case of the current histological finding of CI nephrotoxicity (30). The second option is to start the treatment with reduction of MMF by 50%, followed by CI dose decrease by 25–50% in case of the persistence of virus replication, followed by withdrawal of MMF. The dose of prednisone should be < 10 mg/day in both cases. It is recommended to repeat testing every 2 weeks in this therapy until viraemia disappears; should viraemia persist, the management is individual – further reduction of immunosuppression is recommended with target tacrolimus levels of < 3 ng/ml and cyclosporine levels of < 100 ng/ml. mTORi for therapy of refractory or advanced BKVN is also possible. Supportive antiviral therapy may be considered in patients with persistent BKV viraemia and probable, presumptive or biopsy proven BKVN, despite adequately reduced immunosuppressive therapy (45).

SUPPORTIVE THERAPY OF BKVN

INTRAVENOUS IMMUNOGLOBULINS (IVIG)

IVIGs may contain antibodies against omnipresent BKV and JCV. However, the neutralising effect of these antibodies against all major BKV genotypes is not generally accepted (44). Possible effect of IVIG on strengthening of the overall antibody response may be expected in inadequate cellular reactivity (59). They are mostly administered in a dose of 0.1–2 g/kg with concomitant reduction of immunosuppressive therapy (45).

ALTERNATIVE PROCEDURES IN BKVN THERAPY

Conversion from tacrolimus to low-dose cyclosporine may be considered, taking advantage of the suppressive effects of cyclosporine for BKV replication and at the same time reducing mycophenolate levels. In a study by Chen et al., conversion from tacrolimus to low-dose cyclosporine was effective in BKVN therapy (59). A prospective observational study in patients with BKV viraemia and BKVN to evaluate the effect of this conversion on virus replication is currently ongoing (60). Cidofovir can inhibit polyoma viral DNA replication but is primarily excreted by the kidneys and is nephrotoxic. The lack of randomized studies have led to reluctance to adopt it widely. Prophylaxis with newer less toxic brincidofovir may yet prove effective (61).

POSSIBILITIES OF IMMUNOTHERAPY IN THE TREATMENT OF BKVN

BKV SPECIFIC T CELL IMMUNOTHERAPY

Failure of BKV-specific T cell to control viral replication due to IS overdose results in reactivation of BKV infection (62). A phase II clinical trial showed that administration of BKV-specific T cells manufactured from a patient's stem cell donor or unrelated donors could reduce symptomatic infection and BK viral load effectively in HSCT and solid organ transplant recipients. Virus-specific T cells therapy in this study was safe with no infusional toxicity, de novo graft-versus-host disease, or graft rejection (63). A phase II of multicentre, randomized, double-blind, placebo-controlled trial of adoptively transferred multivirus-specific T cells in kidney transplant recipients with either high or low levels of BK viraemia is also currently underway. Its results are expected in 2023 (64).

ANTIBODIES IN THE TREATMENT OF BK VIRUS

A randomized, double-blind, placebo-controlled study to assess the safety and efficacy of MAU868 for the treatment of BK viraemia in kidney transplant recipients is currently being conducted (65). MAU868 is a human monoclonal antibody (IgG1), which binds to viral capsid protein VP1 and blocks the binding of the virus to the host cell surface. It could be the first effective therapy for BKV infection. Final results of the study are expected in 2023 (66).

BKV VACCINE DEVELOPMENT

Administration of a multi-epitope VLP vaccine, which is associated with a significant response in the form of antibody production that neutralizes all 5 BKV serotypes, appears promising (67). A prospective phase II multicenter study to evaluate the tolerability and safety of BD03, a DNA vaccine administered intramuscularly for the prevention of CMV and BKV reactivation in kidney transplant recipients, is currently in progress (68).

RNA-BASED THERAPY (HYBRIDIZE'S THERAPEUTICS)

A direct acting anti-viral therapy is designed to target the viral mRNA, work intra-cellular and protect the cells from within and therefore provides for low off-target effects. RNA antisense oligonucleotides discontinues the splicing process, preventing viral synthesis and replication (69). Clinical studies to prevent severe disease from BK virus (BKV) infections in immunocompromised patients are expected to start within two years (70).

SUMMARY

BKVN represents a severe complication, threatening function of the kidney graft, particularly during the first year after transplantation. But we have to bear it in mind in every deterioration of function. Its incidence is likely to increase with the increasing number of retransplants and incompatible transplants. Active screening for BKV replication in the post-transplant period represents an essential prophylactic procedure in prevention of the graft damage considering the absence of BKV-specific antiviral therapy. It allows for initiation of preemptive reduction of immunosuppressive therapy in case of demonstration of significant BKV viraemia, thus preventing the development of nephropathy. This approach appears to be effective for reduction of early graft loss due to BKVN, despite a higher risk of alloimmune activation and AR. Post-transplantation screening of BKV replication is also suitable in organ recipients during non-renal transplants considering possible BKV reactivation affecting their own kidney. Non-specific antiviral therapy is utilised in patients with clinically manifest BKVN with graft dysfunction progressing over a few weeks or months despite maximum immunosuppressive therapy reduction. Retransplantation is delayed in patients with BKVN-induced graft failure until BKV viraemia resolution. General nephro-ureterectomy of the original transplanted kidney is not recommended in the absence of BKV replication. Research on multi-epitope anti-BKV vaccination, BKV-specific T cell or antibody mediated immunotherapy or the development of BKV specific antivirals and direct acting anti-viral therapy is of much importance. If shown to be safe and effective, this therapy could be a true game changer in transplantation medicine with the potential to prevent kidney transplant patients from developing graft rejection and organ loss due to BKV.

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