



Advances in BK Virus Complications in Organ Transplantation and Beyond

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Reactivation of BK virus (BKV) remains a dreaded complication in immunosuppressed states. Conventionally, BKV is known as a cause for BKV-associated nephropathy and allograft dysfunction in kidney transplant recipients. However, emerging studies have shown its negative impact on native kidney function and patient survival in other transplants and its potential role in diseases such as cancer. Because BKV-associated nephropathy is driven by immunosuppression, reduction in the latter is a convenient standard of care. However, this strategy is risk prone due to the development of donor-specific antibodies affecting long-term allograft survival. Despite its pathogenic role, there is a distinct lack of effective anti-BKV therapeutics. This limitation combined with increased morbidity and health care cost of BKV-associated diseases add to the complexity of BKV management. While summarizing recent advances in the pathogenesis of BKV-associated nephropathy and its reactivation in other organ transplants, this review illustrates the limitations of current and emerging therapeutic options and provides a compelling argument for an effective targeted anti-BKV drug.

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INTRODUCTION

BK virus (BKV) is a common opportunistic pathogen in kidney transplant recipients and one of the most challenging causes of allograft dysfunction and loss. This virus was named after a Sudanese kidney transplant recipient with ureteric stenosis who was the first patient to have BKV isolated from the urine. It is a double-stranded circular DNA virus, member of the *Betapolyomavirus* genus in the *Polyomaviridae* family.¹ To date, many other polyomaviruses have been identified,¹ including JC virus (the causative agent of progressive multifocal leukoencephalopathy), Simian virus 40 (SV40), and Merckle cell virus.² Based on differences of the VP1 protein or gene sequence, BKV has been divided into 12 subtypes.^{3,4} Their distribution varies across geographical regions. Important features of the BKV biology are shown in Figure 1,^{3,5,6} which includes viral DNA protected by an icosahedral capsid structure consisting of 72 pentamers made up of VP1, a structural protein. Readers are referred to 2 in-depth reviews that discuss the fundamentals of BKV biology.^{2,5}

BACKGROUND

Epidemiology

Several studies suggest that BKV coevolved with humans, which explains the high prevalence and low morbidity in healthy individuals.^{4,7} In the first months of life, maternal antibodies protect infants from BKV infection,⁸ and after their disappearance, BKV infection starts to occur, as demonstrated by 10% to 30% seropositivity in infants⁸ and 65% to >90% between 5 and 10 years of age.⁷⁻¹⁰ Primary BKV infection in immunocompetent patients is usually a subclinical event or associated with mild nonspecific

symptoms,⁸ after which BKV persists in the kidney, peripheral-blood leukocytes, and possibly the brain.⁸

Pathogenesis

Following primary infection, BKV spreads and infects renal tubular epithelial cells and epithelial cells of the urogenital tract, where it remains latent.^{11,12} Several factors including allograft, viral, and host factors influence reactivation of BKV.¹¹⁻¹³

Upon reactivation, the infected renal tubular epithelial cells develop an increase in nuclear size and generate intranuclear basophilic inclusions. These cells detach from the basement membrane and appear in urine as decoy cells.¹² A wide array of genomic changes follows within 48 hours of viral proliferation in the human tubular epithelial cells that regulate fundamental biological processes such as cell cycle, apoptosis, DNA damage, and release of immune mediators, all of which contribute to the lytic phase of viral reactivation and its persistence in the renal allograft.¹⁴ Eventually the virions egress by cell lysis, leading to viruria,¹² and subsequently cross to the interstitium and into capillaries, leading to viremia.¹² All these events culminate in necrosis and lytic destruction of the renal tubulointerstitium with profound inflammation (BKV-associated nephropathy) in kidney transplant recipients or hemorrhagic cystitis in hematopoietic stem cell transplant recipients.^{11,12}

Although the innate immune system is considered important in controlling the primary BKV infection,¹³ its role in controlling BKV reactivation or BKV-associated nephropathy is limited. The adaptive humoral response might play a role in controlling or limiting BKV reactivation given that seronegative recipients experience an increased risk for viremia and BKV-associated

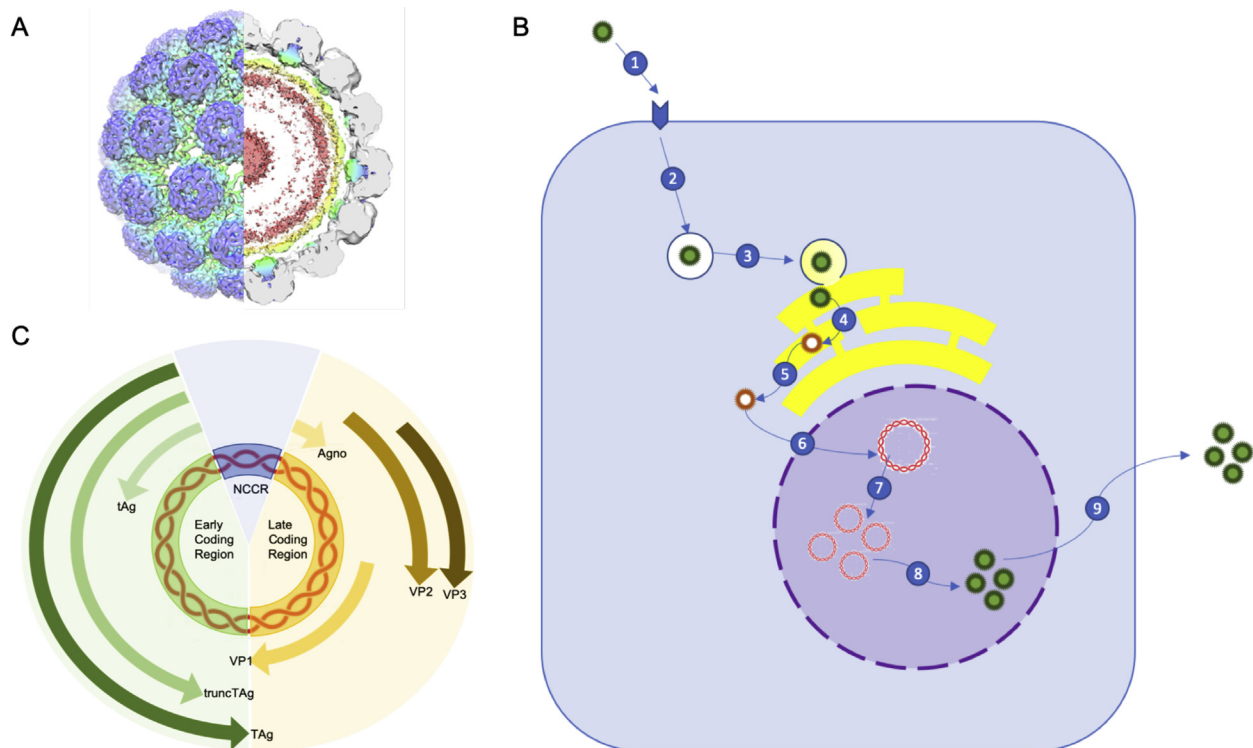


Figure 1. BK virus (BKV) biology. (A) BK virions are 45 nm in diameter, nonenveloped, and enclose the viral genome with host cell histones (packaged DNA is depicted in yellow and red on the right) surrounded by a capsid. The most abundant viral protein is VP1 (depicted in blue on the left and in gray on the right), which arranges in 72 pentamers to form the outer surface of the viral capsid, while the inner part of the capsid is composed of proteins VP2 and VP3 (depicted in blue and green on the right). Adapted from: Hurdiss et al.⁶ (B) BKV infection is initiated by the attachment of VP1 to polysialylated gangliosides (GD3, GD2, GD1b, and GT1b) and sialylated glycoproteins (1), followed by internalization (2). It then moves along microtubules to reach the endoplasmic reticulum (3), where chaperones, disulfide isomerases, and reductases partially uncoat the capsid (4) and release it into the cytosol (5). The viral genome is then transported (through interaction of VP2 and VP3 proteins with the importin α/β import pathway) into the nucleus for replication (6-7) followed by virion self-assembly in the nucleus (8). Virions are then released from the cell by cell lysis (9). (C) Genome map of BKV. BKV genome is ~5 kb in length and replicates bidirectionally from a unique origin within the noncoding control region (NCCR; also called transcriptional control region [TCR]). The early coding region encodes 3 proteins by alternative splicing (large tumor antigen [tAg]; small tumor antigen [sAg]; and the truncated tAg; truncTAg), while the late genes encode structural protein, VP3 and Agno proteins), also by alternative splicing of a common pre-mRNA. The proteins encoded in the early coding region are mostly responsible for viral genome replication, with tAg being particularly important for making a quiescent cell reenter the cell cycle and replicate the viral genome. The structural proteins are important in viral attachment to susceptible cells, cell entry, viral propagation, and assembly of progeny virions.

nephropathy,^{15,16} with the highest risk in donor-positive and recipient-negative pairs.^{15,17-20} Additionally, patients who develop viremia have lower pretransplantation antibody titers against BKV,²¹ and higher BKV antibody titers are correlated with lower plasma viral loads and shorter times until resolution of the infection.²² Although these studies underscore the importance of anti-BKV antibodies, most patients with BKV-associated nephropathy are seropositive before transplantation^{23,24} and develop active infection despite the development of high anti-BKV antibody titers.²¹

This disconnect between the anti-BKV antibodies and their lack of efficacy in preventing viremia was explored in a recent study.²⁵ Solis et al²⁵ showed that in 95% of cases, the replicating BKV strains are of donor origin. This results

in a mismatch between the recipient's anti-BKV neutralizing antibodies (nAbs) and replicating BKV strain, which renders the nAbs ineffective.²⁵ However, they found that the genotype-specific nAbs can be a predictive marker for stratification of patients into lower and higher BKV disease risk groups before and after transplantation.²⁵ Collectively, these studies indicate that BKV-specific nAbs may not protect against BKV-associated nephropathy. However, testing for antibodies against BKV before transplantation is currently not recommended.^{26,27}

Cellular immunity and in particular memory cell function is considered to be the cornerstone for controlling the latent viral state and suppressing viremia and BKV-associated nephropathy.¹³ Healthy seropositive individuals have a strong BKV-specific T-cell response,

Box 1. Risk Factors for BK Virus Infection

Virus-associated factors	• Rearrangement of the NCCR Region ⁵⁴
Transplant factors	<ul style="list-style-type: none"> • Degree of immunosuppression <ul style="list-style-type: none"> ◦ Thymoglobulin use^{23,42,47,53} ◦ Higher steroid use^{23,42,48} ◦ Tacrolimus-based regimens (contraversial)^{15,23,42,47-51,53} • Rejection episodes^{42,47,52} • Delayed allograft function^{42,47,53} • Higher degree of HLA antigen mismatch^{42,47,53} • Blood type ABO-incompatible transplantation^{55,56}
Receptor factors	<ul style="list-style-type: none"> • Decreased cellular immunity^{31,46} • Age (<17-18 and >55-60 y)^{42,47} • Sex (male)^{42,47} • Race (African American)^{42,47} • Ureteral stent placement^{50,57,58}
Donor factors	<ul style="list-style-type: none"> • BK seropositive donor (especially D+/R-pairs)^{15,17-20} • Deceased donor^{42,47} • Donation after circulatory death^{42,47}

Abbreviation: NCCR, noncoding control region.

whereas seronegative healthy individuals do not.²⁸ Following kidney transplantation, patients with no signs of BKV replication or those with viremia but not viremia have a positive BKV-specific T-lymphocyte response compared with healthy seropositive controls.²⁸ In contrast, patients with viremia or BKV-associated nephropathy have undetectable levels of BKV-specific T-cell response.^{11,24,28-31} Patients who develop a self-resolved viremia mount a BKV-specific T-cell response quickly, whereas patients who develop BKV-associated nephropathy elicit a T-cell response only after immunosuppression has been reduced.^{28,29} Taken together, the efficient control of BKV reactivation and its sequela is most likely dependent on the induction of stable antiviral memory T-cell responses.³²

Mounting an effective BKV-specific cellular response is associated with stabilization or reduction of serum creatinine levels in patients with BKV-associated nephropathy.^{29,30} This argues against the notion of the tissue damage being caused by the immune response. In contrast, BKV-induced hemorrhagic cystitis in hematopoietic stem cell transplant recipients occurs after engraftment,^{30,33} raising the possibility of the damage being caused by an immune reconstitution syndrome.

CLINICAL FEATURES

BKV reactivation results in tubulointerstitial nephritis and, infrequently, ureteric stenosis in kidney transplant recipients and hemorrhagic cystitis in hematopoietic stem

cell transplant recipients. However, case reports exist of BKV causing pneumonitis, retinitis, vasculopathy, meningoencephalitis, and Guillain-Barré syndrome, among other manifestations.³⁴ In animal models, BKV infection results in several tumors due to inactivation of tumor suppressors such as p53 and pRb proteins by the large-tumor antigen (TAG).³⁵ The presence of BKV DNA and/or proteins was detected in brain tumors, neuroblastoma, bone, insulinoma, prostate, Kaposi sarcoma, etc and summarized in International Agency for Research on Cancer monographs by the World Health Organization.³⁶ BKV infection increases the risk for invasive bladder cancer in kidney transplant recipients³⁷ and prostate cancer (odds ratio, 1.9-125) in the general population.³⁸ All these studies raise the possibility that BKV is a contributing tumorigenic factor,³⁹ an area that warrants further investigation to define a precise mechanism and the implication of a targeted anti-BKV agent in the therapy of cancer.

BKV-Associated Nephropathy

Clinical Manifestations

Following kidney transplantation, BKV reactivation can manifest as viremia in 30% to 40%, viremia in 10% to 20%, or BKV-associated nephropathy in 1% to 10% of patients.^{23,40-44} When BKV-associated nephropathy develops, it usually manifests as acute or progressive allograft dysfunction with decreasing glomerular filtration rate (GFR), hematuria in 19% of patients, and proteinuria with protein excretion < 1 g/d in 48% of patients.⁴⁵

Risk Factors

Several risk factors have been identified for the development of BKV-associated nephropathy (Box 1^{15,17-20,23,31,42,46-58}). The most important is the level of immunosuppression.^{12,40,59} The degree of immunosuppression as gauged by T-cell function assays has been proposed to determine which patients are at higher risk for BKV replication.^{31,46}

The type of immunosuppressive agent also has bearing on BKV-associated nephropathy. Thymoglobulin, either as induction therapy or treatment of rejection, increases the risk for BKV infection.^{23,42,47} Neither alemtuzumab nor interleukin 2 receptor antibody (ie, basiliximab) use appear to increase the risk for BKV infection.^{42,47} Tacrolimus increases BKV replication in vitro, mediated through FK binding protein 12, independent of its immunosuppressive effect. Conversely, cyclosporine and sirolimus inhibit BKV replication.⁶⁰ However, clinical studies have not proven a direct link between any individual immunosuppressive agent and BK viremia or BKV-associated nephropathy. Some^{42,48,49} but not all^{15,23,47,60,51} clinical studies have shown increased risk with tacrolimus compared to cyclosporine. Of note, a randomized controlled trial (RCT) comparing tacrolimus and cyclosporine showed no difference in viremia development.⁵⁰ Conversely, mammalian target of rapamycin (mTOR) inhibitors appear to be protective from BKV in most

Table 1. Noninvasive Diagnostic Tests for BK Virus–Associated Nephropathy

Test	Threshold Value	Sensitivity	Specificity	PPV	NPV	References
Decoy cells	>10 cells/cytospin	25%-100%	71%-96%	5%-57%	97%-100%	22, 48, 68-70
Urine BK PCR	>1 ×10 ⁷ copies/mL	100%	92%-96%	31%-67%	100%	70,71
Blood/plasma BK PCR	>1 ×10 ⁴ copies/mL	100%	88%-96%	50%-82%	100%	22, 68, 70,71
Haufen	≥1 tight 3-dimensional polyomavirus clusters	100%	99%	97%	100%	72
VP1 urinary mRNA	6.54 ×10 ⁵ copies/ng	93.8%-100%	93.9%-97%	97%	100%	73,74
Blood microRNA	Cq of 31.9	100%	94.9%	77.8%	100%	75
Urinary exosome microRNA	5.9 log ₁₀ copies/mL	100%	98.5%	92.3%	100%	76

Abbreviations: mRNA, messenger RNA; NPV, negative predictive value; PCR, polymerase chain reaction; PPV, positive predictive value.

studies.^{42,47,59,61-63} The risk for BKV replication is increased with higher cumulative steroid dose,⁴⁸ corticosteroid pulses as rejection treatment,²³ and steroid maintenance compared with steroid withdrawal regimens.^{42,47,52}

Although immunosuppression is the most important risk factor, patients with a nonkidney solid-organ transplant requiring similar or even higher immunosuppression than kidney transplant recipients rarely develop BKV-associated nephropathy in native kidneys.⁶⁴⁻⁶⁶ Because BKV remains latent in kidney and urothelial cells^{11,12} and transmission of the virus with organ transplantation is proven,^{19,67} one hypothesis is that the viral load of the transplanted tissue is a major factor predisposing kidney transplant recipients to be more susceptible to BKV infection than patients with nonkidney solid-organ transplants. Ischemia-reperfusion injury experienced by transplanted kidneys but not the native kidneys of nonkidney solid-organ transplant recipients may also play a role.

Screening and Noninvasive Diagnostic Tests

BKV replication can be detected before the development of BKV-associated nephropathy. BK viruria precedes viremia by a median of 4 weeks, and viremia precedes BKV-associated nephropathy by a median of 8 weeks.^{23,50} Moreover, detection of viruria or viremia with subsequent reduction of immunosuppression is effective in preventing BKV-associated nephropathy,^{50,68} and allograft survival in patients with BKV-associated nephropathy is better in those with early histologic changes compared with more advanced disease.⁴⁵ Therefore, monitoring for BKV replication is recommended in all kidney transplant recipients to detect it before histologic damage occurs.²⁶

Screening using molecular techniques with real-time polymerase chain reaction (PCR) either in urine or blood is currently the technique more commonly used. Viruria (>1 ×10⁷ copies/mL) has a negative predictive value for BKV-associated nephropathy of 100% but a positive predictive value of only 31% to 67% (Table 1^{23,49,69-77}).⁴⁰ Viremia (>1 ×10⁴ copies/mL) has the best sensitivity

(100%), specificity (88%-96%), positive predictive value (50%-82%), and negative predictive value (100%) of existing screening methods (Table 1).⁴⁰ Persistently high-level viremia significantly decreases allograft survival.⁷⁸ Therefore, BKV PCR in blood or plasma is the preferred screening method recommended by the 2019 American Society of Transplantation Infectious Disease Community of Practice (AST-IDCOP) guidelines. One important limitation is the lack of an international laboratory standard and high variability between laboratories.⁷⁹ Other screening methods (Table 1) such as detection of infected renal tubular epithelial cells in urine (decoy cells) are less optimal given the operator-dependent variability.^{40,80}

BKV-associated nephropathy occurs most commonly in the first 2 years posttransplantation or following treatment of rejection^{12,41,44,45,81} but rarely has been described early after transplantation and as late as 5 years posttransplantation.^{44,82} The 2009 KDIGO (Kidney Disease: Improving Global Outcomes) guideline for the care of kidney transplant recipients recommends screening for BK viruria or viremia monthly for the first 3 to 6 months, followed by every 3 months until the end of the first year posttransplantation.²⁶ However, the 2019 AST-IDCOP guideline recommends monthly screening with blood or plasma PCR until month 9 and then every 3 months until 2 years posttransplantation.⁸³ BKV replication should also be measured in workup of unexplained allograft dysfunction and after significant increases in immunosuppression.²⁶

Diagnosis and Histology

The definitive diagnosis of BKV-associated nephropathy is made by histologic characteristics in a kidney allograft biopsy specimen.⁴⁵ The characteristic histologic changes on biopsy include tubular damage with tubulitis and interstitial inflammatory infiltrate.^{84,85} These characteristics are similar to allograft cellular rejection. However, features such as intranuclear homogeneous basophilic viral inclusions without surrounding halo seen on light and electron microscopy may make BKV-associated nephropathy more likely.^{84,85} These findings are complemented by

Table 2. Histologic Classification System for BKV-Associated Nephropathy and Associated Outcomes

Histologic Class	Histologic Characteristics	Outcomes at 24 mo After Index Biopsy		
		Cr increase	Allograft failure	Resolution of BKV-associated nephropathy
Class 1	pvl 1 and ci ≤1	0.4 (IQR, 0-1.6) mg/dL	16%	75%
Class 2	pvl 1 and ci >1, or pvl 2 and any ci score, or pvl 3 and ci ≤1	1.0 (IQR, 0.4-4.8) mg/dL	31%	78%
Class 3	pvl 3 and ci >1	4.8 (IQR, 1.3-5.3) mg/dL	50%	50%

Note: pvl 1: ≤1% tubules with BKV replication, pvl 2: >1% and ≤10% of tubules with BKV replication, pvl 3: >10% of tubules with BKV replication, ci 0: interstitial fibrosis in ≤5% of cortical area; ci 1: interstitial fibrosis in >5% and ≤25% of cortical area; ci 2: interstitial fibrosis in >25% and ≤50% of cortical area; and ci 3: interstitial fibrosis in >50% of cortical area.

Abbreviations: BKV, BK virus; Cr, creatinine; ci, interstitial fibrosis of cortical area; IQR, interquartile range; pvl, polyomavirus load. Data from Nickenleit et al.⁴⁵

immunohistochemistry using antibodies against the TAg of SV40, which cross-reacts with the TAg of other polyomaviruses.⁸⁵ The caveat of this technique is that SV40-TAg does not differentiate between BKV and JC virus infection, and in rare cases, polyomavirus-associated nephropathy due to JC virus has been described.⁸⁶ Nevertheless, differentiation between BKV-associated nephropathy and acute rejection can be challenging, and in some instances, both these biological processes co-exist.⁸⁷

The Banff Working Group on Polyomavirus Nephropathy established a classification dividing BKV-associated nephropathy into 3 distinct classes based on 2 histologic characteristics (Table 2).⁴⁵ The intrarenal polyomavirus load (percentage of tubules with polyomavirus replication in the entire biopsy sample, defined as at least 1 cell in the tubule with intranuclear inclusion bodies or SV40-TAg positivity)⁴⁵ and the Banff interstitial fibrosis of cortical area score.⁸⁸ This classification correlates with clinical presentation and allograft outcomes in terms of GFR decline and allograft failure despite similar rates of BKV-associated nephropathy resolution.⁴⁵

Ureteral Stenosis

BKV infection has been implicated in late ureteral stenosis (>1 month posttransplantation) because BKV replication has been demonstrated in the urothelium of patients experiencing ureteral stenosis.⁸⁹⁻⁹² Ureteral BKV infection is initially focal, followed by a destructive phase in which the uroepithelium and smooth muscle cells are affected. This phase is characterized by marked inflammation and ulcerations, ultimately leading to ureteral stenosis.⁸⁹ The clinical presentation consists of asymptomatic hydronephrosis leading to a decrease in GFR. The diagnosis is confirmed by ultrasound. BKV replication should be investigated in cases of late ureteral stenosis.

Hemorrhagic Cystitis

Hemorrhagic cystitis is a serious complication that occurs in 25% of recipients of hematopoietic stem cell transplants in children and young adults. It can present with pain,

urinary obstruction, and hematuria and is associated with prolonged hospitalization and significant morbidity. A recent prospective study⁹³ of 193 hematopoietic stem cell transplant recipients from 2 centers noted hemorrhagic cystitis in 22.3% of participants. Among the 147 asymptomatic patients, 40% had BKV viremia ≥ 10,000 copies/mL. In the entire cohort and asymptomatic subset, BKV viremia was associated with lower eGFRs at 1 and 2 years post-hematopoietic stem cell transplant and 6-fold higher risk for receiving dialysis. This study showed that in hematopoietic stem cell transplant recipients, a significant number of asymptomatic patients developed high-grade BKV viremia and the patients with BKV viremia experienced greater mortality and higher risk for chronic kidney disease irrespective of symptoms.⁹³ The current standard of care does not recommend regular screening for BKV in hematopoietic stem cell transplant recipients and supports the treatment of symptomatic patients with BKV viremia with agents such as cidofovir, which was not found to be effective in controlling viremia in this study. While underscoring the need for regular screening for BKV viremia and viremia in this cohort of patients, this study suggests a need to treat asymptomatic patients with BKV viremia to prevent long-term complications.

MANAGEMENT

Advances in our understanding of polyomavirus-induced diseases are limited by the absence of translationally relevant cell-based and animal models. Unlike other viruses, polyomaviruses lack conventional enzymatic antiviral therapeutic targets such as proteases or integrases. Efforts to target the helicase activity of BK/JC-TAg have been unsuccessful.^{94,95} The VP1 capsid protein is an attractive target due to its critical role in multiple phases of the BKV lifecycle, such as assembly, entry, trafficking, and disassembly,^{3,5} and its implication in BKV-associated nephropathy pathogenesis.⁹⁶ Capsid modifiers have recently been pharmacologically validated and are in clinical development for other viruses.⁹⁷

Table 3. Treatment Strategies for BKV Infection

Study (year)	Study Design	Immunosuppression Adjustment Strategy	Viremia/ BKAN	BKV Clearance	Allograft Loss	Acute Rejection After BK Treatment	Mean Follow-up	Comments
Immunosuppression Reduction								
Hirsch ²³ (2002)	Prospective cohort	Varied: CNI minimization or switch of agent	10/5	3/5	0/10	NR	1.6 y post-KTx	4/5 patients with BKAN also had concurrent rejection and received antirejection treatment and adjustment of IS
Ramos ⁴⁴ (2002)	Retrospective cohort	15/67 no reduction; 34/67 CNI minimization; 8/67 tac → CyA; 3/67 CNI → mTORi; 36/67 MMF d/c; 14/67 MMF 50% reduction	NR/67	5/67	11/67	8/67	1 y post-BKAN	6/67 patients developed ureteral obstruction
Celik ¹¹² (2003)	Case series	Not described; 31/66 biopsies had initial steroid treatment followed by decreased IS, 6/66 no change in IS, 29/66 decreased IS from outset	NR/31	11/45 biopsies at 8 wk; 15/21 biopsies after 8 wk	11/31	NR	NR	No long-term difference was seen with initial treatment with steroids or IS reduction from outset
Brennan ⁵⁰ (2005)	Prospective cohort	Discontinuation of antiproliferative agent (AZA or MMF); if viremia did not clear after 4 wk, CNI dose was reduced (target CyA 100-200 ng/mL, Tac 3-5 ng/mL)	23/0	22/23	0/23	2/23	1 y post-KTx	Patients randomly assigned to Tac or CyA before BK diagnosis; no difference in incidence between groups and no significant differences in patient survival or allograft loss
Saad ¹¹³ (2008)	Case series	50% reduction of MMF, CNI, and/or mTORi	24/16	24/24	1/24	3/24	3.6 y post-KTx; 2.6 y post-BK	71% had stable or improved kidney function; 29% had kidney function decline; the single allograft failure was due to BKAN recurrence during pregnancy
Almeras ¹¹⁴ (2008)	Prospective cohort	Viremia: 25% reduction in CNI and 50% reduction in MMF; BKAN: 25% reduction in CNI and discontinuation of MMF	13/3	8/11 viremic w/o BKAN patients; 1/3 BKAN patients	0/13	3/13	1 y post-KTx	
Weiss ¹¹⁵ (2008)	Case series	BKAN: Withdrawal group (n = 17) d/c either antiproliferative (20%) or CNI (80%); Reduction group (n = 18) Tac 3-6 ng/mL, CyA 75-150 ng/mL, MMF 500 BID, sirolimus 2 mg/d (goal < 8 ng/mL); Viremia w/o BKAN: withdrawal of CNI (n = 2), IS reduction (n = 28)	65/35	NR	BKAN 16/35; viremia w/o BKAN 0/30	2/35	Up to 5 y	65% of patients were on CNI/mTORi regimen before BKAN diagnosis; antiviral therapy used in many patients: cidofovir (n = 7), IVIG (n = 16), leflunomide (n = 9); 1 y allograft survival: 87.8% in withdrawal group vs 56.2% in reduction group (P = 0.03). HR of IS withdrawal, 0.28 (95% CI, 0.08-0.93; P = 0.04)
Schaub ⁶⁸ (2010)	Prospective cohort	Sustained viremia: CNI minimization followed by MMF dose reduction if viremia persisted	38/13	35/38	0/38	10/35 patients who cleared viremia	2.9 y post-KTx	7/38 (18%) patients had concurrent treatment for rejection: 1 with rituximab and IVIG, 6 with steroid pulses

(Continued)

Table 3 (Cont'd). Treatment Strategies for BKV Infection

Study (year)	Study Design	Immunosuppression Adjustment Strategy	Viremia/ BKAN	BKV Clearance	Allograft Loss	Acute Rejection After BK Treatment	Mean Follow-up	Comments
Hardinger ¹¹⁶ (2010)	Retrospective cohort	Discontinuation of antiproliferative agent (AZA or MMF); if viremia did not clear after 4 wk CNI dose was reduced (target CyA 100-200 ng/mL, Tac 3-5 ng/mL)	23/0	22/23	4/23; 1/23 DCGL	5/23	5 y post-KTx	5 y follow-up of study by Brennan et al ⁵⁰
Sawinski ¹¹¹ (2015)	Retrospective cohort	Discontinuation of antiproliferative agent (MMF or AZA); if viremia did not clear, CNI was reduced; if viremia did not clear Tac was switched to CyA	132/12	NR	8/132	NR	3 y post-KTx	Class II DSA development was more common in patients with persistent BK viremia than that in patients with no viremia (OR, 2.53; 95% CI, 1.40-4.59); BK viremia was not associated with allograft loss (HR, 0.80; 95% CI, 0.37-1.73)
Seifert ¹¹⁷ (2017)	Retrospective cohort	Discontinuation of antiproliferative agent (AZA or MMF); if viremia did not clear after 4 wk CNI dose was reduced (target CyA 100-200 ng/mL, Tac 3-5 ng/mL)	20/0	19/20	7/20; 1/20 DCGL	NR	10 y post-KTx	10 y follow-up of study by Brennan et al ⁵⁰ ; 4/20 patients with BK viremia developed rejection, but the timing in respect to viremia (before or after) was not reported
Bischof ¹¹⁸ (2018)	Retrospective cohort	Sustained viremia: CNI minimization followed by MMF dose reduction if viremia persisted	105/33	101/105	Viremia: 6/ 105; BKAN: 2/33; 1/33 DCGL	11/101	6.6 y post-KTx; 5 y post-BK viremia	24 viremia patients had low-level viremia (<10,000 copies/mL); 12/101 who cleared viremia had relapse in viremia; 12/105 had concurrent rejection. 6 of them were treated with increased IS; 5/33 allograft loss due to rejection
Baek ¹¹⁹ (2018)	Retrospective cohort	Not described: minimization or discontinuation or CNI or antiproliferative	79/12	61/79	NR	17/79	6 y post-KTx	MMF discontinuation vs reduction was protective for acute rejection (OR, 0.11; 95% CI, 0.02-0.61); CNI level reduction ≥ 20% associated with acute rejection (OR, 33.75; 95% CI, 4.26-267.25)
LFN								
Josephson ¹⁰⁰ (2006)	Case series	LFN alone (n = 19) or LFN + cidofovir (n = 7) coupled with IS reduction (d/c MMF, Tac through target 4-6 ng/mL). LFN dose: LD 100 mg/d ×5 d, MD 20-60 mg/d; target blood level 50-100 µg/mL	26/26	11/26	4/26	NR	0.5-3.3 y post-KTx	All patients were treated with IS reduction before starting antiviral therapy; there were kidney-pancreas recipients (n = 7), heart-kidney-pancreas recipient (n = 1), and kidney recipients (n = 18)
Faguer ¹⁰¹ (2007)	Case series	MMF replaced by LFN (LD 100 mg/d ×5 d, MD 40 mg/d, target levels 40-80 mg/L), and Tac decreased to target level of 6-10 ng/mL	8/12	5/12	2/12	1/12	1.3 y post-KTx	3 patients had concurrent acute cellular rejection treated with steroid pulses

(Continued)

Table 3 (Cont'd). Treatment Strategies for BKV Infection

Study (year)	Study Design	Immunosuppression Adjustment Strategy	Viremia/ BKAN	BKV Clearance	Allograft Loss	Acute Rejection After BK Treatment	Mean Follow-up	Comments
Basse ¹⁰³ (2007)	Case series	BK viremia (n = 1): MMF halved; BKAN + rejection (n = 4): steroid pulses, MMF replaced by LFN (target level 40-100 µg/L)	7/4	NR	0/7	NR	1.2-2 y post-KTx	All 4 cases of BKAN had concurrent allograft rejection on kidney biopsy
Leca ¹⁰⁴ (2008)	Case series	MMF replaced by LFN (LD 60 mg/d × 3 d, MD 20 mg/d) and Tac level decreased to 5 ng/mL; 2 groups based on LFN levels: "low level" <40 µg/mL (n = 12) and "high level" >40 µg/mL (n = 9)	21/21	11/21; low level 6/12; high level 5/9	4/21; low level 3/12; high level 1/9	2/21; low level 0/12; high level 2/9	1.1 y -KTx	8 patients also received cidofovir, and 3 patients received IVIG; 2 patients developed TMA after leflunomide treatment
Teschner ¹⁰⁵ (2009)	Case series	MMF replaced with LFN (LD 100 mg/d × 3 d, MD 20 mg/d, target level 40 µg/mL) + Tac level decreased to 4-6 ng/mL	13/13	11/13	1/13	0/13	2 y post-KTx; 1.3 y post-BKAN	
Krisl ¹⁰² (2012)	Retrospective cohort	MMF replaced by LFN, CNI minimization (LFN group, n = 52); MMF minimization or d/c, CNI minimization (CNT group, n = 24)	76/33; LFN 52/32; CNT 24/1	LFN 16/52; CNT 15/24; viremia: LFN 8/20; CNT 15/23	LFN 8/52; CNT 2/24	LFN 10/52; CNT 2/24; viremia: LFN 2/20; CNT 0/23	1.1-1.4 y post-BKAN	In multivariate analysis, leflunomide use was not associated with BK viral clearance (OR, 1.10; 95% CI, 0.19-6.5; P = 0.92); 9 patients also received cidofovir
Cidofovir								
Tong ¹²⁰ (2004)	Case series	IS reduction alone (n = 2); IS reduction + cidofovir (0.25 mg/kg q4d; n = 5)	7/7	5/7	0/7	NR	1.5 y post-BKAN	
Kuypers ⁹⁹ (2005)	Retrospective cohort	IS reduction + cidofovir (0.5-1 mg/kg qw) (n = 8); IS reduction alone (n = 13)	21/21	Cidofovir 6/8; no cidofovir 6/13	Cidofovir 0/8; no cidofovir 9/13	NR	2 y post-BKAN	2 patients in the cidofovir group had concurrent rejection and were treated with steroids
Wade ¹¹⁰ (2006)	Case series	IS reduction (either decrease overall IS, or switch to CyA-based regimen; n = 23); IS reduction + cidofovir (0.25 mg/kg q2w × 4, if BKAN persisted 0.5 mg/kg q2w × 4-5) (n = 20); IS reduction + cidofovir + IVIG (2.5 g/kg; n = 10); IS reduction + IVIG (n = 2)	31/55	NR	8/55	9/55; 6/30 in cidofovir treated; 3/25 without cidofovir	1.6 post-BKAN	Neither cidofovir, IVIG, nor CyA conversion was associated with improved allograft functional outcome or BKV clearance in kidney tissue; allograft loss was not reported for each specific treatment group
Kuypers ¹²¹ (2008)	Prospective cohort	IS reduction + cidofovir (0.5-1 mg/kg qw; n = 26); IS reduction alone (n = 15)	41/41	Cidofovir 15/26; no cidofovir 7/15	Cidofovir 4/26; no cidofovir 11/15	Cidofovir 4/26; no cidofovir 1/15	2.5 y post-BKAN	Allograft survival was better in the cidofovir group (P = 0.0002), but no difference in BK viral clearance (P = 0.44); 3 patients treated with cidofovir developed severe anterior uveitis

(Continued)

Table 3 (Cont'd). Treatment Strategies for BKV Infection

Study (year)	Study Design	Immunosuppression Adjustment Strategy	Viremia/ BKAN	BKV Clearance	Allograft Loss	Acute Rejection After BK Treatment	Mean Follow-up	Comments
Fluoroquinolones								
Lee ¹⁰⁶ (2014)	Prospective, double-blind, placebo-controlled, randomized trial	IS reduction + levofloxacin (30-d course; n = 20); IS reduction alone (n = 19)	39/0	Levofloxacin 8/20; control 6/19	Levofloxacin 0/20; control 2/19	Levofloxacin 1/20; control 0/19	0.5 y postviremia	Reduction of BK viral load was similar at 3 and 6 mo in both groups; leflunomide was also used in 6 patients
mTORi								
Wali ¹²² (2004)	Case series	50% reduction in IS followed 12 wk after by d/c of Tac and MMF, and starting sirolimus (target level 10-12 ng/mL)	3/3	3/3	0/3	0/3	1.5 y post-BKAN	
Jacobi ⁹⁸ (2013)	Retrospective cohort	Low viremia (10 ³ -10 ⁴ copies/mL): reduction CNI by 30% and MMF by 50% (n = 15). If viremia persists, change to sirolimus (target 5-8 ng/mL) + low CyA (target 60-80 ng/mL) regimen (n = 7), or other regimens (n = 4); high viremia (>10 ⁴ copies/mL) or BKAN: change to sirolimus (target 5-8 ng/mL) + low CyA (target 60-80 ng/mL) regimen (n = 13), or other regimens (n = 2), or reduction in IS (n = 7)	48/22	43/48	5/48	3/48	1.8 y post-KTx	Overall viral replication did not differ between different treatment groups of patients with either BK viremia or BKAN
IVIg								
Sener ¹⁰⁷ (2006)	Case series	50% reduction in IS + IVIG (2 g/kg)	7/8	4/8	1/8	1/5	1.25 y post-BKAN	2 patients were initially misdiagnosed as having ACR
Vu ¹⁰⁹ (2015)	Retrospective cohort	MMF replaced by LFN (40 mg/d), if persistent after 4 wk CNI was decreased (CyA target 100-200 ng/mL or Tac 3-5 ng/mL; n = 23), if persistent after 4 wk IVIG (1 g/kg) was given (n = 30)	53/10	23/53 with IS reduction only; 27/30 with IVIG	1/30	1/30	1.5 y post-BKAN	
Kable ¹⁰⁸ (2017)	Retrospective cohort	MAT (Tac reduction or conversion to CyA + MMF reduction or conversion to LFN or AZA + ciprofloxacin 500 mg/d × 30 d + cidofovir 0.5 mg/kg q2w × 10 wk) + IVIG 100 mg/kg qw × 10 wk (n = 22); MAT alone (n = 28)	50/50	MAT + IVIG 18/22; MAT 16/28	DCGL 21/50; MAT + IVIG 6/22 MAT 15/28	MAT + IVIG 14/22; MAT 16/28	5 y post-KTx	In multivariate analysis, IVIG was associated with more effective clearance of viremia (HR, 6.82; 95% CI, 1.03-45.11; P = 0.046); salvage IVIG was used in 7 patients after multidimensional antiviral therapy failed

Abbreviations: ACR, acute cellular rejection; AZA, azathioprine; BKAN, BK virus-associated nephropathy; BKV, BK virus; CNI, calcineurin inhibitor; CNT, control; CyA, cyclosporine A; d/c, discontinue; DCGL, death-censored graft loss; DSA, donor-specific antibody; HR, hazard ratio; IS, immunosuppression; IVIG, intravenous immunoglobulin; KTx, kidney transplant; LD, loading dose; LFN, leflunomide; MAT, multidimensional antiviral therapy; MD, maintenance dose; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitor; NR, not reported; OR, odds ratio; q4d, every 4 days; qw, every week; Tac, tacrolimus; TMA, thrombotic microangiopathy; w/o, without.

Due to lack of a direct targeted anti-BKV agent, most current therapeutic options are empirical and backed up by suboptimal studies that use different inclusion criteria (ie, viruria vs viremia vs biopsy-proven BKV-associated nephropathy) and not all reported allograft loss or rejection episodes, making it difficult to reach definitive conclusions (Table 3^{23,44,50,68,98-122}). The need for a direct, targeted, safe, and orally available anti-BKV agent is urgent.

Immunosuppression Reduction

Immunosuppression reduction is the most widely accepted management option. A 2010 systematic review¹²³ described 8 cohort studies and 13 case series in which immunosuppression reduction alone was instituted. The strategy used to decrease immunosuppression varied significantly, including discontinuation of antiproliferative agents, decreasing immunosuppression by 25% or 50%, and switching calcineurin inhibitors.¹²³ The pooled allograft failure rate was 8/100 patient-years (95% CI, 4-12; range, 0-44). Other outcomes included rejection rates (0%-75%), allograft failure (0%-67%), and clearance of viruria (40%-96%) and viremia (7%-80%; Table 3). No consensus exists regarding what agent should be reduced or stopped following diagnosis of BKV infection. Intuitively different strategies for patients with stable versus decreased GFRs and high versus low immunologic risk would be prudent. However, any recommendations on an optimal approach to decrease immunosuppression are opinion based.

mTOR Inhibitors

Immunosuppression regimens have also been modified in patients with BKV infection to include an mTOR inhibitor given evidence that they inhibit BKV replication in vitro⁶⁰ and the lower incidence of BKV infection with mTOR inhibitor use at baseline.^{42,47,59,61,62} In contrast, the data supporting mTOR inhibitor–based immunosuppression as treatment for BKV infection are limited and mainly originate from a retrospective study that compared immunosuppression reduction or conversion to an mTOR inhibitor in patients with BKV-associated nephropathy.⁹⁸ Conversion to mTOR inhibitor therapy was associated with short-term higher GFRs, but clearance of viremia was similar between groups and episodes of rejection were not reported.⁹⁸ Currently, the use of mTOR inhibitors as treatment of BKV infection cannot be recommended. However, 2 RCTs comparing immunosuppression reduction versus changing to an mTOR inhibitor–based regimen (NCT01649609 and NCT01624948) will hopefully determine the role of mTOR inhibitors in BKV-associated nephropathy management.

Cidofovir

Cidofovir is an antiviral agent with broad activity against DNA virus infections.¹²⁴ In vitro, cidofovir inhibits BKV replication in primary human renal proximal tubular

epithelial cells.¹²⁵ A small retrospective study compared low-dose cidofovir (0.5-1.0 mg/kg) in only 8 kidney transplant recipients with no cidofovir in patients with BKV-associated nephropathy in conjunction with immunosuppression reduction.⁹⁹ Of cidofovir-treated patients, 75% cleared the infection. No allograft loss was seen in 24.8 months of follow-up and cidofovir-related toxicity was not observed. In comparison, in the control group, only 46% cleared the infection and 70% lost their allograft after a median of 8 months. A 2010 systematic review¹²³ found 11 additional case series with a pooled allograft failure rate of 8/100 patient-years (95% CI, 3-13), similar to the effect of immunosuppression reduction alone. The potential nephrotoxicity and reported incidence of anterior uveitis and an effect similar to immunosuppression reduction make this agent less attractive.

Brincidofovir (CMX001, a lipid conjugate of cidofovir that is not yet commercially available) has an EC₉₀ 400 times lower than that of cidofovir in in vitro studies¹²⁶ and with no apparent nephrotoxicity¹²⁷ but is not commercially available. Overall, the clinical benefit of both these agents cannot be established.

Leflunomide

Leflunomide is an immunosuppressive agent used for rheumatoid arthritis. However, in vitro studies show activity against BKV.¹²⁴ Leflunomide has always been paired with immunosuppression reduction¹⁰⁰⁻¹⁰⁴ and with cidofovir in 3 studies.^{100,102,104} Acute rejection and viremia clearance occurred in 0% to 19% and 30% to 92% of patients treated with leflunomide, respectively.^{100-102,104,105} A 2010 systematic review¹²³ found a pooled allograft failure rate with leflunomide use of 13/100 patient-years (95% CI, 2-23). A recent retrospective study with larger sample size found no difference in allograft failure (15% vs 7%; *P* = 0.32), acute rejection (19% vs 9%; *P* = 0.32), or viral clearance (odds ratio, 1.10; 95% CI, 0.19-6.5; *P* = 0.92).¹⁰² Furthermore, leflunomide use resulted in anemia in up to 50% of patients, with 19% developing hemolytic anemia; thrombotic microangiopathy, mild thrombocytopenia, and elevated liver enzyme levels.^{100,101,104} Of note, its level is difficult to monitor (measured as teriflunomide) and shows wide interpatient fluctuations due to variable leflunomide metabolism. Overall, RCTs are needed to precisely define its role in BKV-associated nephropathy and to balance putative benefit against potential complications.

Fluoroquinolones

Fluoroquinolones interfere with the helicase function of the TAg and the DNA topoisomerase of BKV, thus inhibiting its replication in vitro.^{124,128} However, the clinical experience has been disappointing. Prophylactic fluoroquinolone use does not decrease the rate of BKV infection and increases the risk for bacterial resistance.¹²⁹⁻¹³¹ Furthermore,

a prospective, multicenter, double-blind, placebo-controlled trial in patients with BK viremia found that a 30-day course of levofloxacin did not significantly improve allograft function or BK viral load reduction.¹⁰⁶

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) is an attractive option because commercially available IVIG formulations contain neutralizing antibodies against all BKV genotypes.¹³² IVIG is used in transplant recipients as treatment for antibody-mediated rejection, and an impact on BKV-associated nephropathy management would be convenient because both diseases can coexist and are difficult to differentiate.

Clinical experience with IVIG as treatment for BKV infection is limited to case series and retrospective studies. In a case series of 8 patients with biopsy-proven BKV-associated nephropathy who were treated with 50% reduction of immunosuppression and 2 g/kg of IVIG,¹⁰⁷ after a mean follow-up of 15 months, 1 patient lost the allograft and the rest had reduced but stable allograft function; 4 patients cleared the viremia, and no acute rejection occurred.¹⁰⁷ A retrospective analysis of 50 patients with biopsy-proven BKV-associated nephropathy treated with various strategies including immunosuppression reduction, leflunomide, ciprofloxacin, and cidofovir included 22 patients who also received 1 g/kg of IVIG.¹⁰⁸ Despite heterogeneity in immunosuppression modifications, patients who received IVIG cleared the viremia more frequently than the no-IVIG group (81% vs 57%) and had less allograft loss (27% vs 53%).¹⁰⁸ A retrospective study reported 30 patients with BKV-associated nephropathy treated with 1 g/kg of IVIG after failing to clear BK viremia after 8 weeks of immunosuppression reduction and leflunomide treatment.¹⁰⁹ BK viremia was cleared in 90% of patients, GFRs remained stable in most patients, and only 1 patient experienced allograft failure due to cellular rejection.¹⁰⁹ Another retrospective study of 55 patients with biopsy-proven BKV-associated nephropathy that included 12 treated with IVIG found no difference in the rate of allograft loss or decreased GFR.¹¹⁰

In all studies, IVIG was well tolerated¹⁰⁷⁻¹¹⁰ but a major limitation to its use is the cost. An RCT (NCT02659891) of IVIG as treatment of BKV-associated nephropathy will hopefully clarify its role. Recently, a monoclonal antibody against BKV VP1 (MAU868; Amplyx Pharmaceuticals) was developed that can bind and likely prevent BKV entry into the cells. However, no clinical data are available about its efficacy.

There are key limitations of immunoglobulins for BKV-associated nephropathy, including their inability to pass through the glomerular basement membrane to suppress BKV viremia and penetrate intracellularly, where BKV is known to induce profound changes and eventual graft loss.^{14,133} Moreover, the short half-life of immunoglobulin and the lack of cumulative effect after 3 doses further

compromise the cost-effectiveness.¹³⁴ Importantly, as mentioned, neutralizing anti-BKV antibodies is not sufficient to prevent BKV replication. Taken together, use of the immunoglobulin approach warrants rigorous clinical studies and is less likely to affect fundamental biological processes within the renal tubular cells induced by BKV that result in allograft failure.

Adoptive Immunotherapy

Given the importance of cellular immunity in the fight against BKV, augmenting the BKV-specific cellular response by infusing autologous BKV-specific T cells from kidney transplant recipients expanded ex vivo could be beneficial for the treatment of BKV-related diseases.¹³⁵ Only a few hematopoietic stem cell transplant recipients have been treated with adoptive immunotherapy against BKV.^{136,137} Some crucial issues, such as the safety, scalability, cost, and ability of the cells to expand and persist after transfer into patients, represent some of the limitations in widely adopting cellular therapies.

PROGNOSIS

Following diagnosis with BKV-associated nephropathy, a large proportion of patients experience allograft dysfunction and allograft loss,⁴⁵ with a 3-year allograft survival of 79% compared to 90% in patients without BKV-associated nephropathy.⁵³ A recent biopsy series reported allograft loss rates of 15% to 38%, with half due to rejection episodes in the setting of reduced immunosuppression due to BKV-associated nephropathy.^{45,78,138} BKV-associated nephropathy has also been associated with the development of class II de novo donor-specific antibodies (hazard ratio, 2.55; 95% CI, 1.30-4.98),¹¹¹ a widely accepted risk factor for kidney allograft failure. It remains unclear whether immunosuppression can be safely increased after resolution of BKV infection. An individualized approach to immunosuppression modifications is advised considering the immunologic risk of the patient and close monitoring of GFR, BK viremia, and donor-specific antibodies.

BKV-associated nephropathy in kidney transplant recipients leads to significant financial burden to the health care system due to the need for close monitoring with frequent BKV real-time PCR, allograft biopsies, and Lumindex single-antigen bead assays to detect donor-specific antibody formation. Furthermore, the development of acute rejection post-BKV-associated nephropathy would require treatment with expensive therapies that usually include plasmapheresis and IVIG, among others. Finally, the higher risk for allograft loss and return to kidney replacement therapies after BKV-associated nephropathy is probably the highest financial burden to Medicare.

Retransplantation appears to be safe among patients who lost their allograft to BKV-associated nephropathy. In one study,¹³⁹ 126 patients were identified who received a second transplant after losing their first allograft to BKV-associated nephropathy. Following retransplantation, 1 of

3 allograft failures was attributed to BKV-associated nephropathy recurrence.¹³⁹ The 1- and 3-year allograft survival rates were 98.5% and 93.6%, respectively.¹³⁹ This study did not report BK viremia status before retransplantation, but a common practice is to wait until resolution of viremia before retransplantation. Because BKV remains latent in the failed allograft, some have advocated for allograft nephrectomy before retransplantation,¹⁴⁰ but this approach remains a controversial practice with inadequate evidence to support or reject it.

CONCLUSIONS

Despite advances in our understanding of BKV biology and the risk factors that predispose kidney transplant recipients to develop BKV-associated nephropathy, it continues to be one of the most challenging causes of allograft dysfunction. Screening and early diagnosis of viral replication and BKV-associated nephropathy are of paramount importance to allow effective management strategies before severe allograft damage ensues. Although immunosuppression reduction is the standard of care of BKV-associated nephropathy, it is associated with harmful effects by increasing the risk for donor-specific antibody development and acute rejection episodes. Emerging therapeutic strategies have several limitations that highlight the imminent need for a targeted anti-BKV therapy.

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