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MINIREVIEWS

BK viral infection: A review of management and treatment

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Abstract

BK viral infection remains to be a challenging post-transplant infection, which can result in kidney dysfunction. The mainstay approach to BK infection is reduction of immunosuppression. Alterations in immunosuppressive regimen with minimization of calcineurin inhibitors, use of mechanistic target of rapamycin inhibitors, and leflunomide have been attempted with variable outcomes. Over the past few years, investigators have explored potential therapeutic options for BK infection. Fluoroquinolone prophylaxis and treatment was found to have no benefit in kidney transplant recipients. The utility of cidofovir is limited by its nephrotoxicity. Intravenous immunoglobulin is becoming a popular option for treatment and prophylaxis for BK infection, as it increases the neutralizing antibody titers against the most common BK virus serotypes. Virus-specific T cell therapy is an emerging treatment option for BK viremia. In this review, we will explore management and therapeutic options for BK infection and recent evidence available in literature.

Key Words: BK infection; Kidney transplant; Treatment; Management

Core Tip: BK viral infection is a significant post-transplant infection, which can result in kidney dysfunction if left unaddressed. The mainstay approach to BK infection is reduction of immunosuppression. Data on specific therapies have remained equivocal. In this article, we will review recent evidence available in literature on treatment approaches to BK viral infection.

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INTRODUCTION

BK virus is a DNA virus that belongs to the human polyomavirus family. It was first isolated in 1971 from the urine of a Sudanese kidney transplant recipient with initials B.K[1]. BK infection is common in the general population, approaching >90% seroprevalence by age 4[2]. It persists following primary infection and may reactivate following immunosuppression[1]. BK virus infection is a common and important post-transplant viral infection that can result in kidney dysfunction if left unaddressed. The evolution of BK infection often involves viruria, that progresses to viremia, and eventually leads to nephropathy. Severe BK virus-associated nephropathy (BKVAN) can result in loss of the kidney allograft. Effective treatment for the eradication of BK infection remains elusive. The most recent guidelines from the American Society of Transplantation Infectious Diseases Community of Practice (AST-IDCOP) recommends a stepwise approach in immunosuppression reduction as the primary intervention for BK viremia and nephropathy. The AST-IDCOP did acknowledge the lack of randomized controlled trials to provide evidence for using tacrolimus or cyclosporine, switching mycophenolate to mechanistic target of rapamycin (mTOR) inhibitor or leflunomide, and using intravenous immunoglobulin (IVIg) and cidofovir[2]. Studies that employed the use of fluoroquinolones in either prophylaxis or treatment have had varying outcomes. Finally, virus-specific T-cell therapy (VST) is a new emerging therapeutic option under current investigation. In this systematic review, we seek to present the most recent evidence surrounding management approaches and therapeutic options for BK infection following organ transplantation.

ALTERATIONS IN IMMUNOSUPPRESSIVE REGIMEN

BK virus infection poses a threat to the survival of kidney transplants, and a considerable proportion of infected patients face irreversible graft failure. The occurrence of this infection appears to be linked to the level of immunosuppression rather than any specific immunosuppressive agent. The optimal approach for treating BK infection is still uncertain, however, reducing immunosuppression is widely recognized as a primary therapy for BK infection. Although systematic studies in this area are lacking, several studies have shown that reduction in immunosuppression results in better viral clearance and preservation of graft function.

A retrospective study done in the Medical College of Wisconsin on 24 kidney transplant recipients with BK viremia (> 7000 copies/mL) showed that a 44% and 41% reduction in mycophenolate mofetil (MMF) and tacrolimus respectively, caused a significant decline in the BK DNA copies per milliliter of plasma ($P < 0.0001$) within a mean period of 5.8 mo. Only three patients (13%) developed acute cellular rejection, successfully treated with intravenous bolus steroids. After 43.5 mo, all except for one patient have a stable functioning graft[3]. In a similar study, post-transplant surveillance for BK DNA polymerase chain reaction and urinary cytology was done in 229 kidney transplant recipients. Patients found to have BK viremia and BKVAN received treatment with a 30%-50% reduction in tacrolimus and/or MMF dosages. After 5 years, overall patient survival and graft survival were 95.6% and 92.1% respectively. Following the reduction of immunosuppression, complete resolution of BK viremia was achieved in all patients and without any increase in acute rejection rates. Among the viremic patients without BKVAN, recurrent BK viremia did not occur. The seven patients diagnosed with BKVAN successfully cleared viremia within an average time of 5.9 mo, while having a stable glomerular filtration rates (GFR) in five years[4]. There have been several studies that compared reduction of immunosuppression *vs* other treatment approach in controlling BK virus infection. In 2010, Johnston *et al*[5] published a systemic review of 40 studies examining the effect of immunosuppression reduction alone or in combination with cidofovir, leflunomide, IVIg, or ciprofloxacin. Results showed a death-censored graft loss rate of 8/100 patient-years for immunosuppression reduction alone and 8 and 13/100 patient-years for the addition of cidofovir or leflunomide respectively, suggesting that there does not seem to be a graft survival benefit of adding cidofovir or leflunomide to immunosuppression reduction for the management of BKVAN. The same finding was seen in the study done by Halim *et al*[6] in 55 kidney transplant recipients where administration of three different anti-BK virus agents (leflunomide, IVIg, ciprofloxacin) added no benefit to long-term outcome in patients with BKVAN ($P = 0.32$). A recent retrospective study compared treatments for BK DNAemia in 43 kidney transplant recipients. The study evaluated immunosuppression reduction *vs* mTOR inhibitors plus IVIg. Results indicated that the immunosuppression reduction group experienced a significantly faster decrease in BK DNAemia compared to the mTORi±IVIg group ($P < 0.001$). Viral clearance was notably higher in the immunosuppression reduction group compared to the mTORi ± IVIg group ($P = 0.033$). There were no significant differences in death-censored graft loss, rejection rates, or graft function at 12 mo. This study further supports that standard BK virus (BKV) DNAemia treatment of reduction in immunosuppression as having superior outcomes compared to any other treatment approach[7].

LEFLUNOMIDE

Leflunomide, an immunosuppressive medication, has been explored as a potential treatment for BKVAN in kidney transplant recipients. The therapeutic benefit of using leflunomide in this context lies in its antiviral activity against various viruses such as herpes simplex (HSV-1) and cytomegalovirus (CMV). In vitro studies have shown that the active metabolite of leflunomide (A77 1726) has some anti-viral properties by a dose-dependent reduction in BK large T antigen expression. This reduction in antigen expression, however, did not translate to a reduction in BK virus DNA replication [8]. This finding was echoed by a retrospective single-center study done by Krisl *et al*[9] where 52 patients with BK viremia (with or without nephropathy) did not show any significant BK viral clearance after treatment with leflunomide compared to the control group. The rate of BK clearance was 30.8% in the leflunomide group *vs* 60.9% in the group that did not receive leflunomide (P = 0.02). Furthermore, graft failure occurred in 15% of patients in the leflunomide group and 7% in the no leflunomide group (P = 0.32).There are some studies that showed partial improvement in BK virus clearance and renal function. A prospective open-label study where 12 kidney transplant recipients diagnosed with BKVAN had MMF changed to leflunomide. Results showed that renal function improved in 50% of patients, remained stable in 16.6%, and deteriorated in 33.4%, with graft loss in 17% of cases. Clearance of BK viremia was observed in 42% of cases[10]. A similar study was done in 12 kidney transplant recipients whose MMF was changed to leflunomide upon diagnosis of BKVAN. Results showed that T-cell proliferation tend to be higher with leflunomide treatment compared to MMF therapy (8.4 ± 7.7% *vs* 12.4 ± 10%, P = 0.2). However, the difference was not statistically significant. BK viral clearance was observed in 41.6% of cases treated with leflunomide within 6 mo. Stable creatinine clearance was also noted in 50% of these patients within 6 mo of treatment. Of note, however, one patient in this study developed end-stage kidney disease because of concurrent acute antibody-mediated rejection and BKVAN[11].

Although these studies have shown dismal results, several case reports and studies have shown encouraging findings with the use of leflunomide in treating BK infection in kidney transplant recipients. One such study was done in 13 patients with biopsy-proven BKVAN treated with leflunomide in combination with a low-dose calcineurin inhibitors and prednisone after cessation of MMF therapy. Findings showed that 12 patients (93%) had undetectable viral load after mean treatment of 109 d. There was noted graft improvement in 13% of cases. However, overall graft function at follow-up was not significantly better than at diagnosis (P = 0.69). Leflunomide was well-tolerated and no serious adverse effects or episodes of graft rejection were reported[12]. Another study involving 26 patients with biopsy proven BKVAN investigated treated with either leflunomide alone or leflunomide plus a course of cidofovir and followed them for six to 40 mo. Results showed that 84% of cases had viral clearance in six months (P < 0.001). Follow-up after 12 mo or more showed creatinine levels not significantly changed compared to baseline in 16 patients. After follow-up of 40 mo, graft loss was at 15%[13].

The utilization of leflunomide in kidney transplant recipients with BK virus infection remains a topic of ongoing debate. A high-powered and robust randomized trial could prove essential in definitively establishing the relationship between this treatment and critical clinical outcomes such as effective viral clearance and the enduring maintenance of long-term graft function.

FLUOROQUINOLONES

Fluoroquinolones are often utilized in kidney transplant recipients due to their broad spectrum of activity. They have been demonstrated to inhibit BK replication in its natural host cells by blocking large T antigen helicase activity in polyomavirus, and possibly by inhibition of host cell proteins like topoisomerase II[14]. This perceived efficacy against the said virus was the impetus for several retrospective studies to investigate its role as prophylaxis for BK virus among kidney transplant recipients. One such study was performed by Gabardi *et al*[15] wherein they compared two groups of kidney transplant recipients with documented BK virus infection, one that used a fluoroquinolone (ciprofloxacin or levofloxacin adjusted according to renal function) for 30 d and another group that did not. In this study, sulfamethoxazole/trimethoprim was the primary antibiotic used for pneumocystis prophylaxis, whereas fluoroquinolone in combination with atovaquone use was used for those with sulfa allergy or G6PD deficiency. The results showed that there was lower BK viremia rate at one year post-transplant among those who received a fluoroquinolone compared to those who did not (4% *vs* 22.5%, respectively; P = 0.03). Another study retrospectively analyzed two groups of kidney transplant recipients, one with no BK virus prophylaxis (group I, n = 106), and another that used ciprofloxacin for 30 d to cover for BK virus prophylaxis (group 2, n = 130). The investigators evaluated the levels of BK viruria and viremia between the two groups over a period of 12 mo. On the third month after transplantation, there was a higher risk of developing BK viruria and viremia in group 1 *vs* group 2 (viremia: 0.161 *vs* 0.065, P = 0.0378; viruria: 0.303 *vs* 0.146, P = 0.0067). In the subsequent six, nine, and 12 mo though, there was no difference in the mean blood and urine BK viral load between the two groups, even after adjusting for corticosteroid regimen. This raised the possible benefit of increasing the duration of prophylactic treatment[16]. These studies were among those that inspired the randomized controlled trials that ensued.

Lee *et al*[17] conducted the first prospective, multicenter, double-blind, placebo-controlled trial that investigated the efficacy of levofloxacin in the treatment of BK viremia among adult kidney transplant recipients. A total of 43 patients were randomized to either receive levofloxacin 500 mg daily (with renal dose adjustment), or placebo for 30 d, with appropriate adjustment of immunosuppression according to the standard of practice at each institution. After three months of treatment, there was no significant difference in the percentage of BK viral load reduction between the levofloxacin-treated group and placebo (70.3% *vs* 69.1%, respectively, P = 0.93). Results were similar at one month (58% *vs*

67.1%; *P* = 0.47) and six months (82.1% *vs* 90.5%; *P* = 0.38). Hence, the use of levofloxacin did not improve BK viral load reduction, BK viral load clearance, or allograft function. Furthermore, those who used levofloxacin had a higher rate of Achilles tendonitis. Knoll *et al*[18] carried out a randomized clinical trial among 154 adult kidney transplant recipients looking into the efficacy of a three-month course of levofloxacin for the prevention of BK viruria within the first year of transplant. Apparently, levofloxacin administration showed no advantage as the rate of BK viruria was not significantly different between the two groups [29% in the levofloxacin group *vs* 33.3% in the placebo group; hazard ratio 0.91; 95% confidenceinterval (CI): 0.51-1.63; *P* = 0.58]. In addition, there was an increased risk of resistant infection among isolates usually sensitive to quinolones in the levofloxacin group *vs* placebo (58.3% *vs* 33.3%, respectively; risk ratio 1.75; 95%CI: 1.01-2.98), and increased risk of suspected tendinitis (7.9% *vs* 1.3%; risk ratio, 6.16; 95%CI: 0.76-49.95), albeit not statistically significant. Another point against the use of fluoroquinolone for the prevention of BK virus infection was noted in a trial that compared BK viremia between a group that received a three-month course of ciprofloxacin *vs* placebo. At six months post-transplant, more patients in the ciprofloxacin group had BK viremia compared to the placebo group (18.8% *vs* 7.5%, respectively, *P* = 0.03). Moreover, prolonged fluoroquinolone use resulted in a significantly higher rate of fluoroquinolone-resistant gram-negative urinary tract and bloodstream infections in the ciprofloxacin arm[19]. A meta-analysis that included two randomized controlled trials and six retrospective cohort studies reinforced that fluoroquinolones are not effective for prevention of BK viremia in kidney transplant recipients, and do not reduce the incidence of BKVAN or graft loss[20]. The latter studies constitute the evidence that fluoroquinolones have no role for the prevention of post-transplantation BK polyomavirus infection.

CIDOFOVIR

Cidofovir is a nucleotide analog of cytosine that is approved for the treatment of CMV in human immunodeficiency virus-positive patients, and has demonstrated *in vitro* activity against murine and simian polyomavirus strains[21,22], as well as a related human polyomavirus (JC virus) *in vivo*[23]. It decreases viral DNA synthesis upon incorporation with the nascent chain. Nephrotoxicity is its major adverse effect because it is taken up rapidly by proximal tubular cells by organic anion transporters at their basolateral membrane but secreted slowly into the lumen, resulting in high intracellular drug concentrations that can cause tubular necrosis. Hydration and co-administration with probenecid, a competitor of cidofovir for the transporter, can have a nephroprotective effect[24]. It is this adverse effect that precludes its recommendation for treatment of BK, such that its use should be weighed against the possible risk of worsening renal function.

In a cohort of 21 kidney transplant recipients with biopsy-proven BKV interstitial nephritis (BKVIN), Kuypers *et al*[25] investigated the effect of adjuvant low-dose cidofovir treatment *vs* no cidofovir, after lowering immunosuppressive drug therapy, on graft function, viral load, and graft outcome. Eight patients received cidofovir at 0.5-1.0 mg/kg at four to ten weekly courses. In the cidofovir-treated group, there was an improvement in creatinine clearance from 29.3 mL/min to 32.0 mL/min (range: 24-46) after a median follow up period of 24.8 mo (range 8-41) upon completion of treatment. Graft function did not acutely deteriorate during treatment except for one patient, but ultimately no graft loss occurred in this group. Blood viral load decreased in all patients treated with cidofovir. Once the BK viremia resolved, graft function improved but did not attain baseline levels. Adverse reactions noted include nausea in three patients, and development of pruritic maculopapular rashes in one patient. In contrast, nine of the 13 patients who did not receive cidofovir lost their graft after a median of eight (4-40) months. They also noted in this study that peak cidofovir concentrations were dose-dependent, and that probenecid treatment appeared to be unnecessary as it did not influence peak serum concentrations. This study was designed to be a preliminary report suggestive of the favorable effect of cidofovir on renal graft survival, function, and preservation, warranting a randomized controlled prospective study to follow suit. Another study by Kuypers done four years later investigated 41 kidney transplant patients with BKVIN, of whom 26 received cidofovir at 1 mg/kg to a maximum of ten weeks, without probenecid, and 15 did not receive cidofovir. Both groups had immunosuppression reduction. Similar to the previously mentioned study, there was a significantly higher occurrence of graft loss in the group that did not receive cidofovir (73.3% *vs* 15.4%, *P* = 0.0002). No renal toxicity was noted in the cidofovir group. The observed adverse effects include anterior uveitis in three patients, and skin rash during infusion with cidofovir[26].

A retrospective review of kidney and kidney-pancreas transplant recipients who received cidofovir combined with reduced immunosuppression for BKVAN or high-level viremia showed that adjunct cidofovir administration resulted in preserved renal function and no graft loss when viral clearance happened within six months of treatment. On the other hand, long term cases of BK infection (more than six months) were associated with a 15% decline in estimated glomerular filtration rate. Factors associated with long term BK infection include older age, delayed graft function, and higher peak BK viral load, suggesting that this subset of patients will not benefit as much from adjunctive cidofovir[27]. The course of cidofovir treatment among BK- infected individuals following bone marrow transplant manifesting as hemorrhagic cystitis have also been useful as the findings suggest applicability to kidney transplant recipients. In an open-label, non-randomized, single-dose pilot study done among hematopoietic stem cell transplant (HSCT) pediatric patients with symptomatic infection of adenovirus, nucleoside-resistant CMV, human polyomavirus (BK or JC virus), and/or nucleoside-resistant HSV, cidofovir was used to investigate virologic response, as well as safety and pharmacokinetics, with a focus on nephrotoxicity. Of the 12 patients in the study, four had BK viruria, and all four had unsuccessful viral clearance. One out of the four developed nephrotoxicity[28]. In a systematic review that compared intravesical *vs* intravenous route of cidofovir administration among stem cell transplant patients with BK polyomavirus hemorrhagic cystitis, there were more patients in the intravesical cidofovir group *vs* the intravenous cidofovir group who achieved a complete treatment response (88.2% *vs* 68%). Furthermore, no nephrotoxicity was observed in those that received the intravesical route,

whereas 9.3% had renal failure in those that received the drug intravenously. This better toxicity profile warrants more investigation due to its potential benefit[29]. All of the above mentioned studies are either preliminary or pilot studies done on a small population, or descriptive, retrospective ones. One randomized, double-blind, placebo-controlled, dose escalation study of cidofovir in kidney transplant patients with BKVAN was initiated in 2006 by the National Institute of Allergy and Infectious Diseases but closed early in 2013 due to failure to enroll in a timely manner.

Brincidofovir, a prodrug of cidofovir, which is less nephrotoxic due to its decreased accumulation in proximal tubules, is approved for the treatment of smallpox in pediatric and adult patients. Its use in BKVAN was described in a HSCT patient who had no reduction in immunosuppression. No drug-related adverse reactions occurred. Stable kidney function was maintained without the need for dialysis[30]. Another case was described in a pediatric kidney transplant recipient with BKVAN who was treated with brincidofovir after treatment failure with decreased immunosuppression, ciprofloxacin, and leflunomide. The treatment resulted in decrease in BK viral load, decrease in serum creatinine to baseline levels, and stabilization of renal function thereafter[31]. A phase 2, open-label, randomized, controlled, multiple ascending dose study on the safety and tolerability of IV brincidofovir in adult kidney transplant recipients with BK infection is currently underway in multiple study sites in Australia and Japan.To date, the role of cidofovir in the treatment of BK infection in kidney transplant recipients remains to be adjunctive at best, until a well-designed and high-grade study can better define its potential benefit.

IVIG

The effectiveness of IVIg against BK infection is still uncertain. IVIg is currently considered an additional treatment choice for patients with refractory BK infection despite aggressive adjustment in immunosuppressive medications. The proof of the effectiveness of IVIg is limited to case series, retrospective studies, and prospective cohort studies.

IVIg is believed to quell BKV-associated kidney disease by acting on various parts of the immune system, including dendritic cells, macrophages, and granulocytes. It is thought to demonstrate its effect by interacting with certain receptors like Fc gamma receptors[32]. Commercially available IVIg preparations contain strong antibodies that can counteract different strains of the BK[33].

In 2006, Sener *et al*[34] suggested that IVIg could be used as a treatment for BKVAN. A case report from 2009 demonstrated that IVIg helped restore kidney function, reduced BK levels, and improved histopathological findings in a pediatric kidney transplant recipient who did not respond adequately to immunosuppression reduction and cidofovir [35].

A study showed that 0.4 g/kg/d (n = 16) or 1 g/kg/d (n = 17) of IVIg administration resulted in increased BKV-neutralizing antibodies (NAbs), which persisted for 22 ± 7 days[36]. In one retrospective study involving 30 patients with BKVAN, 1 g/kg of IVIg was administered to patients who did not respond to eight weeks of the immunosuppression adjustment and leflunomide, with mean BKV loads of 205314 copies/mL. After one year of follow-up, 27 patients (90%) showed a positive response in clearing viremia, with decrease of BK viral loads to 697 copies/mL. It also showed a good graft survival in 12 mo[37].

Another retrospective, single-center cohort study involving 50 patients with BKVAN showed that 1g/kg of IVIg in addition to immunosuppression adjustment led to better clearance of viremia. It showed fewer graft losses with IVIg group (27.3% *vs* 53.6% for control, P = 0.06), although graft and patient survivals were not statistically different[38]. In contrast, a retrospective analysis by Naef *et al*[39] yielded conflicting outcomes. This study involved 860 kidney transplant recipients with BK viremia. A total of 52 out of 131 patients with high-level BK viremia received IVIg. At one year follow-up, the IVIg group exhibited lower estimated GFR compared to patients who did not receive IVIg (44 mL/min *vs* 52 mL/min) and failed to show advantages in shortening the duration of BK viremia or reducing rejections. On the other hand, IVIg might play a role in preventing BKVAN. In one study, 174 kidney transplant recipients were divided into the following three groups retrospectively based on their risk of BKV infection: patients with low NAbs (high-risk) with IVIg, high-risk patients without IVIg, and patients with high NAbs (low-risk) without IVIg. The IVIg group received 0.4 g/kg of IVIg every three weeks for one to three doses, for the first three months following transplant. At 12 mo post-transplant, the incidence of BK viremia in high-risk patients who received IVIg was significantly lower than untreated high-risk group (6.8 % *vs* 36.6%, P < 0.001), and similar to the low-risk group (10.1%)[40].

The AST-IDCOP states that these studies are difficult to evaluate given other concurrent antiviral intervention, widely variable empirical dosing, and initiation of treatment late in the course of the disease[2]. An ongoing randomized controlled trial (NCT 02659891), aims to shed more light on the potential benefits of IVIg in treating BKVAN.

MONOCLONAL ANTIBODIES

Efficacy and safety of first-in-class human IgG1 monoclonal high-affinity neutralizing antibody against BKVAN is currently under investigation (NCT 04294472). This phase 2, randomized, double-blind, placebo-controlled clinical trial evaluated the safety and efficacy of monoclonal antibody (MAU868) in kidney transplant recipients who had BK viremia within one year of enrolment. It involved 28 patients of whom 20 received MAU868 and eight received placebo. Results showed that the MAU868 group had more effective viral load clearance than the placebo group at week 16 through week 36. All patients tolerated MAU868 well. Further investigation regarding its safety and efficacy is warranted.

VST

VST is an emerging therapeutic option for BK infection. Pioneering work towards the development of T-cell therapy started in the early 1990s, mostly geared towards reconstitution of cellular immunity against CMV and isolation of antigen-specific T cells[41]. Over the recent few years, several trials have been conducted to test the clinical utility of VST for BK infection. In a study that included 16 HSCT recipients who developed BK infection, all achieved clinical benefit following VST. Viral load reduction of 85.5% and 96% were noted at week 6 and 12 post-infusion, respectively. Thirteen out of 14 patients who had hemorrhagic cystitis had resolution of hematuria. One of two patients with BKVAN had improvement in renal function[42]. In another study involving 59 HSCT patients with BK hemorrhagic cystitis who received BK-specific cytotoxic T-cell therapy, 67.7% mounted a response and had significant clinical improvement at day 14. Response rate increased to 81.6% at day 45 and was noted to be durable thereafter. Significant decrease in urine BK viral load was also noted among responders[43]. A phase II trial on Posoleucel, a multivirus-specific T-cell therapy derived from healthy, seropositive, third-party donors, was conducted among 59 HSCT recipients who developed CMV, epstein-barr virus (EBV), HHV-6, adenovirus, JC, and BK infection. Of the 27 patients who developed BK infection, all had partial response after 6 wk of treatment with Posoleucel. Of the 23 patients who had BK hemorrhagic cystitis, 74% had resolution of symptoms and macroscopic hematuria. Nine of 24 patients also had documented increase in IFN-γ ELISpot levels[44].

Multivirus-specific T-cell (MVST) lines that target CMV, EBV, Adenovirus, and BK were generated by Roubalová *et al*[45] and they found predominance of CD8+ phenotype in CMV-specific T cells and CD4+ phenotype in BK-specific T cells. The authors suggested modification of the protocol to prevent antigenic competition for MVST to be efficacious treatment of BK infection. Koukoulias *et al*[46] developed a glucocorticoid-resistant, multi-pathogen specific T cell product named Cerberus that targets Adenovirus, CMV, EBV, BK, and Aspergillus. This allows capture of common opportunistic infections among transplant recipients regardless of the intensity of immunosuppression.

In general, most trials conducted on VST claim potential widespread utility of this therapy against multiple post-transplant viral infections while avoiding the nephrotoxic and myelosuppressive effects of certain antivirals. VST is more widely utilized in HSCT recipients. Conceptually, since T-cell reconstitution is central to the management of viral infections, it seems intuitive that VST should have application in the management of BK infection in other solid organ transplant (SOT) recipients. Adenoviral vector-based multivirus-specific T-cell immunotherapy that targets CMV, EBV, Adenovirus, and BK has been developed and demonstrated rapid *in vitro* expansion of multivirus-specific T cells from SOT recipients and *in vivo* priming of antiviral T-cell immunity[47]. Autologous BK-specific T cell lines have been generated from viremic kidney transplant recipients[48]. BK-specific CD8+ T-cells have also been generated *in vitro* from peripheral mononuclear cells derived from healthy donors and pulsed with synthetic peptide pools[49]. These proofs of concept of T-cell therapy paved the way for a promising novel therapy for the prevention of BK infection before kidney and other solid organ transplantation and the treatment of BKVAN after transplantation[48,49]. Jahan *et al*[50] reported a case of a 54-year-old female kidney transplant recipient who developed BKVAN, necessitating reduction in mycophenolate and tacrolimus, administration of IVIg, leflunomide, cidofovir, and ciprofloxacin, but had worsening BKVAN and graft dysfunction. The patient eventually received BK-specific T-cell therapy derived from the patient's daughter and infused over ten sessions. Despite note of significant reduction in BK viral load, the kidney allograft eventually failed due to interstitial fibrosis and tubular atrophy. The authors proposed that early T-cell therapy might be more effective in treating BKVAN. Administration of VST in three SOT recipients, including kidney, heart, and heart-kidney transplants, elicited complete response in one and partial response in two patients[51]. Of the case reports that described the use of VST in kidney transplant recipients who developed BK infection, there were no reports of acute rejection, graft-versus-host disease (GVHD), or death with use of VST[52].

It is worth noting that rare but serious adverse effects of VST, including cytokine release syndrome, diffuse alveolar damage, hepatic sinusoidal obstruction syndrome, multi-organ failure[53], and GVHD[52] have been reported in literature. Other potential logistical limitations of VST include the need for donor immunity to the viral target, as well significant cost, labor, time, and regulatory burden for manufacturing the therapy[52,54]. Some investigators opted to utilize HLA-matched or partially matched T-cell donors, although this did not seem to affect the clinical outcome[43]. Other concerns involve antigenic competition between high and low frequency T-cells and multiple antigens[55] and the efficacy of VST in the setting of lifelong and more intense immunosuppression among SOT recipients[52].

BK VACCINE

An emerging preventative measure for BK infection is the administration of virus-like particle vaccines to induce high levels of neutralizing antibodies against BK even prior to transplantation. Peretti *et al*[56] immunized macaques and mice and were able to demonstrate broad neutralizing response to heterologous BK and JC virus genotypes following the priming dose in macaques and the booster dose in mice. The authors proposed the potential clinical value of BK vaccination among patients awaiting organ transplant to prevent kidney dysfunction and failure from BKVAN or potential transplant rejection following immunosuppression reduction.

DISCUSSION

BK viral infection poses a significant threat to SOT and HSCT recipients and may eventually lead to renal dysfunction and even loss of the renal allograft. Immunosuppression reduction is the mainstay approach to the management BK viral infection. This treatment, however, has a risk of acute rejection that may necessitate use of other anti-rejection therapy that can worsen the current BK virus infection. A cautious and stepwise approach in immunosuppression reduction coupled with close monitoring of renal function, have been found to be an effective approach to find the right balance between treating the BK virus and preserving graft function.

Changes in immunosuppressive regimen do not seem to have significantly different outcomes. Outcomes data on the use of leflunomide, fluoroquinolones, cidofovir, and brincidofovir remain equivocal. Leflunomide and fluoroquinolones are readily available and relatively well-tolerated. However, leflunomide has a potential risk of leukopenia, peripheral neuropathy, gastrointestinal effects, and liver dysfunction or damage[57]. Fluoroquinolones pose a risk of gastrointestinal effects, tendinitis, tendinopathy, tendon rupture, aortic aneurysm and dissection, neuropathy, arrhythmia, and labile blood sugars[58] and potentially higher rates of fluoroquinolone-resistant infections. Cidofovir may be nephrotoxic and myelosuppressive while brincidofovir may cause gastrointestinal effects, predominantly diarrhea[59]. IVIg and monoclonal antibodies are relatively well-tolerated but might carry the risk of headaches, flu-like symptoms, and rarely renal dysfunction, thrombosis, and hemolytic anemia[60]. Viral-specific T-cell therapy and vaccines are some of the emerging management approaches to BK viral infection. Viral-specific T-cell therapy may incur significant time, labor, and cost, while posing rare but potential risks of multi-organ failure and GVHD[52,53]. Certainly, the use of the above agents in addressing BK viral infection should be weighed against their potential adverse effects (Table 1).

Future perspectives

There are definite unmet needs in therapeutic options for BK viral infection. High quality ideally randomized controlled trials, on currently existing medications, as well agents in development, should be conducted. The value of viral-specific T-cell therapy and vaccines should be further investigated.

CONCLUSION

BK viral infection is an important post-transplant infection that can eventually lead to renal dysfunction. Mainstay for management is reduction in immunosuppression. However, this poses a risk for acute rejection. Over the years, alterations in immunosuppressive regimen, use of mTOR inhibitors and leflunomide, fluoroquinolones, cidofovir, and IVIg have been attempted and investigated, and resulted in variable outcomes. BK-specific T-cell therapy and vaccines are emerging options for the management and prevention of BK infection. Nevertheless, effective and durable treatment for BK infection remains elusive. In addition, there is paucity of randomized, controlled trials to provide high-level evidence to support certain management strategies. Indeed, there is a need to pursue studies that will provide evidence to support best management approaches for BK infection post-transplant. These studies might define the future landscape for BK management, while minimizing adverse effects of treatment and optimizing graft and patient survival.

Table 1 Summary table of studies on management of BK infection

Ref.	Study type/period	Subjects	Key findings (include *P* value if available)
Alterations in immunosuppression			
Vela *et al*[7], 2022	Retrospective study; Mar 2013-Oct 2020	43 kidney transplant recipients with BK DNAemia; 26 received mTORi + IVIg; 17 had immunosuppression reduction	BK DNAemia and viral clearance reduced faster and more significantly in subjects with reduced immunosuppression (P < 0.001 and P = 0.033 respectively). Death-censored graft loss, rejection rates, and kidney graft function at 12 mo did not differ significantly
Halim *et al*[6], 2016	Cohort study	55 kidney transplant recipients with BK viremia and/or BKVAN nephropathy; 22 received leflunomide + IVIg + ciprofloxaci; 33 had immunosuppression reduction alone	Administration of leflunomide, IVIg, and ciprofloxacin added no benefit to the long-term outcome of patients with established BKVAN. Treatment of BKVAN by reduction of immunosuppression alone appears to be more effective
Huang *et al*[4], 2015	Prospective study; Mar 2006-Oct 2008	229 kidney transplant recipients with BK viremia and BKVAN 30%-50% reduction in FK and/or MPA	BK viremia resolved in 100% of patients without increased acute rejection. All patients with BKVAN had viral clearance and showed no decline in GFR
Saad *et al*[3], 2008	Retrospective, single center study; Sept 2001-Dec 2003	24 kidney transplant recipients: 16 with BKVAN; 8 with BK viremia	Reduction in immunosuppression alone results in clearance of the BK viremia with good long-term outcome
Leflunomide			
Krisl *et al*[9], 2012	Retrospective, single center study; Jun 2001-Dec 2009	76 kidney transplant recipients with BK viremia with or without BKVAN; 52 received leflunomide; 24 did not receive	No difference in BK viral clearance. Multivariate analysis demonstrated that mycophenolate mofetil discontinuation, BK viremia without nephropathy, and mean BK viral load were

		leflunomide	significantly associated with BK viral clearance. Leflunomide use lacked this association
Canivet *et al* [11], 2009	Prospective study; Jan 2006-May 2008	12 kidney transplant recipients with BKVAN; MMF switched to leflunomide	Not statistically significant T cell markers, BK DNAemia clearance in 41.6%, creatinine clearance stable or improved in 50%, no significant adverse events
Teschner *et al* [12], 2009	Prospective study	13 kidney transplant recipients with BKVAN; MMF switched to leflunomide	12 had viral clearance at a mean of 109 d. Graft function stabilized or improved (mean [median] creatinine concentration at diagnosis, 2.39 [2.5] mg/mL, *vs* 2.27 [2.0] mg/dL at follow-up). 1 graft loss due to refractory rejection. Leflunomide concentration did not correlate with treatment efficiency
Faguer *et al* [10], 2007	Prospective study; Jul 2002-Apr 2006	12 kidney transplant recipients with BKVAN; MMF switched to leflunomide	42% had BK clearance. 66.6% had stable or improved renal allograft function
Josephson *et al* [13], 2006	Prospective study; Apr 2001-Apr 2004	26 kidney transplant recipients with BKVAN; 17 received leflunomide alone; 9 received leflunomide + cidofovir	84% of cases blood and urine viral load levels uniformly decreased over time ($P < 0.001$). Mean serum creatinine levels stabilized over the first 6 months of treatment, and with 12 mo or more of follow-up. 16 patients had fairly unchanged serum creatinine
Fluoroquinolones			
Patel *et al*[19], 2019	Prospective, randomized, placebo-controlled trial; Jan 2013 -Oct 2016	200 adult solitary kidney transplant recipients; 133 received ciprofloxacin as BK prophylaxis; 67 did not receive ciprofloxacin	BK viremia at 6 mo post-transplant occurred in 25 (18.8%) patients in the ciprofloxacin group and 5 (7.5%) in the placebo group ($P = 0.03$). Increased risk of fluoroquinolone-resistant infections in those who received ciprofloxacin
Knoll *et al*[18], 2014	Prospective, double-blind, placebo-controlled randomized trial; Dec 2011 -Jun 2013	154 adult kidney transplant recipients; 76 received a 3-mo course of levofloxacin; 78 received placebo	BK viruria occurred in 22 (29%) in the levofloxacin group *vs* 26 (33.3%) in the placebo group (HR 0.91, 95%CI: $P = 0.58$). Increased risk of resistant infection among isolates usually sensitive to quinolones in the levofloxacin group *vs* placebo (58.3% *vs* 33.3%, respectively); (RR 1.75; 95%CI: 1.01-2.98) as well as a nonsignificant increased risk of suspected tendinitis (7.9% *vs* 1.3%; RR 6.16; 95%CI: 0.76-49.95)
Lee *et al*[17], 2014	Prospective, multicenter, double-blinded, placebo-controlled trial; Jul 2009 -Mar 2012	43 adult kidney transplant recipients with documented BK viremia; 22 received levofloxacin for 30 d; 21 received placebo	At the 3-mo follow up, there was no significant difference in BK viral load reduction between the levofloxacin and placebo group (70.3% *vs* 69.1%, respectively, $P = 0.93$). The percentage reductions in BK viral load were also equivalent at 1 mo (58% *vs* 67.1%, $P = 0.47$), and 6 months (82.1% *vs* 90.5%, $P = 0.38$)
Wojciechowski *et al*[16], 2012	Retrospective study; First cohort (group 1): Jul-Dec 2009 Second cohort (group 2): Jan-Jun 2010	236 adult renal transplant recipients; Group 1: 106 did not receive BK virus prophylaxis; Group 2: 130 received ciprofloxacin as BK virus prophylaxis	At 3 mo post-transplant, the group that did not receive ciprofloxacin (group 1) had a higher risk of developing BK viremia than the group that received ciprofloxacin (group 2) (0.161 *vs* 0.065, $P = 0.0378$) and viruria (0.303 *vs* 0.146, $P = 0.0067$), but this difference progressively narrowed until there was no significant difference anymore at 12 mo for both viremia (0.297 *vs* 0.261, $P = 0.6061$) and viruria (0.437 *vs* 0.389, $P = 0.5363$)
Gabardi *et al* [15], 2010	Retrospective analysis; Jan 2004-Dec 2008	185 adult kidney transplant recipients; 25 received a 30-d course of ciprofloxacin; 160 did not receive a fluoroquinolone	Higher rate of BK viremia in those who did not receive a 1-mo course of levofloxacin 36 (22.5%) *vs* 1 (4%) who received levofloxacin; $P = 0.03$
Cidofovir			
Schneidewind *et al*[29], 2018	Systematic review	189 adult patients with BK virus associated hemorrhagic cystitis after allogenic stem cell transplant; 172 received intravenous cidofovir; 17 patients received intravesical cidofovir (2 patients received both routes of administration)	Complete response: 68% in intravenous cidofovir group, 88.2% in intravesical cidofovir. Kidney toxicity: 9.3% in intravenous cidofovir group, none in intravesical cidofovir group
Papanicolaou *et al*[30], 2015	Case report	58 yr old male post hematopoietic stem cell transplant; developed biopsy-proven polyomavirus associated nephropathy; received brincidofovir 100 mg twice weekly for 6 mo; no immunosuppression reduction	4-log decrease in BK virus viremia. No drug-related adverse events. Stable kidney function, and did not require dialysis
Caruso Brown *et al*[28], 2015	Open-label, non-randomized, single-dose, pilot study	12 pediatric patients (ages 6-18) with a hematopoietic stem cell transplant within 2 yr, with symptomatic infection of adenovirus, nucleoside-resistant CMV, human polyomavirus (BK or JC virus), and/or nucleoside-resistant HSV diagnosed by viral culture or PCR; all patients received cidofovir	2/12 acute kidney injury after the first dose 2/12 developed nephrotoxicity. Mean drug half-life 9.5 h (longer than documented half-life for adults based on other studies). No correlation between nephrotoxicity and plasma maximum concentration, clearance, or half-life. Cidofovir was well- tolerated in majority of patients
Kuten *et al*[27], 2014	Single-center, retrospective review; Jan 2007 to	75 kidney and kidney-pancreas transplant recipients who received cidofovir combined with reduced immunosuppression	32 (43%) had short-term BK (≤ 6 mo); 43 (57%) had long-term BK. 53 (71%) eventually cleared BK at a median of 4.2 mo (interquartile range 2.1-9.3 mo). Factors associated with long-term BK: older age

	Jun 2012		(OR 1.1, P = 0.02), Delayed graft function (OR 31.4, P = 0.01); higher peak BK (OR 12.8, P = 0.02. This group was associated with a 15% decline in estimated glomerular filtration rate. Factor associated with short-term BK: BK reduction by at least 1 $\log_{10}$copies/mL at 1 mo of treatment (OR 49.3, P < 0.01). This group maintained stable graft function and no graft loss was noted
Reisman, *et al* [31], 2014	Case report	pediatric patient who received kidney transplant for bilateral dysplastic kidneys, developed BKVAN; did not respond to decreased immunosuppression, ciprofloxacin, leflunomide; given brincidofovir	BK viral load decreased, but still detectable. Urine viral load declined but still elevated. Creatinine declined to baseline level and was stable for 2 yr. No drug-related adverse events
Kuypers *et al* [26], 2009	Single-center study	41 adult renal transplant recipients with biopsy-proven BKVIN; 26 received cidofovir at 1 mg/kg for a maximum duration of 10 wk and without probenecid; 15 did not receive cidofovir; All patients had immunosuppression reduction	Graft loss: 4/26 (15.4%) in cidofovir group, 11/15 (73.3%) in no cidofovir group (P = 0.0002). Percentage of patients who completely cleared the virus from the blood was not different between the 2 groups. 3 patients in the cidofovir group developed severe anterior uveitis at 6, 7 and 8 doses, respectively (later switched to leflunomide). No BM or renal toxicity was observed in the cidofovir group. One patient developed a skin rash during infusion of cidofovir
IVIg			
Naef *et al*[39], 2021	Retrospective analysis; Jan 2009-Mar 2019	Kidney transplant recipients with high level BK viremia; 79 transplanted before 2014 and had immunosuppression reduction alone; 52 transplanted after 2014 and had immunosuppression reduction + IVIg	IVIg group showed lower eGFR (44 mL/min *vs* 52 mL/min). IVIg did not shorten duration of BK viremia
Kable *et al*[38], 2017	Retrospective, single-center cohort study	50 BKVAN patients received IVIg 1 g/kg	Better clearance of BK viremia and fewer graft loss (not statistically significant)
Vu *et al*[37], 2015	Retrospective analysis; 2008-2012	30 kidney transplant recipients with BKVAN received IVIg 2 g/kg	90% of patients showed positive response in clearing viremia. Graft survival rate was 96.7% at 12 mo follow-up
Sener *et al*[34], 2006	Case series; Jul 2000-Jul 2003	8 kidney transplant recipients with IVIg 2 g/kg	88% of patients showed functioning graft at 15 mo follow-up
Monoclonal antibodies			
In the study	Ongoing RCT (NCT 04294472)	30 kidney transplant recipients with BK viremia; 22 received MAU868; 8 received placebo	Better BK viral clearance in MAU group
Virus-specific T-cell therapy			
Pfeiffer *et al* [44], 2023	Open-label, phase II trial; Apr 2014-Jul 2021	27 pediatric and adult HSCT recipients with BK infection; 25 with hemorrhagic cystitis; 2 with nephritis	100% had partial response at 6 weeks of treatment. 74% of patients who developed hemorrhagic cystitis had symptom resolution. 9/24 (37.5%) had increase in IFN-γ ELISpot counts
Koldehoff *et al* [1], 2023	Sequential analysis	17 HSCT recipients with BK hemorrhagic cystitis; 7 received VST; 10 did not receive VST (immunosuppression reduction or cidofovir)	6/7 from the VST group *vs* 6/10 from the non-VST group had T-specific cellular response, in most cases parallel to decrease in BK viral load
Olson *et al*[43], 2021	Single-arm, phase II clinical trial; Oct 2015-Sept 2019	59 HSCT recipients with BK hemorrhagic cystitis; received single IV infusion of partially HLA-matched BKV-CTL	Response rate and clinical improvement following the off-the-shelf BK-specific cytotoxic T-cells: 67.7% at day 14; 81.6% at day 45
Nelson *et al* [51], 2020	Phase II study; Jun 2017-Dec 2019	38 HSCT recipients; 3 solid organ transplant recipients: 1 kidney transplant recipient; 1 heart transplant recipient; 1 heart-kidney transplant recipient	Response rates: 86% in patients with BK viremia, 100% in patients with hemorrhagic cystitis, 87% in patients with BK viremia and hemorrhagic cystitis. Of the 3 solid organ transplant recipients, 1 had complete response and 2 had partial response
Tzannou *et al* [42], 2017	Phase II study	16 HSCT recipients; 14 with BK hemorrhagic cystitis; 2 with BKVAN	Decrease in urine BK viral load following VST: 85.5% at week 6, 96% at week 12. 13/14 with hemorrhagic cystitis had resolution of hematuria. 1/2 with BKVAN had improved renal function
Jahan *et al*[50], 2020	Case report; Sept 2018	1 kidney transplant recipient with BKVAN who failed other treatments	BK viral load decreased significantly following T-cell therapy, but allograft eventually failed due to interstitial fibrosis and tubular atrophy

BKVAN: BK virus-associated nephropathy; BKVIN: BK virus interstitial nephritis; CMV: Cytomegalovirus; eGFR: Estimated glomerular filtration rate; FK: Tacrolimus; GFR: Glomerular filtration rate; HLA: Human leukocyte antigen; HSCT: Hematopoietic stem cell transplant; IVIg: Intravenous immunoglobulin; MMF: Mycophenolate mofetil; MPA: Mycophenolic acid; mTOR: Mechanistic target of rapamycin; PCR: Polymerase chain reaction; RCT: Randomized controlled trial; VST: Virus-specific T-cell therapy.

FOOTNOTES

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