Efficacy and adverse effects of cidofovir for treatment of BK virus infection in kidney transplant recipients

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A B S T R A C T

Kidney transplant provides patients with end-stage kidney disease a clear survival benefit compared to patients who remain on dialysis. Immunosuppressive therapy is crucial for maintaining graft survival. However, high level of suppression can increase the susceptibility for BK virus reactivation following transplantation, leading to BK virus-associated nephropathy (BK-VAN) and allograft loss. Its clinical presentations are often asymptomatic or solely rising of serum creatinine. While reduction of immunosuppression remains the mainstay treatment of BK viremia/nephropathy, there have been many proposed adjuvant therapy such as antiviral agents, fluoroquinolone, immunoglobulin, and immunotherapy. Cidofovir is one of the adjuvant therapies that have been studied in many case series and cohort studies with unclear data on benefit-risk assessment. This review aims to present the current literature on the efficacy, potential adverse effects and cost-effectiveness of cidofovir treatment for BK viremia/nephropathy.

Implication for health policy/practice/research/medical education:
This review aims to present the evidence of benefit-risk assessment of cidofovir treatment for BK virus infection in kidney transplant recipients. In this review, we discussed the efficacy and adverse side effects, which help physicians in the clinical judgment for the use of cidofovir addition to a reduction of immunosuppressant. Moreover, this review also provides brief review of current view in BK virus burden, clinical manifestation, diagnosis and other treatment methods which can be beneficial in clinical practice and future research.


Introduction
End-stage renal disease (ESRD) remains the global health problem, associated with high morbidity and mortality (1). Kidney transplantation is the treatment of choice for ESRD patients and a successful kidney transplant offers improved quality of life and survival benefit compared to staying on dialysis (2,3). Advances in immunosuppression and transplant techniques over the last two decades have led to significant improvements in short-term survival of kidney allografts (4). However, inversely proportional to the use of immunosuppressive therapy, BK virus infection has become one of common complications following kidney transplantation, resulting in allograft loss (5).

BK virus was first discovered in 1971 from the urine of the ureteric stricter-kidney transplant recipient (6). However, BK virus infection was initially believed to have non-clinical significant until two decades later (7), when studies revealed its association with acute and chronic allograft rejection (8,9). Subsequently, many aspects of the research on BK virus including clinical manifestation, pathophysiology, diagnosis and treatment have been rapidly increasing over the past years. One of the proposed treatments of BK virus as an adjunct to the reduction of immunosuppression is cidofovir. However, studies have shown conflicting data on efficacy of cidofovir for BK virus-associated nephropathy (BK-VAN). In addition,
adverse effects following cidofovir therapy have also been reported. Thus, this review aims to present the current knowledge, efficacy and adverse effects of cidofovir for treatment of BK virus infection and BK-VAN in kidney transplant recipients.

Materials and Methods
This review article discusses benefit-risk assessment of cidofovir treatment for BK-VAN including the efficacy, potential adverse effects and cost-effectiveness. We report the available evidence of clinical outcomes, cost effectiveness and adverse side effects following cidofovir treatment for BK-VAN. Moreover, this review also provided brief review of current view in BK virus burden, clinical manifestation, diagnosis and other treatment methods which can be beneficial in clinical practice and future research.

For this review, we used a variety of sources by searching through MEDLINE, EMBASE and the Cochrane databases. The study protocol is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42017060939). The search was performed using combinations of the following key words and or their equivalents; cidofovir, vistide, BK, BK nephropathy, BK viremia, BK infection, BK virus, polyoma, polyomavirus, and transplantation.

Burden of BK virus in kidney transplant recipient
The real burden of BK virus infection in kidney transplant recipient is unknown. Most of studies showed that prevalence of seropositive BK virus in general adult population is 55 to 85% depending on sensitivity of the essay (10). After receiving kidney transplant, urine is the earliest detectable site of BK virus (10). Approximately 30% to 60% of post-transplant recipient has developed BK viruria, and 10% to 20% has BK viremia (11). About 1% to 10% has developed BK-VAN during the first year after transplant (5,12,13). During BK virus replication, BK viruria usually precedes BK viremia by a median of ~4 weeks. Subsequently, BK viremia precedes and results in BK nephropathy by a median of ~8 weeks (5,14-16). The association between the quantitative measurement of BK viral load in either urine or blood and the development of BK-VAN is still unclear. However, the prevalence of graft loss after developing BK-VAN can be very high, up to 80% (5,17).

Clinical manifestations and diagnostic tools
Primary infection of BK virus is mostly asymptomatic, and it can occur in early life without detection from the host immune system (18). Although the route of transmission of BK virus remains unclear, kidney and urinary tract are known to be the primary site of BK virus infection (18,19). In the patient who receives an intense immunosuppressive therapy, the replication of BK virus can be prolific which is called BK virus reactivation. BK virus reactivation in kidney transplant recipient may present with several manifestations. The most common manifestation is BK-VAN which can present with asymptomatic creatinine rising and progress to graft loss (15,20). BK virus-associated hemorrhagic cystitis and ureteric sticture are also rare manifestation of BK virus infection (21,22). Screening test for BK virus infection can be done in both blood and urine. Cytology and polymerase chain reaction (PCR) for BK virus DNA are two effective methods for detecting BK virus in urine (16). Presenting of decoy cell, the group of renal tubular epithelium infected with BK virus in urine has low sensitivity but high specificity. In contrast with the direct detection of viral DNA in urine, it has higher sensitivity and specificity (23,24). Detection of BK virus DNA in blood by PCR method has nearly 100% sensitivity and specificity (24). The 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for care of kidney transplant recipient suggest that plasma BK virus should be screened in all kidney transplant recipient (25). Nonetheless, it has uncertain cut-point to predict the association between BK viremia and BK-VAN. Recent studies have demonstrated that urine Haufen, the aggregation of BK viral particle visualized by electron microscope was highly correlated with BK-VAN (26,27). However, future external validation studies in diverse kidney transplant population are required. Even though there are several screening methods for BK virus, transplanted kidney biopsy is still the gold standard for diagnosis of BK-VAN (25,28).

Current treatments of BK virus
Providing optimal treatments for patients with BK-VAN is a controversial challenge requiring balance between the treatment of BK infection and the risk of graft rejection. Reduction of immunosuppression remains the mainstay treatment for BK-VAN (29). In addition to immunosuppression reduction, there are various medications that have been proposed and used as adjunctive therapies for BK-VAN (Table 1). Johnston et al (29) conducted the systematic review of BK virus treatment in kidney transplant recipients. They found that there was no difference of death-censored graft survivals between reduction of immunosuppression alone versus reduction of immunosuppression plus other medications including cidofovir and leflunomide. However, most of studies were case reports and case series with only few randomized controlled trials. Recently, fluoroquinolone for prevention of BK infection post kidney transplant was studied in two randomized control trials (30,31). Unfortunately, both studies failed to show the benefit of fluoroquinolone in BK virus suppression. Moreover, fluoroquinolone may increase risk of bacterial resistance. Intravenous immunoglobulin (IVIG) showed the potential inhibition of BK virus in-vitro by BK virus neutralizing antibodies (32). However, there was only limited studies using IVIG in BK virus infection (33). In addition, more recently, Leboeuf et al (34) demonstrated that BK-specific T-cell responses, but not neutralizing antibodies, was crucial in clearance of BK viremia in kidney transplant patients. Another novel approach to
the treatment of BK infection is T cell adoptive therapy or immunotherapy. The principle of T cell adoptive therapy is to transfer T cell that recognizes the BK virus antigen to patient infected with BK virus. Papadopoulou et al (35) transferred viral-specific T cell to 7 hematopoietic stem cell transplant patients with BK viremia and demonstrated some response without toxicity. However, it is too low level of evidence to prove the benefit.

**Introduction to cidofovir**

Cidofovir was first introduced in 1987, as known as (S)-1-[3-hydroxy-2 (phosphonylmethoxy) propyl] cytosine (HPMPC). In-vitro studies showed that this nucleotide analog had potent activity against many types of DNA virus including herpes virus family especially CMV (36,37). Inside the host cell, cidofovir is activated by uridine/cytosine monophosphate kinase (UMP-CMP kinase), nucleoside 5-diphosphate kinase and pyruvate kinase or creatine kinase respectively to become cidofovir-diphosphate, the active form of cidofovir (38,39). The active form of cidofovir can be the effective competitive inhibitor of deoxy-cytosine triphosphate (dCTP), or it can incorporate into the normal chain of viral DNA synthesized by viral DNA polymerase causing interruption of viral DNA chain (40). Cidofovir has been approved by the Food and Drug Administration (FDA) for treatment of CMV retinitis. Apart from activity against herpes virus family, Andrei et al (41) demonstrated that cidofovir had inhibitory effect on murine polyomavirus in-vitro. In 2002, Bjoarg et al (42) reported the successful case of using low dose of intravenous cidofovir in BK virus-infected kidney transplant recipient. After successful case report of using cidofovir in BK virus infected patient, there are many clinical studies that explore the efficacy of cidofovir in BK virus treatment.

**Clinical study of cidofovir in BK virus treatment**

Johnston et al (29) conducted a systematic review and meta-analysis of 11 case series and 1 retrospective cohort studies assessing the efficacy of cidofovir in BK virus infected kidney transplant recipient. The investigators reported no clear benefit of adjunctive cidofovir in BK-VAN with the estimated death-censored pooled graft failure rate of 8/100 patient-years. Kuypers et al (13) conducted first retrospective cohort study of 21 kidney transplant recipients with biopsy proven BK-VAN. Eight patients received 0.5 mg/kg per week of cidofovir with immunosuppressant reduction. The results showed 0% graft loss in cidofovir group versus 70% in control group during mean follow up time of 24.8 months. However, the control group received more intensive immunosuppressive therapy compared to cidofovir group and criteria for allocating patient to both groups were unclear which could lead to selection bias. Second retrospective cohort was conduct by Kuten et al (43), 75 patients with biopsy proven BK-VAN or BK viral load more than 750 copies per milliliter received 0.5 mg/kg per 2 weeks addition to immunosuppressive reduction. The study demonstrated that 71% of case can clear BK virus either in blood or biopsy at a median of 4.2 months. However, there was no control group in this study. Thus, it was unclear if the resolution of BK viremia was contributed by conventional immunosuppressive reduction or cidofovir treatment. Future studies optimally with randomized controlled trials are required to assess the efficacy between the adjunctive cidofovir plus immunosuppressive reduction versus solely reduced immunosuppression.

**Cidofovir administration**

Prior to cidofovir treatment, patients should have baseline complete blood count, serum creatinine and urinalysis tested since potential toxicities of cidofovir include neutropenia, renal insufficiency, proteinuria and uveitis (44-48). Due to potential nephrotoxicity, low-dose cidofovir therapy (0.25 mg/kg IV infusion over 1 hour) is suggested for treatment of BK-VAN in renal transplant recipients (49, 50), and treatment may be repeated once every 2 weeks for a total of four doses. In resistant cases, if patients tolerate cidofovir treatment at 0.25 mg/kg, dosage may increase to 0.5 mg/kg. In addition, hydration both pre- and post-infusion have also been recommended (49).

**Adverse effects of cidofovir**

Major adverse effects of cidofovir are nephrotoxicity, ocular toxicity and neutropenia. Nephrotoxicity is dose-dependent. The risk factor is co-administration with

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**Table 1. Adjuvant therapies for BK virus treatment in addition to the reduction of immunosuppressive therapy alone**

<table>
<thead>
<tr>
<th>Adjuvant therapy</th>
<th>Mechanism of action</th>
<th>Reported adverse effects</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cidofovir</td>
<td>Inhibiting viral replication via interruption of viral DNA chain</td>
<td>Nephrotoxicity, uveitis, neutropenia</td>
<td>The results remain controversial</td>
<td>(13,43,69-82)</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Inhibiting synthesis of uridine monophosphate (UMP) and possible interfere with viral replication</td>
<td>Thrombocytopenia, hemolysis</td>
<td>The results remain controversial</td>
<td>(77,83-86)</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>Possible inhibiting large T-antigen (LT-ag) helicase activity in BK virus</td>
<td>Increase risk of bacteria resistance</td>
<td>The studies failed to show the benefit</td>
<td>(30, 31,87)</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>Neutralizing antibody</td>
<td>Suspected paradoxical increasing of viral load</td>
<td>Too low evidence</td>
<td>(32,33)</td>
</tr>
<tr>
<td>Adoptive T cell therapy</td>
<td>Inhibiting BK virus by viral-specific T cell</td>
<td>Unknown</td>
<td>Too low evidence</td>
<td>(35)</td>
</tr>
</tbody>
</table>
other nephrotoxic agent (51). Proteinuria and serum creatinine rising are two common presentations and can occur up to 50% of all adverse effect (52). Apart from two common nephrotoxicity manifestation there are some rare presentations have been report including Fanconi syndrome (53,54) nephrogenic diabetes insipidus (55) and ESRD (56). Nevertheless, the incident of cidofovir induced nephrotoxicity in post-kidney transplant recipient is unknown. Anterior uveitis is a known complication of cidofovir used in CMV retinitis patient (57-59). The rate of anterior uveitis is approximately 0.2 per person-year (60). In the patient with BK-VAN, Lopez et al (61) found that 5 out of 14 patients (35%) with BK-VAN developed anterior uveitis after received cidofovir. They also found that impair renal function is increasing the risk of developing anterior uveitis. Neutropenia is one of common adverse effect that can be found but the incident and the pattern of neutropenia are not well studied. One study found that neutropenia can occur about 35% of total adverse effects, but it may not affect the clinical outcome (52). Box 1 shows relative contraindication to cidofovir therapy. Cidofovir treatment should be discontinued for unexplained elevation in serum creatinine, new onset or worsening of proteinuria or metabolic acidosis, visual changes, worsening neutropenia with absolute neutrophil count < 1.0 x10^9/L.

Cost-effectiveness of cidofovir in BK-VAN treatment
Hua et al (62) studied a probabilistic decision analytic model from available clinical studies to determine the cost-effectiveness of cidofovir plus immunosuppressant reduction versus immunosuppressant reduction alone. They found that adjuvant cidofovir therapy can reduce the cost of treatment by $20756 and save 2.2 days of life. Notwithstanding that the calculation was based on few clinical studies including retrospective cohort and case-series which it is difficult to extrapolate to the general population, but it was the only model that demonstrate the cost versus outcome of adjunctive cidofovir use in BK-VAN.

Future direction
Novel agent such as brincidofovir (CMX001) has been developed to eliminate side effect and enhance the efficacy of cidofovir. Brincidofovir, is the hexadecyloxypropyl lipid conjugate of cidofovir. In-vitro study showed that brincidofovir can inhibit BK virus replication, protein expression and production of new virion in human urothelial cell with high cellular absorption less toxicity (63). Some case reports demonstrated the efficacy of brincidofovir in BK-VAN (64, 65). Recently, the data on brincidofovir treatment of cytomegalovirus (CMV) infection has been presented (66, 67). Unfortunately, brincidofovir was not found to be more effective than placebo, and the rate of CMV infection was higher after drug discontinuation. The drug has worrisome gastrointestinal adverse effects, mimicking graft-versus-host disease (GVHD) (68). However, future studies are needed to show the efficacy of brincidofovir for treatment of BK-VAN in kidney transplant recipients.

Conclusion
From the current evidence, the data on efficacy of cidofovir treatment as adjuvant therapy for BK-VAN in kidney transplant recipients are limited. Potential major adverse side effects include nephrotoxicity (elevated serum creatinine and proteinuria), uveitis and neutropenia. Thus, low dose cidofovir treatments with pre- and post-hydration have been suggested. Overall, adjuvant cidofovir therapy for BK-VAN after kidney transplant is cost effective and may reduce the cost of treatment by $20756 and save 2.2 days over the lifetime of a transplant recipient. Future studies optimally with randomized controlled trials are required to assess the efficacy between the adjunctive cidofovir plus immunosuppressive reduction versus solely reduced immunosuppression.

Box 1. Relative contraindications to Cidofovir therapy [88-90]
- Pregnancy
- History of uveitis
- Pre-existing renal insufficiency: serum creatinine >3.5 mg/dL
- Pre-existing leukopenia/neutropenia
- Pre-existing metabolic acidosis (HCO3 <20 mmol/L)
- Proteinuria > 2 g in 24 h (2+)

Authors’ contribution
All authors had access to the data and a role in writing the manuscript. All authors read and signed the final paper.

Conflicts of interest
The authors declare that they have no conflicting interest.

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Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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