J Nephropharmacol. 2018; 7(1): 10–17.

http://www.jnephropharmacology.com DOI: 10.15171/npj.2018.04

Journal of Nephropharmacology

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

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ARTICLEINFO

Article Type:
Review

Article History:
Received: 19 May 2017
Accepted: 27 August 2017
ePublished: 19 September 2017

Keywords:
BK virus
Cidofovir
Kidney transplantation
Polyoma virus
Transplantation

ABSTRACT

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.

Review

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.

Please cite this paper as: Chesdachai S, Thongprayoon C, Bruminhent J, Cheungpasitporn W. Efficacy and adverse effects of cidofovir for treatment of BK virus infection in kidney transplant recipients. J Nephropharmacol. 2018;7(1):10-17. DOI: 10.15171/npj.2018.04.

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,

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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 stricture 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

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

Adjuvant therapy	Mechanism of action	Reported adverse effects	Comments	References
Cidofovir	Inhibiting viral replication via interruption of viral DNA chain	Nephrotoxicity, uveitis, neutropenia	The results remain controversial	(13,43,69-82)
Leflunomide	Inhibiting synthesis of uridine monophosphate (rUMP) and possible interfere with viral replication	Thrombocytopenia, hemolysis	The results remain controversial	(77,83-86)
Fluoroquinolone	Possible inhibiting large T-antigen (LT-ag) helicase activity in BK virus	Increase risk of bacteria resistance	The studies failed to show the benefit	(30, 31,87)
Intravenous immunoglobulin	Neutralizing antibody	Suspected paradoxical increasing of viral load	Too low evidence	(32,33)
Adoptive T cell therapy	Inhibiting BK virus by viral-specific T cell	Unknown	Too low evidence	(35)

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 50-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, Bjorang 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 compare 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

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 $\times 10^9$/L.

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+)

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 $20 756 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 unwanted 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 $20 756 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.

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.

Ethical considerations

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

Funding/Support

None.

References

1. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global prevalence of chronic kidney disease – a systematic review and meta-analysis. PLoS One. 2016;11:e0158765. doi: 10.1371/journal.pone.0158765.
2. Schnuelle P, Lorenz D, Trede M, Van Der Woude FJ. Impact of renal cadaveric transplantation on survival in end-stage renal failure: evidence for reduced mortality risk compared with hemodialysis during long-term follow-up. J Am Soc Nephrol. 1998;9:2135-41. doi: 10.1681/ASN.1998050577.
3. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999;341:1725-30. doi: 10.1056/nejm199912023412303.

4. Pascual M, Theruvath T, Kawai T, Tolkoff-Rubin N, Cosimi AB. Strategies to improve long-term outcomes after renal transplantation. N Engl J Med. 2002;346:580-90. doi: 10.1056/NEJMra011295.
5. Hirsch HH, Brennan DC, Drachenberg CB, Ginevri F, Gordon J, Limaye AP, et al. Polyomavirus-associated nephropathy in renal transplantation: interdisciplinary analyses and recommendations. Transplantation. 2005;79:1277-86. doi: 10.1097/TP.0000000000000750.
6. Gardner SD, Field AM, Coleman DV, Hulme B. New human papovavirus (B.K.) isolated from urine after renal transplantation. Lancet. 1971;1:1253-7. doi: 10.1016/S0140-6736(71)90562-9
7. Andrews CA, Shah KV, Daniel RW, Hirsch MS, Rubin RH. A serological investigation of BK virus and JC virus infections in recipients of renal allografts. J Infect Dis. 1988;158:176-81.
8. Randhawa PS, Finkelstein S, Scantlebury V, Shapiro R, Vivas C, Jordan M, et al. Human polyoma virus-associated interstitial nephritis in the allograft kidney. Transplantation. 1999;67:103-9. 9921805. doi:10.1097/00007890-199901150-00018.
9. Purighalla R, Shapiro R, McCauley J, Randhawa P. BK virus infection in a kidney allograft diagnosed by needle biopsy. Am J Kidney Dis. 1995;26:671-3. doi: 10.1053/j.ajkd.1995.06.028.
10. Knowles WA. Discovery and epidemiology of the human polyomaviruses BK virus (BKV) and JC virus (JCV). Adv Exp Med Biol. 2006;577:19-45. doi: 10.1007/0-387-32957-9_2.
11. Brennan DC, Agha I, Bohl DL, Schnitzler MA, Hardinger KL, Lockwood M, et al. Incidence of BK with Tacrolimus Versus Cyclosporine and Impact of Preemptive Immunosuppression Reduction. Am J Transplant. 2005;5:582-94. doi: 10.1111/j.1600-6143.2005.00742.x.
12. Chon WJ, Aggarwal N, Kocherginsky M, Kane B, Sutor J, Josephson MA. High-level viruria as a screening tool for BK virus nephropathy in renal transplant recipients. Kidney Res Clin Pract. 2016;35:176-81. doi: 10.1016/j.krcp.2016.05.005.
13. Kuypers DR. Management of polyomavirus-associated nephropathy in renal transplant recipients. Nat Rev Nephrol. 2012;8:390-402. doi: 10.1038/nrneph.2012.64.
14. Lamarche C, Orio J, Collette S, Senecal L, Hebert MJ, Renoult E, et al. BK Polyomavirus and the Transplanted Kidney: Immunopathology and Therapeutic Approaches. Transplantation. 2016;100:2276-87. doi: 10.1097/tp.0000000000001333.
15. Ambalathingal GR, Francis RS, Smyth MJ, Smith C, Khanna R. BK Polyomavirus: Clinical Aspects, Immune Regulation, and Emerging Therapies. Clin Microbiol Rev. 2017;30:503-28. doi: 10.1128/cmr.00074-16.
16. Sawinski D, Goral S. BK virus infection: an update on diagnosis and treatment. Nephrol Dial Transplant. 2015;30:209-17. doi: 10.1093/ndt/gfu023.
17. Ramos E, Drachenberg CB, Papadimitriou JC, Hamze O, Fink JC, Klassen DK, et al. Clinical course of polyoma virus nephropathy in 67 renal transplant patients. J Am Soc Nephrol. 2002;13:2145-51. doi: 10.1097/01.ASN.0000023435.07320.81
18. Gardner SD. Prevalence in England of antibody to human polyomavirus (B.k.). Br Med J. 1973;1:77-8. doi: 10.1136/bmj.1.5845.77
19. Barth H, Solis M, Lepiller Q, Sueur C, Soulier E, Caillard S, et al. 45 years after the discovery of human polyomaviruses BK and JC: Time to speed up the understanding of associated diseases and treatment approaches. Crit Rev Microbiol. 2017;43:178-195. doi: 10.1080/1040841x.2016.1189873.
20. Trofe-Clark J, Sawinski D. BK and Other Polyomaviruses in Kidney Transplantation. Semin Nephrol. 2016;36:372-85. doi: 10.1016/j.semnephrol.2016.05.014.
21. Helantera I, Hirsch HH, Wernli M, Ortiz F, Lempinen M, Raisanen-Sokolowski A, et al. Simultaneous BK Polyomavirus (BKPyV)-associated nephropathy and hemorrhagic cystitis after living donor kidney transplantation. J Clin Virol. 2016;76:4-7. doi: 10.1016/j.jcv.2015.12.008.
22. Reddy YN, Trabert J, Wunderer F, Abraham G, Reddy YN. Recurrent renal allograft dysfunction due to ureteric stenosis in a patient with the BK virus infection. Saudi J Kidney Dis Transpl. 2014;25:101-4. doi: 10.4103/1319-2442.124508
23. Hirsch HH, Knowles W, Dickenmann M, Passweg J, Klimkait T, Mihatsch MJ, et al. Prospective Study of Polyomavirus Type BK Replication and Nephropathy in Renal-Transplant Recipients. N Engl J Med. 2002;347:488-96. doi: 10.1056/NEJMoa020439.
24. Viscount HB, Eid AJ, Espy MJ, Griffin MD, Thomsen KM, Harmsen WS, et al. Polyomavirus polymerase chain reaction as a surrogate marker of polyomavirus-associated nephropathy. Transplantation. 2007;84:340-5. doi: 10.1097/01.tp.0000275205.41078.51.
25. Kasiske BL, Zeier MG, Chapman JR, Craig JC, Ekberg H, Garvey CA, et al. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. Kidney Int. 2010;77:299-311. doi: 10.1038/ki.2009.377.
26. Singh HK, Andreoni KA, Madden V, True K, Detwiler R, Weck K, et al. Presence of urinary Haufen accurately predicts polyomavirus nephropathy. J Am Soc Nephrol. 2009;20:416-27. doi: 10.1681/asn.2008010117.
27. Singh HK, Donna Thompson B, Nickeleit V. Viral Haufen are urinary biomarkers of polyomavirus nephropathy: New diagnostic strategies utilizing negative staining electron microscopy. Ultrastruct Pathol. 2009;33:222-35. doi: 10.3109/01913120903241081.
28. Masutani K, Shapiro R, Basu A, Tan H, Wijkstrom M, Randhawa P. The Banff 2009 Working Proposal for polyomavirus nephropathy: a critical evaluation of its utility as a determinant of clinical outcome. Am J Transplant. 2012;12:907-18. doi: 10.1111/j.1600-6143.2012.03993.x.
29. Johnston O, Jaswal D, Gill JS, Doucette S, Fergusson DA, Knoll GA. Treatment of polyomavirus infection in kidney transplant recipients: a systematic review. Transplantation. 2010;89:1057-70. doi: 10.1097/TP.0b013e3181d0e15e.
30. Knoll GA, Humar A, Fergusson D, Johnston O, House AA, Kim SJ, et al. Levofloxacin for BK virus prophylaxis following kidney transplantation: a randomized clinical trial. JAMA. 2014;312:2106-14. doi: 10.1001/jama.2014.14721.
31. Lee BT, Gabardi S, Grafals M, Hofmann RM, Akalin E, Aljanabi A, et al. Efficacy of levofloxacin in the treatment

of BK viremia: a multicenter, double-blinded, randomized, placebo-controlled trial. Clin J Am Soc Nephrol. 2014;9:583-9. doi: 10.2215/cjn.04230413.
32. Randhawa PS, Schonder K, Shapiro R, Farasati N, Huang Y. Polyomavirus BK neutralizing activity in human immunoglobulin preparations. Transplantation. 2010;89:1462-5. doi: 10.1097/TP.0b013e3181daaaf1
33. Sener A, House AA, Jevnikar AM, Boudville N, McAlister VC, Muirhead N, et al. Intravenous immunoglobulin as a treatment for BK virus associated nephropathy: one-year follow-up of renal allograft recipients. Transplantation. 2006;81:117-20. doi: 10.1097/TP.0b013e200681
34. Leboeuf C, Wilk S, Achermann R, Binet I, Golshayan D, Hadaya K, et al. BK Polyomavirus-Specific 9mer CD8 T Cell Responses Correlate With Clearance of BK Viremia in Kidney Transplant Recipients: First Report From the Swiss Transplant Cohort Study. Am J Transplant. 2017. doi: 10.1111/ajt.14282.
35. Papadopoulou A, Gerdemann U, Katari UL, Tzannou I, Liu H, Martinez C, et al. Activity of broad-spectrum T cells as treatment for AdV, EBV, CMV, BKV, and HHV6 infections after HSCT. Sci Transl Med. 2014;6:242ra83. doi: 10.1126/scitranslmed.3008825.
36. De Clercq E, Sakuma T, Baba M, Pauwels R, Balzarini J, Rosenberg I, et al. Antiviral activity of phosphonylmethoxyalkyl derivatives of purine and pyrimidines. Antiviral Res. 1987;8:261-72. doi: 10.1987/s13337-013-0145-0.
37. Snoeck R, Sakuma T, De Clercq E, Rosenberg I, Holy A. (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine, a potent and selective inhibitor of human cytomegalovirus replication. Antimicrob Agents Chemother. 1988;32:1839-44. doi: 0066-4804/88/121839.
38. Ho HT, Woods KL, Bronson JJ, De Boeck H, Martin JC, Hitchcock MJ. Intracellular metabolism of the antiherpes agent (S)-1-[3-hydroxy-2-(phosphonylmethoxy)propyl] cytosine. Mol Pharmacol. 1992;41:197-202. doi: 10.1128/AAC.01343-13
39. Cihlar T, Chen MS. Identification of enzymes catalyzing two-step phosphorylation of cidofovir and the effect of cytomegalovirus infection on their activities in host cells. Mol Pharmacol. 1996;50:1502-10. doi: 10.1128/AAC.01809-10.
40. Andrei G, Topalis D, De Schutter T, Snoeck R. Insights into the mechanism of action of cidofovir and other acyclic nucleoside phosphonates against polyoma- and papillomaviruses and non-viral induced neoplasia. Antiviral Res. 2015;114:21-46. doi: 10.1016/j.antiviral.2014.10.012.
41. Andrei G, Snoeck R, Vandeputte M, De Clercq E. Activities of various compounds against murine and primate polyomaviruses. Antimicrob Agents Chemother. 1997;41:587-93.
42. Bjorang O, Tveitan H, Midtvedt K, Broch LU, Scott H, Andresen PA. Treatment of polyomavirus infection with cidofovir in a renal-transplant recipient. Nephrol Dial Transplant. 2002;17(11):2023-5. doi: 10.1093/ndt/17.11.2023.
43. Kuten SA, Patel SJ, Knight RJ, Gaber LW, DeVos JM, Gaber AO. Observations on the use of cidofovir for BK virus infection in renal transplantation. Transpl Infect Dis. 2014;16:975-83. doi: 10.1111/tid.12313.
44. Vittecoq D, Dumitrescu L, Beaufils H, Deray G. Fanconi syndrome associated with cidofovir therapy. Antimicrob Agents Chemother. 1997;41:1846.
45. Izzedine H, Launay-Vacher V, Deray G. Antiviral drug-induced nephrotoxicity. Am J Kidney Dis. 2005;45:804-17. doi: 10.1053/j.ajkd.2005.02.010
46. Lalezari JP, Holland GN, Kramer F, McKinley GF, Kemper CA, Ives DV, et al. Randomized, controlled study of the safety and efficacy of intravenous cidofovir for the treatment of relapsing cytomegalovirus retinitis in patients with AIDS. J Acquir Immune Defic Syndr Hum Retrovirol. 1998;17:339-44. doi: 10.2165/00003495-199958020-00015.
47. Akler ME, Johnson DW, Burman WJ, Johnson SC. Anterior uveitis and hypotony after intravenous cidofovir for the treatment of cytomegalovirus retinitis. Ophthalmology. 1998;105:651-7. doi: 10.1016/S0161-6420(98)94019-2
48. Martinez C, Luks-Golger D. Cidofovir use in acyclovir-resistant herpes infection. Ann Pharmacother. 1997;31:1519-21. doi: 10.1001/ annpharmacother.1997.31
49. Kuypers DR, Vandooren AK, Lerut E, Evenepoel P, Claes K, Snoeck R, et al. Adjuvant low-dose cidofovir therapy for BK polyomavirus interstitial nephritis in renal transplant recipients. Am J Transplant. 2005;5:1997-2004. doi: 10.1111/j.1600-6143.2005.00980.x
50. Kadambi PV, Josephson MA, Williams J, Corey L, Jerome KR, Meehan SM, et al. Treatment of Refractory BK Virus-Associated Nephropathy With Cidofovir. Am J Transplant. 2003;3:186-91. doi: 10.1034/j.1600-6143.2003.30202.x
51. Izzedine H, Launay-Vacher V, Deray G. Antiviral drug-induced nephrotoxicity. Am J Kidney Dis. 2005;45:804-17. doi: 10.1053/j.ajkd.2005.02.010.
52. Lalezari JP, Holland GN, Kramer F, McKinley GF, Kemper CA, Ives DV, et al. Randomized, controlled study of the safety and efficacy of intravenous cidofovir for the treatment of relapsing cytomegalovirus retinitis in patients with AIDS. J Acquir Immune Defic Syndr Hum Retrovirol. 1998;17:339-44. doi: 10.2165/00003495-199958020-00015.
53. Vittecoq D, Dumitrescu L, Beaufils H, Deray G. Fanconi syndrome associated with cidofovir therapy. Antimicrob Agents Chemother. 1997;41(8):1846.
54. Kazory A, Singapuri S, Wadhwa A, Ejaz AA. Simultaneous development of Fanconi syndrome and acute renal failure associated with cidofovir. J Antimicrob Chemother. 2007;60:193-4. doi: 10.1093/jac/dkm143.
55. Schliefer K, Rockstroh JK, Spengler U, Sauerbruch T. Nephrogenic diabetes insipidus in a patient taking cidofovir. Lancet. 1997;350:413-4. doi: 10.1016/s0140-6736(05)64137-2.
56. Vandercam B, Moreau M, Goffin E, Marot JC, Cosyns JP, Jadoul M. Clin Infect Dis. 1999;29:948-9. doi: 10.1086/520475.
57. Bainbridge JW, Raina J, Shah SM, Ainsworth J, Pinching AJ. Ocular complications of intravenous cidofovir for cytomegalovirus retinitis in patients with AIDS. Eye. 1999;13:353-6. doi: 10.1038/eye.1999.89.
58. Ambati J, Wynne KB, Angerame MC, Robinson MR. Anterior uveitis associated with intravenous cidofovir use in patients with cytomegalovirus retinitis. Br J Ophthalmol. 1999;83:1153-8. doi: 10.1055/s-2008-1027317

59. Cochereau I, Doan S, Diraison MC, Mousalatti H, Guvenisik N, Ren L, et al. Uveitis in patients treated with intravenous cidofovir. Ocul Immunol Inflamm. 1999;7:223-9. doi: 10.3109/09273948.2016.1134221
60. Long-term follow-up of patients with AIDS treated with parenteral cidofovir for cytomegalovirus retinitis: the HPMPC Peripheral Cytomegalovirus Retinitis Trial. The Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group. AIDS. 2000;14:1571-81. doi: 10.3390/v2122803
61. Lopez V, Sola E, Gutierrez C, Burgos D, Cabello M, Garcia I, et al. Anterior uveitis associated with treatment with intravenous cidofovir in kidney transplant patients with BK virus nephropathy. Transplant Proc. 2006;38:2412-3. doi: 10.1016/j.transproceed.2006.08.067.
62. Hua DK, Howard K, Craig JC, Chapman JR, Wong G. Cost-effectiveness of cidofovir treatment of polyomavirus nephropathy in kidney transplant recipients. Transplantation. 2012;93:188-94. doi: 10.1097/TP.0b013e31823e7b0e.
63. Tylden GD, Hirsch HH, Rinaldo CH. Brincidofovir (CMX001) inhibits BK polyomavirus replication in primary human urothelial cells. Antimicrob Agents Chemother. 2015;59:3306-16. doi: 10.1128/aac.00238-15.
64. Reisman L, Habib S, McClure GB, Latiolais LS, Vanchiere JA. Treatment of BK virus-associated nephropathy with CMX001 after kidney transplantation in a young child. Pediatr Transplant. 2014;18:E227-31. doi: 10.1111/petr.12340.
65. Papanicolaou G, Kolitsopoulos Y, Young J, Boruchov A, Sankaranarayanan N, Hull D, et al. BK virus-associated nephropathy (BKVN), an under-recognized cause of renal dysfunction in severely immunosuppressed hematopoietic stem cell transplant (HSCT) patients: report of 5 cases of Bkvn and the Potential Role of CMX001 for Treatment. Biol Blood Marrow Transplant. 2013;19:S302-3. doi: 10.1016/j.bbmt.2012.11.442.
66. Marty F, Winston D, Chemaly R, Boeckh M, Mullane K, Shore T, et al. Brincidofovir for prevention of cytomegalovirus after allogeneic hematopoietic cell transplantation in CMV-seropositive patients. BMT Tandem Meetings; 2016.
67. El-Haddad D, El Chaer F, Vanichanan J, Shah DP, Ariza-Heredia EJ, Mulanovich VE, et al. Brincidofovir (CMX-001) for refractory and resistant CMV and HSV infections in immunocompromised cancer patients: A single-center experience. Antiviral Res. 2016;134:58-62. doi: 10.1016/j.antiviral.2016.08.024.
68. Detweiler CJ, Sung AD, Saullo JL, Prasad VK, Cardona DM. Brincidofovir (CMX001) Toxicity: Another Potential Mimicker of Gastrointestinal Graft Versus Host Disease. Laboratory Investigation; 2016;96:169A.
69. Scantlebury V, Shapiro R, Randhawa P, Weck K, Vats A. Cidofovir: A method of treatment for BK virus-associated transplant nephropathy. Graft. 2002;5:S82.
70. Ramos E, Drachenberg CB, Portocarrero M, Wali R, Klassen DK, Fink JC, et al. BK virus nephropathy diagnosis and treatment: experience at the University of Maryland Renal Transplant Program. Clin Transpl. 2002:143-53. doi: 10.1097/TP.0b013e31828423cd.
71. Lim WH, Mathew TH, Cooper JE, Bowden S, Russ GR. Use of cidofovir in polyomavirus BK viral nephropathy in two renal allograft recipients. Nephrology (Carlton). 2003;8:318-23. doi: 10.1038/sj.bmt.1705886
72. Kadambi PV, Josephson MA, Williams J, Corey L, Jerome KR, Meehan SM, et al. Treatment of refractory BK virus-associated nephropathy with cidofovir. Am J Transplant. 2003;3:186-91. doi: 10.1034/j.1600-6143.2003.30202.x
73. Trofe J, Gaber LW, Stratta RJ, Shokouh-Amiri MH, Vera SR, Alloway RR, et al. Polyomavirus in kidney and kidney-pancreas transplant recipients. Transpl Infect Dis. 2003;5:21-8. doi: 10.1034/j.1399-3062.2003.00009.x
74. Tong CY, Hilton R, MacMahon EM, Brown L, Pantelidis P, Chrystie IL, et al. Monitoring the progress of BK virus associated nephropathy in renal transplant recipients. Nephrol Dial Transplant. 2004;19:2598-605. doi: 10.1093/ndt/gfh391.
75. Araya CE, Lew JF, Fennell RS, 3rd, Neiberger RE, Dharnidharka VR. Intermediate-dose cidofovir without probenecid in the treatment of BK virus allograft nephropathy. Pediatr Transplant. 2006;10:32-7. doi: 10.1111/j.1399-3046.2005.00391.x.
76. Burgos D, Lopez V, Cabello M, Sola E, Gutierrez C, Garcia I, et al. Polyomavirus BK nephropathy: the effect of an early diagnosis on renal function or graft loss. Transplant Proc. 2006;38:2409-11. doi: 10.1016/j.transproceed.2006.08.027.
77. Josephson MA, Gillen D, Javaid B, Kadambi P, Meehan S, Foster P, et al. Treatment of renal allograft polyoma BK virus infection with leflunomide. Transplantation. 2006;81:704-10. doi: 10.1097/01.tp.0000181149.76113.50.
78. Wadei HM, Rule AD, Lewin M, Mahale AS, Khamash HA, Schwab TR, et al. Kidney transplant function and histological clearance of virus following diagnosis of polyomavirus-associated nephropathy (PVAN). Am J Transplant. 2006;6:1025-32. doi: 10.1111/j.1600-6143.2006.01296.x.
79. Benavides CA, Pollard VB, Mauiyyedi S, Podder H, Knight R, Kahan BD. BK virus-associated nephropathy in sirolimus-treated renal transplant patients: incidence, course, and clinical outcomes. Transplantation. 2007;84:83-8. doi: 10.1097/01.tp.0000268524.27506.39.
80. Akioka K, Okamoto M, Ushigome H, Nobori S, Kaihara S, Yoshimura N. BK virus-associated nephropathy in a kidney transplant recipient successfully treated with cidofovir, the first case in Japan. Int J Urol. 2008;15:369-71. doi: 10.1111/j.1442-2042.2008.01998.x.
81. Cabello V, Margarit N, Diaz Pedrero M, Bernal G, Pereira P, Gentil MA. Treatment of BK virus-associated nephropathy with Cidofovir in renal transplantation. Transplant Proc. 2008;40(9):2930-2. doi: 10.1016/j.transproceed.2008.09.002.
82. Lamoth F, Pascual M, Erard V, Venetz JP, Nseir G, Meylan P. Low-dose cidofovir for the treatment of polyomavirus-associated nephropathy: two case reports and review of the literature. Antivir Ther. 2008;13:1001-9. doi: 10.1111/j.1399-3046.2008.00937.x.
83. Basse G, Mengelle C, Kamar N, Guitard J, Ribes D, Esposito L, et al. Prospective evaluation of BK virus DNAemia in renal transplant patients and their transplant outcome. Transplant Proc. 2007;39:84-7. doi: 10.1016/j.transproceed.2006.11.001.

84. Faguer S, Hirsch HH, Kamar N, Guilbeau-Frugier C, Ribes D, Guitard J, et al. Leflunomide treatment for polyomavirus BK-associated nephropathy after kidney transplantation. Transpl Int. 2007;20:962-9. doi: 10.1111/j.1432-2277.2007.00523.x.
85. Williams JW, Javaid B, Kadambi PV, Gillen D, Harland R, Thistlewaite JR, et al. Leflunomide for polyomavirus type BK nephropathy. N Engl J Med. 2005;352:1157-8. doi: 10.1056/nejm200503173521125.
86. Leca N, Muczynski KA, Jefferson JA, de Boer IH, Kowalewska J, Kendrick EA, et al. Higher levels of leflunomide are associated with hemolysis and are not superior to lower levels for BK virus clearance in renal transplant patients. Clin J Am Soc Nephrol. 2008;3:829-35. doi: 10.2215/cjn.03930907.
87. Sharma BN, Li R, Bernhoff E, Gutteberg TJ, Rinaldo CH. Fluoroquinolones inhibit human polyomavirus BK (BKV) replication in primary human kidney cells. Antiviral Res. 2011;92:115-23. doi: 10.1016/j.antiviral.2011.07.012.
88. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009;9:S1-155. doi: 10.1111/j.1600-6143.2009.02834.x.
89. Lalezari JP, Kuppermann BD. Clinical experience with cidofovir in the treatment of cytomegalovirus retinitis. J Acquir Immune Defic Syndr Hum Retrovirol. 1997;14:S27-S31.
90. Plosker GL, Noble S. Cidofovir. Drugs. 1999;58:325-45. doi: 10.2165/00003495-200565060-00012