Antiviral treatment of BK virus viremia after kidney transplantation

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Purpose. The various antiviral treatment options in the management of BK virus (BKV) viremia and BKV-associated nephropathy (BKVAN) are reviewed.

Summary. Review of the PubMed database from 1990 to 2016 for all English language case series, cohort studies, and randomized controlled trials detailing antiviral treatment of BKV viremia or BKVAN in kidney transplant recipients returned only 16 published reports. The majority of these reports were based on small case series or protocol-based cohort studies, with no prospective head-to-head data and only modest benefit reported for cidofovir, leflunomide, i.v. immunoglobulin (IVIG), and fluoroquinolone therapy. Given the lack of comparative data, appropriate antiviral treatment of BKV viremia should be determined based on institutional immunosuppressive protocols and posttransplantation outcomes. In appropriate patients who are not immunologically sensitized, substituting leflunomide for mycophenolate as part of immunosuppression reduction is reasonable and may result in viral clearance in up to 43% of patients at 4 weeks. In patients with persistent viremia despite immunosuppression reduction, either IVIG 2 g/kg administered over 2–5 days or cidofovir 0.5 mg/kg per week until viral clearance is achieved is generally well tolerated. Otherwise, there is insufficient evidence to recommend the use of fluoroquinolone therapy in either the treatment or prophylaxis of BKV viremia at this time.

Conclusion. A review of the published literature revealed that certain populations of patients with BKV viremia or BKVAN can benefit from cidofovir, leflunomide, and IVIG therapy, but these data were derived from case series or protocol-driven cohort studies. Providers should treat patients on an individual basis to maximize clinical effectiveness while limiting adverse reactions.

Keywords: antiviral drugs, BK virus, cidofovir, fluoroquinolone, kidney transplantation, leflunomide

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Polyomavirus hominis 1, more commonly known as BK virus (BKV), is classified within the Polyomaviridae family of viruses. These viruses are small, uncovered, and icosahedral with a double-circular DNA chain consisting of approximately 5,000 base pairs. The overall seroprevalence for anti-BKV immune globulin G antibodies is 70–90% in North Americans, with the majority of these exposures attributed to the genotype 1 virus. Primary infection is thought to occur during childhood via airborne transmission, after which time the virus establishes latency in the kidney tubular epithelium. The BKV may then become reactivated after periods of prolonged immunosuppression, leading to viruria, viremia, and potentially virus-associated nephropathy and end-stage renal disease.

The first case of BKV-linked nephropathy in a transplant recipient was reported by Mackenzie et al. in 1978; however, with the introduction
of more-potent immunosuppressive agents, BKV-associated nephropathy (BKVAN) has become an increasing cause of allograft loss among kidney transplant recipients, with viruria, viremia, and BKVAN rates of 35–40%, 11–13%, and 1–10%, respectively.\(^1\)\(^4\) Peak incidence occurs 9–12 months after transplantation, but cases of viruria have been reported as early as 7 days postengraftment.\(^2\) Although not an all-inclusive list, risk factors commonly associated with high rates of viremia include cadaveric donation, degree of ischemia reperfusion injury, advanced age of recipient, African-American race, acute rejection, presence of a ureteral stent, and overall degree of immunosuppression.\(^1\) Higher rates of BKVAN have also been reported for patients receiving tacrolimus-based immunosuppression versus cyclosporine-based or a mammalian target of rapamycin inhibitor–based therapies despite the lower rates of cellular rejection observed with tacrolimus. These differences in BKVAN rates are thought to be due to antiviral properties inherent to the mechanisms of these agents rather than overall reduced immunosuppressive potency.\(^1\)

The current standard of care in the management of BKV viremia consists of a monitoring strategy for the first 2 years after transplantation or in the setting of a rising creatinine level of unknown etiology at any time, with subsequent reductions in immunosuppression in the setting of measured viremia.\(^5\) Commonly reported potential monitoring strategies include (1) monthly viremia testing for the first 6 months after transplantation and then every 3 months for up to 2 years or (2) viruria screening every 2 weeks for the first 3 months, monthly until 6 months, and then every 3 months for up to 2 years with viremia testing following any BKV-positive urine sample.\(^6\)\(^7\) When choosing an appropriate monitoring regimen, clinicians should consider that some tests have a low positive predictive value, and there may be a 2- to 6-week period between viruria and the subsequent development of viremia. Numerous strategies have also been reported with regard to the stepwise reduction in immunosuppression necessary after the development of BKV viremia. One common strategy employs a 25–50% reduction in calcineurin inhibitor dose in 1 or 2 steps, followed by a 50% reduction in the antiproliferative agent, followed by discontinuation of the antiproliferative agent with simultaneous reduction in corticosteroid dose.\(^1\) However, despite reductions in immunosuppressive therapy, Schaub et al.\(^2\) reported progression to BKVAN in up to one third of transplant recipients with viremia, with an additional 8–12% developing acute rejection in the setting of reduced immunosuppression. Given these relatively poor outcomes observed in kidney transplant recipients developing BKV viremia, interest in antiviral treatment for BKV has understandably increased. This article reviews the most recent literature regarding antiviral treatment for BKV viremia, including cidofovir, leflunomide, i.v. immunoglobulin (IVIG), and fluoroquinolone therapy, with the goal of identifying a potential place in therapy for these commonly prescribed agents.

**Methods**

A search of the PubMed database from 1990 to 2016 was conducted for all English-language case series, cohort studies, and randomized controlled trials detailing antiviral treatment of BKV viremia or BKVAN in kidney transplant recipients using the MeSH terms BK virus, antiviral drugs, kidney transplantation, cidofovir, leflunomide, intravenous immunoglobulin, and fluoroquinolones. Each published report was independently reviewed by the investigators to establish its appropriateness for inclusion. A total of 16 published articles were included in the literature review.

**Results**

**Cidofovir.** Cidofovir is an inhibitor of viral DNA polymerase and confers activity against a wide variety of viral pathogens.\(^8\) This agent is approved by the Food and Drug Administration to treat invasive cytomegalovirus disease (weekly dose of 5 mg/kg); however, several reports have detailed the use of lower dosages of cidofovir (0.25–1 mg/kg weekly) in the management of BKV viremia.\(^9\)\(^10\) Despite this reduced-dosage regimen, concerns still remain regarding the use of cidofovir in kidney transplant recipients given its potential to cause nephrotoxicity and myelosuppression as well as the requirement for weekly i.v. infusion.\(^8\)

In a review of the pharmacokinetics of low-dose cidofovir, 9 kidney transplant recipients with BKV viremia were treated with 0.25–1 mg/kg of cidofovir with or without probenecid in order to evaluate the distribution of cidofovir within the renal allograft.\(^9\) Although probenecid has been historically used in conjunction with cidofovir for its renal protective properties through inhibition of the proximal tubule organic anion transport protein (OATP), it was unclear whether this effect would be desirable.
when treating BKV, which concentrates within the urothelium. Results of this study found that peak cidofovir concentrations on the low-dose regimen averaged 1 µg/mL, well below the in vitro 50% effective concentration previously reported. Cidofovir half-life and elimination rates were also unaffected by probenecid administration. The authors theorized that the lack of effect observed with probenecid could be partly due to downregulation of the OATP in the setting of acute inflammation of the virally infected kidney. Cidofovir was well tolerated in all patients, and no changes were observed in markers of kidney or liver function after administration, making the routine administration of probenecid unnecessary in conjunction with reduced-dose regimens of cidofovir.

In a small retrospective study evaluating the use of cidofovir in the treatment of BKVAN, 21 patients who received a kidney transplant between 1998 and 2004 with biopsy-confirmed nephropathy were retrospectively evaluated for response. Eight patients were ultimately treated with low-dose cidofovir (0.5–1 mg/kg) in conjunction with reductions of immunosuppressive therapy, while the remaining patients were managed with reductions in immunosuppressive therapy alone. After 4–10 weeks of treatment, cidofovir-treated patients had a stable creatinine clearance rate (29.3 mL/min at time of diagnosis versus 32.0 mL/min after treatment). No cases of allograft loss were observed in the cidofovir-treated group, with a mean follow-up of 24.8 months (range, 8–41 months), while 9 patients in the group who did not receive adjuvant cidofovir treatment lost their allografts after a median of 8 months. Immunosuppressant levels were similar between the two groups, and no cases of bone marrow toxicity or nephrotoxicity were observed with cidofovir treatment. However, there was a difference in immunosuppressant induction therapy between the groups, with only 2 cidofovir-treated patients (25%) receiving induction therapy, while 6 patients (50%) managed with immunosuppression reduction alone received basiliximab or antithymocyte globulin, potentially conferring a higher level of immunosuppression in these patients.

A larger, protocol-driven cohort study identified 151 kidney and kidney–pancreas transplant recipients between January 2007 and June 2012 with detectable BKV viremia. Seventy-five of these patients had viral loads exceeding 10,000 copies/mL and were subsequently treated with 1 dose of cidofovir 1 mg/kg, followed by 0.5 mg/kg every 2 weeks until laboratory test results showed 2 undetectable viral loads or until viremia was determined to be unresponsive. All patients were simultaneously treated with concomitant reductions in immunosuppressant therapy, with tacrolimus trough targets of 4–6 ng/mL as well as reductions in corticosteroid and antimetabolite therapies. Ultimately, 53 patients (71%) cleared their BKV viremia after a median of 4.2 months, with 32 patients (43%) clearing the virus within 6 months of treatment initiation. Analysis of the 43 patients (57%) with prolonged viremia revealed that older age, delayed graft function, longer time to BKV diagnosis after transplantation, higher baseline viral load, and failure to reduce viral load by 1 log₁₀ copies/mL after 1 month of treatment with cidofovir were risk factors for delayed or incomplete treatment response. No ocular toxicity or nephrotoxicity was reported during treatment, and 4 patients cleared their BKV viremia. No cases of nephrotoxicity or increasing proteinuria were reported with cidofovir use; however, 1 patient developed anterior uveitis after the completion of treatment.

Johnston et al. conducted a systematic review comparing the effectiveness of cidofovir and leflunomide adjunctive therapy to immunosuppression reduction alone. The results of this meta-analysis were based entirely on observational studies, with no substantial differences in allograft failure reported between immunosuppression reduction (8%; 95% confidence interval [CI], 4–12%), cidofovir (8%; 95% CI, 3–13%), or leflunomide (13%; 95% CI, 2–23%) therapy. However, the analysis included patients with viremia as well as viremia and BKVAN, and the authors stated that the overall quality of the evidence was relatively poor.

Given the potential renal, ocular, and hematologic toxicities reported with cidofovir as well as the requirement for i.v. infusion, a promising new option with improved pharmacokinetics is orally-administered brincidofovir. This agent is a lipid acrylic nucleoside phosphate that is intracellularly converted to cidofovir di-phosphate. Studies of radiolabeled brincidofovir have reported high concentrations of the active drug in the renal tubules after oral administration without the associated nephrotoxicity. This phenomenon is thought to be related to brincidofovir’s lack of affinity for OATP, resulting in the spar-
ing of the proximal tubules. A case of brincidofovir use was previously reported in a 58-year-old man after hematopoietic stem cell transplantation for the management of BKVAN via an open-label expanded-access study.\textsuperscript{15} On posttransplantation day 572, the patient was diagnosed with biopsy-confirmed BKVAN and subsequently initiated on brincidofovir 100 mg twice weekly for 6 months. During the 6-month treatment period, the patient demonstrated stable renal function and was maintained without the need for renal replacement therapy. No drug-related adverse events were reported at the time of treatment discontinuation. However, brincidofovir subsequently failed to meet its primary endpoint—prevention of clinically significant cytomegalovirus infection at 24 weeks after hematopoietic cell transplantation—in the Phase III SUPPRESS trial and has been returned to evaluation in Phase II studies.\textsuperscript{16}

**Leflunomide.** Leflunomide is a prodrug that displays both antiviral and immunosuppressant properties.\textsuperscript{17} Its antiviral properties are thought to be due to inhibition of DNA replication which has been demonstrated in vivo for BKV and other DNA viruses such as cytomegalovirus and herpes simplex virus.\textsuperscript{18} The immunosuppressant activity of leflunomide derives from its ability to inhibit pyrimidine synthesis, leading to diminished cellular proliferation.\textsuperscript{19} For this reason, leflunomide should not be used in conjunction with other antiproliferative drugs such as mycophenolate products or azathioprine. Dosing of leflunomide for BKV viremia has been reported with and without loading doses of 60–100 mg daily for 3 days followed by maintenance doses of 20–60 mg daily to maintain trough levels of the active metabolite A771726 of 40–100 \( \mu \)g/mL.\textsuperscript{19-24}

Zavos et al.\textsuperscript{25} reported a case of leflunomide use for BKV viremia in 2004 in a 46-year-old man with biopsy-confirmed BKVAN who had previously not responded to immunosuppression reduction alone. The patient was treated with leflunomide 100 mg daily, resulting in a sustained improvement in serum creatinine levels 1 year after initiating leflunomide, but the authors provided no discussion of treatment duration or treatment-related adverse events. Two subsequent case reports described leflunomide loading doses of 100 mg daily for 3 days, followed by a maintenance dosage of 20 mg daily.\textsuperscript{20,21} Ott et al.\textsuperscript{21} described treating 4 patients who had initially received treatment with cidofovir or immunosuppression reduction or both to achieve target trough levels of 40–100 \( \mu \)g/mL. These patients also demonstrated stable serum creatinine levels 1 year after treatment initiation without any reported cases of allograft loss.

Additional data from 26 patients with biopsy-confirmed BKVAN were reported in a study by Josephson et al.\textsuperscript{22} All patients were treated with baseline immunosuppression reduction, including discontinuation of mycophenolate and decreased target tacrolimus trough levels of 4–6 ng/mL. Treatment with leflunomide was initiated with loading doses of 100 mg for 5 days, followed by maintenance doses of up to 60 mg daily to maintain a target level of 40–100 \( \mu \)g/mL. Of the 26 patients included in this case series, 6 were treated with leflunomide after not responding to immunosuppression reduction, 13 were treated with leflunomide plus baseline immunosuppression reduction, 5 received cidofovir in conjunction with leflunomide and immunosuppression reduction, and 2 were treated with cidofovir after not responding to leflunomide and immunosuppression reduction. The authors reported that 23 of the 26 patients maintained stable leflunomide levels exceeding 40 \( \mu \)g/mL, leading to reductions in BKV viremia and viruria in 22 patients and viral clearance in 11 patients. The rate of viral clearance was consistent across all treatment groups. The 4 patients who did not respond to antiviral therapy had serum A771726 levels of <35 \( \mu \)g/mL and eventually lost their renal allografts. Two patients required dosage reductions and eventually discontinued leflunomide due to elevations in liver enzymes (\( n = 1 \)) and the appearance of a drug-induced rash (\( n = 1 \)).

Krisl et al.\textsuperscript{23} reported conflicting findings in a retrospective longitudinal analysis that compared the outcomes of 52 leflunomide-treated patients with 24 patients managed with immunosuppression reduction alone (control group). All patients underwent protocol immunosuppression reduction, consisting of discontinuation of mycophenolate and reduction in goal trough calcineurin inhibitor levels. Patients diagnosed with BKVAN were subsequently treated with leflunomide, while patients without nephropathy were treated with leflunomide at the discretion of their physician. The observed rates of BKV clearance were 30.8% in the leflunomide group and 60.9% in the control group (\( p = 0.02 \)). A subgroup analysis of 48 patients who received leflunomide with therapeutic drug monitoring to achieve a goal trough level of 40–100 \( \mu \)g/mL found no meaningful difference in mean or maximum serum leflunomide levels or in the rate of therapeutic trough levels between those who cleared their BKV (\( n = 14 \)) and those who did not (\( n = 34 \)). The authors also compared log changes in BKV polymerase chain reaction concentrations to leflunomide drug concentrations and again found no correlation between therapeutic trough levels and clinical efficacy (\( R^2 < 0.001 \)). After performing multivariate analysis, the authors concluded that leflunomide therapy was not significantly associated with BKV clearance (odds ratio, 1.1; 95% CI, 0.19–6.5; \( p = 0.92 \)). It should be noted that physician discretion played a role in leflunomide treatment initiation, potentially conferring a selection bias toward treating patients with more clinically significant viremia.

Faguer et al.\textsuperscript{24} reported on leflunomide treatment in combination with immunosuppression reduction in
12 kidney transplant recipients with biopsy-confirmed BKVAN. After 16 months of treatment and follow-up, 5 patients eventually cleared their viremia. Mean baseline serum creatinine concentrations decreased from 45 mL/min at BKVAN diagnosis to 36 mL/min at the conclusion of the trial; however, 6 patients demonstrated an improvement in renal function, and 2 patients maintained stable serum creatinine levels. Two cases of allograft loss were reported, 1 of which was due to a combination of BKVAN and acute rejection. Anemia was the most commonly reported adverse effect associated with leflunomide, ultimately resulting in drug discontinuation in 2 patients.

FK778, a dihydroorotate dehydrogenase inhibitor and derivative of the active metabolite of leflunomide, has also been studied in the treatment of biopsy-proven BKVAN in a Phase II, open-label, parallel-group study.25 Forty-six patients were randomized in a 2:1 ratio to receive treatment with FK778 or the standard of care (reduction in immunosuppression). After 6 months of treatment, no substantial differences were observed in allograft survival rates, biopsy-confirmed rejection, and creatinine clearance between groups. Patients receiving FK778 did demonstrate a larger decrease in plasma BKV load compared with patients receiving immunosuppression reduction (~1.9 copies/µL versus 1.3 copies/µL, p = 0.049). However, the prevalence of serious adverse events was more common in the FK778 group (40% versus 25%), with the most common adverse events including increased serum creatinine levels, dyspnea, and Escherichia coli urinary tract infection.

IVIG. IVIG is the immunoglobulin product of pooled plasma from thousands of donors.26 Although its exact mechanism of action is still unknown, IVIG has well-described immunomodulatory effects as well as the potential for immunoglobulin binding and clearance of viral and bacterial toxins.26 A variety of dosing strategies have been used in the treatment of BKV viremia to achieve a total IVIG dose of 2 g/kg over anywhere from 2 to 14 days.26 Care should always be taken with the selection of IVIG product, as a variety of brands are available with unique concentrations, base solutions, and infusion rates. It is generally accepted that sucrose-based IVIG products should be avoided in patients with renal disease, given their potential to cause acute kidney injury.26

A review by Randhawa et al.27 demonstrated that commercially available IVIG products contain neutralizing antibodies against all major genotypes of BKV. The most robust neutralizing capacity was demonstrated against the 1a genotype, which is thought to account for the majority of invasive infections, with sequentially reduced affinity for the 1c, 2, 1b2, 3, and 4 genotypes. While the clinical significance of these differences is still unknown, these results suggest that the classification of viruses by genotype may help better identify which patients will respond to IVIG-based treatment regimens.

A single-center, protocol-driven study by Vu et al.28 investigated the outcomes of BKVAN in 280 patients receiving renal allografts between 2008 and 2012. Antimetabolite therapy was discontinued, and leflunomide 40 mg daily was initiated at the time of BKV viremia diagnosis. If the patient’s viremia was not cleared within 4 weeks, the calcineurin inhibitor dosage was decreased stepwise, and IVIG was initiated at a dose of 1 g/kg with the option of a second dose after 2 weeks if viremia persisted. Viremia ultimately developed in 53 patients (18.9%), with 23 (43%) of the 53 patients achieving viral clearance after the transition to leflunomide therapy and reduction in immunosuppression. Of the remaining 30 patients treated with IVIG, 20 patients had baseline viral loads exceeding 10,000 copies/mL, and 10 patients required repeated doses of IVIG. Final follow-up at 12 months after treatment initiation revealed significantly reduced mean BKV plasma viral loads compared with the start of IVIG therapy (697 copies/mL versus 205,314 copies/mL, p < 0.001) as well as high rates of patient and allograft survival (100% and 96.7%, respectively). There were 6 episodes of acute rejection that were reversible with corticosteroid and lymphocyte-depleting therapy, and no significant adverse reactions related to IVIG administration were reported throughout the study.

Another longitudinal study by Sener et al.29 evaluated 8 renal allograft recipients diagnosed with BKVAN and treated with IVIG at a dose of 2 g/kg divided over 2–5 days in conjunction with 50% immunosuppression reduction. All patients exhibited stable serum creatinine levels (mean, 1.4 mg/dL; range, 1.2–2.1 mg/dL) before the diagnosis of BKVAN. After a mean follow-up period of 15 months, 7 (88%) of the 8 patients maintained functioning renal allografts without the need for hemodialysis, and 4 patients (50%) demonstrated eradication of their viremia. However, mean serum creatinine levels increased from those observed before BKVAN diagnosis despite rescue IVIG treatment (mean, 3.5 mg/dL; range, 1.9–4.3 mg/dL). No notable adverse effects related to the administration of IVIG were reported.

A case series by Anyaegbu et al.30 described the successful clearance of BKV in 3 pediatric patients after a reduction in immunosuppression and the administration of IVIG. Eight patients initially developed BKV viremia after transplantation, necessitating de-escalation of immunosuppression. Viral clearance was achieved in 4 patients after immunosuppression reduction alone (range, 15–27 days), while the remaining 4 patients received IVIG 2 g/kg over 12–24 hours. After IVIG administration, viral clearance was achieved in 3 patients after 16–35 days, while the remaining patient with biopsy-confirmed BKVAN demonstrated improvement in tubulointerstitial disease 27 days after IVIG therapy. At 12 months posttreatment, all 4 patients maintained functioning
alloplants, and baseline serum creatinine levels did not significantly differ between patients managed with immunosuppression reduction alone and those requiring IVIG rescue therapy (0.95 mg/dL versus 0.88 mg/dL, respectively; p = 0.84).

IVIG therapy was also studied in combination with leflunomide and ciprofloxacin in 19 kidney transplant recipients in Kuwait. All patients received IVIG 2 g/kg over 5 days in combination with maintenance leflunomide 20–40 mg and ciprofloxacin 500 mg twice daily for 4 weeks. When compared with 14 historical controls who received a kidney transplant between 2004 and 2009, no meaningful differences were observed in renal function or allograft survival among patients receiving IVIG, leflunomide, and ciprofloxacin and historical controls. Of note, a higher proportion of the historical controls were receiving sirolimus-based immunosuppression, and the study protocol failed to mention the degree to which immunosuppression was decreased after the diagnosis of BKVAN.

Fluoroquinolones. While fluoroquinolones remain one of the most widely prescribed classes of antibiotics for the treatment of common bacterial infections, the effect of these agents on DNA gyrase also imparts partial activity against a variety of atypical pathogens as well as several viruses. Fluoroquinolones have been studied at common doses both in the treatment and the prophylaxis of BKV viremia with mixed results. However, concerns remain regarding the potential to foster bacterial resistance as well as muscle injury in transplant recipients requiring long-term exposure to these agents.

Levofloxacin was studied in the treatment of BKV viremia in a double-blind, randomized controlled trial by Lee et al. This study enrolled 39 kidney transplant recipients between July 2009 and March 2012 and randomized them to receive levofloxacin 500 mg daily adjusted for renal function (n = 20) or placebo (n = 19) for 30 days. All patients underwent concomitant reduction in immunosuppression at the time of diagnosis based on institution-specific practices. At the conclusion of the trial, no meaningful differences in BKV load or serum creatinine levels were observed between groups at 1, 3, or 6 months after treatment initiation. Two patients in the levofloxacin group were withdrawn from the study after an Achilles tendon injury at 8 and 16 days. The results of this study revealed that levofloxacin did not provide any benefit in the reduction of BKV viremia or allograft function despite a higher prevalence of previous transplantation (6 versus 1, p = 0.04) and desensitization (3 versus 0, p = 0.11) in the placebo group.

Knoll et al. evaluated fluoroquinolone for BKV prophylaxis in a prospective study by randomizing patients to levofloxacin 500 mg daily or placebo for 3 months after kidney transplantation. Adherence to prescribed therapy was assessed via pill counts at each study visit. A total of 154 patients were initially identified from 7 Canadian transplantation centers for inclusion in the study to assess the rate of BKV viruria up to 1 year after transplantation. At the conclusion of the trial, viruria had occurred in 22 patients (29%) in the levofloxacin group and 26 (33%) in the control group (p = 0.58). The authors also found an increase in fluoroquinolone-resistant bacterial isolates among the patients receiving active prophylaxis (14 [58%] of 24 patients versus 15 [33%] of 45 patients; 95% CI, 1.01–2.98) as well as a nonsignificant increase in tendonitis in the treatment group (6 [7.9%] of 76 patients versus 1 [1.3%] of 78 patients; 95% CI, 0.76–49.95). No remarkable differences in viremia rates were observed between groups, and no cases of *Clostridium difficile* infection were reported. Of note, this study excluded patients who were diagnosed with BKVAN with a previous kidney allograft.

Two retrospective studies have also reported on fluoroquinolone use for BKV prophylaxis in kidney transplant recipients. Wojciechowski et al. studied 130 patients who received a kidney transplant between January and June 2010 and were treated with ciprofloxacin 250 mg twice daily for 30 days posttransplantation. These patients were compared with 106 patients who received a kidney transplant between July and December 2009 but received no BKV prophylaxis (control group). Induction immunosuppression and 1-year rates of acute cellular rejection were similar between groups; however, patients in the treatment group were more often continued on maintenance corticosteroid therapy than patients in the control group (83.2% versus 65.1%, p < 0.01). At 3 months posttransplantation, the control group had a significantly higher rate of BKV viremia (16.1% versus 6.5%, p = 0.03), though this difference was not observed at 12 months for viremia (26.1% versus 29.7%, p = 0.60) or viruria (38.9% versus 43.7%, p = 0.54).

A single-center, retrospective analysis by Gabardi et al. looked at rates of BKV viremia in kidney transplant recipients treated with 6–12 months of sulfamethoxazole–trimethoprim compared with 6–12 months of atovaquone in addition to 1 month of either ciprofloxacin 250 mg twice daily or levofloxacin 250 mg daily for bacterial prophylaxis. Between January 1, 2004, and December 31, 2008, 160 patients were treated with sulfamethoxazole–trimethoprim compared with 25 sulfal-allergic patients treated with atovaquone plus a fluoroquinolone. At the conclusion of the study, 1-year rates of BKV viruria were significantly higher in the sulfamethoxazole–trimethoprim group compared with the fluoroquinolone-treated group (22.5% versus 4%, p = 0.03). Of note, the sulfamethoxazole–trimethoprim treatment group had nonsignificantly higher rates of cadaveric donation (54.4% versus 48.0%) and previous transplantation (15.6% versus 4.0%). The potential impact of concomitant atovaquone therapy in fluoroquinolone-treated patients can
also not be entirely excluded from these data. An additional subgroup analysis found that 40 patients in the sulfamethoxazole–trimethoprim treatment group were treated with a fluoroquinolone for bacterial infection within 1 year after transplantation. The rate of BKV viremia was lower in these patients compared with those treated with sulfamethoxazole–trimethoprim who never received a fluoroquinolone (7.5% versus 27.5%, \( p = 0.008 \)). Neither of these retrospective analyses evaluated adverse effects associated with fluoroquinolone treatment as a part of their protocols.

**Discussion**

Despite numerous case reports of successful antiviral treatment of BKV viremia, a review of the literature revealed that the majority of these data come from relatively low-quality evidence consisting of case series or protocol-driven cohort studies with historical comparators. No randomized controlled trials have been published evaluating cidofovir, leflunomide, or IVIG adjunctive therapy in the management of BKV viremia and BKVAN, and the randomized controlled trials examining BKV treatment and prevention with levofloxacain and FK778 failed to meet their primary endpoints. In addition, there was little consistency among antiviral dosing protocols, which were all used in conjunction with immunosuppression reduction, and few studies adequately reported adverse events related to antiviral therapy. However, given the high cost and patient morbidity associated with renal allograft loss, there will continue to be interest in improving antiviral treatment for BKVAN. The literature does show that certain populations of patients will derive benefit from cidofovir, leflunomide, and IVIG therapy, leaving it to the practitioner to determine the most appropriate course of therapy on an individual basis to maximize clinical effectiveness of these adjuvant agents while limiting exposure to potentially toxic medications.

Several important factors always bear consideration when assessing the appropriateness of antiviral therapy for BKVAN, including comorbidities, concomitant medications, immunologic risk of rejection, and patient access to antiviral therapy. Cidofovir is a known nephrotoxin and should generally be avoided in patients with documented proteinuria or receiving concomitant nephrotic medications such as amphotericin, aminoglycosides, or tenofovir disoproxil fumarate. There is also the potential for the development of uveitis or myelosuppression with cidofovir, which should be considered in patients with a history of autoimmune disorders, cirrhosis, or malignancy. Leflunomide is contraindicated in pregnancy and should be avoided in women of childbearing age who are not actively using contraception. Careful consideration should also be given before prescribing leflunomide in conjunction with other antimetabolites or hepatotoxins such as methotrexate. IVIG can increase the risk of thrombosis and should be used with caution in patients with a documented history of venous thromboembolism or a known hypercoaguable state. The IVIG infusion can also provide patients with a substantial amount of fluid volume, depending on the dose and formulation administered, which can be of concern in patients with existing edema, such as those with congestive heart failure or nephrotic syndrome. Individual immunologic risk is an additional consideration when selecting therapy, as IVIG can have benefit in the management of concomitant antibody-mediated rejection in the setting of elevated donor-specific antibody titers. Alternatively, substituting leflunomide for mycophenolate during immunosuppression reduction, as this combination was shown to result in viral clearance in 4 weeks for up to 43% of patients. In patients with persistent viremia despite appropriate immunosuppression reduction, either IVIG or cidofovir is a potential treatment option. The largest studies of IVIG and cidofovir by Vu et al. and Kuten et al. both demonstrated patient allograft survival rates exceeding 90%, with complete viral clearance in approximately 75% of patients. However, given the absence of head-
to-head data and the increased ease of administration and better tolerability reported with IVIG, we recommend IVIG 2 g/kg administered over 2–5 days before considering cidofovir therapy. As DNA sequencing technology continues to develop, genotype-guided IVIG therapy for BKVAN may also become a future consideration to select patients with viral genotypes highly susceptible to neutralization by commercially available IVIG products. Cidofovir rescue therapy may be considered as a last-line therapy in patients with BKVAN refractory to all other treatments, given the requirement for long-term intravenous infusions, associated kidney and bone marrow toxicity, and pharmacokinetic data demonstrating that urothelial concentrations of cidofovir may be insufficient with reduced-dose treatment regimens. In addition, data from Josephson et al. suggest that cidofovir may be used in this role as rescue therapy after the failure of immunosuppression reduction without any change in the eventual rate of viral clearance. At this time, 2 randomized controlled trials have demonstrated that there is insufficient evidence to support the use of fluorouracilone therapy in either the treatment or prophylaxis of BKV viremia. However, fluorouracilone prophylaxis in patients who previously lost a kidney allograft to BKVAN and are at high risk of recurrence has never been studied and may represent a future direction in the prevention of BKV viremia. Regardless of therapeutic intervention, close follow-up remains a staple of BKV management to ensure timely treatment and alterations to therapy. Serum creatinine levels should be monitored in 1- to 2-week intervals and BKV viral load in 2- to 4-week intervals until viral clearance is maintained or allograft failure occurs.

Conclusion
A review of the published literature revealed that certain populations of patients with BKV viremia or BKVAN can benefit from cidofovir, leflunomide, and IVIG therapy, but these data were derived from case series or protocol-driven cohort studies. Providers should treat patients on an individual basis to maximize clinical effectiveness while limiting adverse reactions.

References
25. Guasch A, Roy-Chaudhury P, Woodle E et al. Assessment of efficacy and

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