Review

Fluoroquinolones and BK Virus Nephropathy: A Myth or a Reality

Abstract

BK polyomavirus (BKV) is a challenging problem for the transplant nephrologist. Various strategies have been used to prevent or treat BK virus nephropathy (BKVN). These include reduction in immunosuppression, intravenous immune globulin, cidofovir, leflunomide, and the fluoroquinolone antibiotics. All these agents have their own toxicities. Great interest was shown to use fluoroquinolones to prevent BKVN after its useful experience was reported in bone marrow transplant. Fluoroquinolones being cheap and easily available, attracted nephrologists to use it, for prevention of BKVN. These agents have been shown *in vitro* studies to be effective. However, there are mixed results about their effectiveness in prevention of BKVN in clinical setting. This review will focus the evidence available for using fluoroquinolones in prevention of BKVN and its usefulness. Furthermore, a way forward to use these agents or not for prevention of BKVN will also be discussed.

Keywords: *BK polyomavirus, BK virus nephropathy, fluoroquinolones*

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Introduction

BK polyomavirus (BKV) is a common infection after kidney transplantation. It infects up to 90% of the general population in their childhood.[1] The virus remains latent in immunocompetent individual and rarely causes disease. However, the virus can reactivate in immunocompromised patients causing clinical disease. BK viruria develops in 30% of kidney transplant recipients, with viremia and nephropathy (BKVN) in 11% –13% and 8%, respectively.[2-4] BK viremia peaks in first 3 months[5] while BKVN typically occurs 9–12 months after transplantation. However, some cases of BKVN have been reported as early as 1 week posttransplantation.[6,7] Around 50% of kidney transplant recipients lose their graft after developing BKVN.

There are various strategies to treat BKVN. Reduction in immunosuppression is widely regarded as the cornerstone treatment for BKVN. This strategy focuses on routine patient monitoring for development of BK viremia and with reduction of immunosuppression on diagnosis.[8-10] However, there is no widely accepted standardization for this strategy.[3,11] Naturally, there is an inherent risk of rejection with immunosuppression reduction and any strategies employed must take into account the delicate and precarious balance of infection and rejection. Various anti-BKV agents are used for treatment of BKVN. These include intravenous immune globulin (IVIG), cidofovir, leflunomide, and the fluoroquinolone antibiotics.[7,12,13] Each therapy has its limitations and usage must be tailored to individual patients. IVIG is expensive, nephrotoxic and requires hospital admission for intravenous administration.[13] IVIG through osmotic injury causes vacuolation in proximal tubular epithelial cells leading to acute kidney injury[14] Cidofovir is nephrotoxic and reportedly has less potent anti-BKV activity than the other therapies.[15,16] Leflunomide has a relatively long half-life (15 days), wide interpatient variability, and significant hematological and hepatic toxicity.[17] On the other hand, fluoroquinolones are cheap, widely available, and have lower incidence of side effects.

Brief Pharmacology of Fluoroquinolones

Mechanism of action and its relevance to BK polyomavirus

Fluoroquinolones target two important enzymes in bacterial pathogen. These include type II topoisomerase (gyrase) and topoisomerase IV.[17-21] These enzymes are

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important for critical processes involved in nucleic acid synthesis. They control under- or over-winding of DNA coils and remove knots and tangle from the bacterial chromosome. Fluoroquinolones cause inhibition through interaction with helicase component of DNA gyrase. Inhibition of these enzymes leads to cleavage of bacterial DNA leading to rapid bacterial death.[22-24] BK virus is a nonenveloped, encapsulated DNA virus that belongs to the Papovaviridae family. Helicase component of DNA gyrase and topoisomerase are important enzymes for BKV replication. Theoretically, through these mechanisms, fluoroquinolone should also prevent the proliferation and replication of BKV. Anti-BK properties through inhibition of DNA topoisomerase and polyomavirus-associated large T-antigen helicase by fluoroquinolones have been reported earlier.[9,13] Various fluoroquinolones including levofloxacin, trovafloxacin, ciprofloxacin, ofloxacin, nalidixic acid, oxolinic acid, and norfloxacin have been shown *in vitro* that to be effective against BKV.[25-27]

Potential side effects and toxicity in general population and in kidney transplant recipients

As compared with IVIG, cidofovir, and leflunomide, fluoroquinolones are cheap and less toxic. However, long-term use for 1–3 months as a prophylaxis may not be without sequelae. Gastrointestinal and central nervous system (CNS) effects are the most frequent adverse events, occurring in 2–20% of patients treated with fluoroquinolones.[28] Gastrointestinal side effects include nausea, vomiting, diarrhea, and abdominal pain. CNS side effects include headache, dizziness, drowsiness, confusion, insomnia, fatigue, malaise, depression, somnolence, seizures, vertigo, lightheadedness, restlessness, tremor. Rarely, it causes QTc prolongation, hepatotoxicity, abnormal or bitter taste, and tendon rupture.[28-31] In kidney transplant recipients, QT prolongation, hypoglycemia, diarrhea, and rash were not significantly higher with use of levofloxacin. However, a nonsignificant increased risk of tendinitis (6/76 [7.9%] vs. 1/78 [1.3%] was reported by Knoll.[32]

Drug resistance in bacteria and BK polyomavirus

Drug resistance is an emerging problem. Bacterial resistance to fluoroquinolones occurs either with the induction of amino acid changes in specific areas of the parC and parE genes of topoisomerase IV or in the gyrA gene of topoisomerase II. Increased efflux is another mechanism of drug resistance.[33-37] Little is known about BKV resistance. However, long duration of prophylaxis for a period of 1–3 months may provoke resistance in BKV.

Selectivity index against BK polyomavirus

Selectivity index is defined as the ratio of the 50% reduction in host cell replication value to the 50% virus inhibitory concentration value. The safety and effectiveness of antimicrobial agents are measured by their minimal inhibitory concentration of the organism as well as the host. Effective and safe antimicrobial should have a selectivity index of >10. Unfortunately, till this date, no effective anti-BKV therapy is available. Farasati *et al*.[38] used quantitative polymerase chain reaction (PCR) assay enabling them to get viral culture sensitivity results within 7 days. They tested leflunomide and cidofovir against BKV and found selectivity index 2.3 ± 0.8 and 3.8 ± 0.8 for cidofovir and leflunomide, respectively. Randhawa *et al*.[39] used the same assay to determine 50% virus inhibitory concentrations and 50% reduction in host cell for ciprofloxacin, levofloxacin, gatifloxacin, norfloxacin, moxifloxacin, ofloxacin, novobiocin, and coumermycin. The selectivity index ranged from 0.6 ± 0.2 to 3.6 ± 0.8 for all these agents. Unfortunately, none of these agents have selectivity index >10 to be considered effective.[39] From this, we can assume that various anti-BKV agents though have some activities but due to low selectivity index, they may not be efficacious in eradication of the virus.

In vitro Studies on Effect of Fluoroquinolones on BK Polyomavirus

In vitro studies on efficacy of fluoroquinolones for treatment of BKV began in the 1980s. Encouraging *in vitro* results led to subsequent *in vivo* studies in clinical settings involving real patients. Portolani *et al*.[25] used nalidixic acid and oxolinic acid against BKV in vero cell cultures in 1988. They exposed the virus to 0.02–0.04 mM of nalidixic acid and 0.2 mM of oxolinic acid. The inhibition of virus replication was detectable at day 4 postinfection in cultures. The inhibition of development of cytopathology and of virus-induced cell death was demonstrable in cultures treated for 12 days with the drugs. Through their experiment, they showed that fluoroquinolones act through a mechanism involving DNA topoisomerase. In the same year, another group published similar results using norfloxacin, coumermycin A1, and nalidixic acid. They studied these agents against BKV in BSC-1 and vero cell culture and showed that all three agents suppress BKV replications.[26] Ali *et al*. used levofloxacin, trovafloxacin, ciprofloxacin, and ofloxacin using DNA tumor virus as their model. All four quinolones tested were effective in the inhibition of SV40 plaque formation and DNA replication. In addition, they found that each of these quinolones was inhibitory to the helicase activity of SV40 large tumor antigen.[27] Sharma *et al*.[40] assessed the effect of ofloxacin and levofloxacin on BKV replication in proximal tubular epithelial cell. Ofloxacin and levofloxacin inhibited BKV load in a dose-dependent manner yielding a 90% inhibition at 150 μg/ml. They concluded that ofloxacin and levofloxacin inhibit but do not eradicate BKV replication in proximal tubular epithelial cells.[40] The presence of BKV in salivary gland in patients with HIV infection led Jeffers-Francis *et al*.[41] to check the effectiveness of ciprofloxacin, cidofovir, and leflunomide in salivary gland

and vero cells. Human salivary gland cells and vero cells were infected with BKV and treated with antiviral drugs and assessed for BKV gene expression and viral replication for up to 5 days postinfection. The kinetics of BKV replication was different in salivary gland cells compared to kidney cells. Treatment of human salivary gland cells with each of the three drugs produced modest decreases in BKV genome replication. Thus concluded that the *in vitro* activity of cidofovir and leflunomide is modest, and the selectivity index is low and there is a need to develop more effective and less toxic anti-BK virus drugs for clinical use.[38]

Ciprofloxacin was first reported to decrease BKV viruria in a study involving hematopoietic stem cell transplant recipients.[42] In this study, effective urinary concentration of ciprofloxacin was comparable to *in vitro* studies suggesting a useful prophylactic role for ciprofloxacin in the targeted patients.[42] Table 1 summarizes various *in vitro* studies done on fluoroquinolones against BKV.

In vivo Studies on Fluoroquinolones Effectiveness against BK Polyomavirus

Evidence in favor of fluoroquinolones

Fluoroquinolones have been used in both hematopoietic stem cell and kidney transplant recipients for prevention of BKV infection. Its effectiveness was first reported in a prospective observational study in hematopoietic stem cell transplant in 2005. Ciprofloxacin oral (500 mg twice a day) or intravenous (200 twice a day) was compared with cephalosporin for 50 days. The study showed that ciprofloxacin is more effective than cephalosporin in decreasing BKV reactivation after hematopoietic stem cell transplantation.[42] Another study showed similar results with 60 days course of ciprofloxacin (500 mg twice a day) after hematopoietic stem cell transplantation in preventing severe BKV hemorrhagic cystitis.[43] In a report of three cases, a daily dose of levofloxacin 500 mg for 2 months has also been used successfully to treat established

Table 1: *In vitro* studies done on fluoroquinolones against BKV

Author	Details of study
Ali *et al*.[27]	Study: The group evaluated the effect of fluoroquinolones on viral DNA replication using the DNA tumor virus SV40 as their model Drug Used: Levofloxacin, trovafloxacin, ciprofloxacin, and ofloxacin Results: All quinolones were effective in the inhibition of SV40 plaque formation and DNA replication in CV1-P cells. Also, each of these quinolones was inhibitory to the helicase activity of SV40 large tumor antigen
Portolani *et al*.[25]	Study: Quinolones inhibit bacterial DNA gyrase and suppress the replication, as well as the cytopathic effect, of BK virus in vero cell cultures Drug Used: Nalidixic acid and oxolinic acid Results: The inhibition of virus replication was detectable at day 4 postinfection in cultures which had been continuously exposed to drugs at concentrations as low as 0.02-0.04 mM of nalidixic acid and 0.2 mM of oxolinic acid. These active concentrations are inferior to plasma levels attained in the course of clinical use of the drugs for antibacterial chemotherapy. Furthermore, under these circumstances, no cytotoxicity occurred. The inhibition of development of cytopathology and of virus-induced cell death was demonstrable in cultures treated for 12 days with the drugs
Ferrazzi *et al*.[26]	Study: Studied quinolones in BSC-1 and vero cell cultures Drug Used: Norfloxacin, coumermycin A1, and nalidixic acid Results: All agents suppressed viral replication
Sharma *et al*.[40]	Study: Assessed the effect of ofloxacin and levofloxacin on BKV replication in proximal tubular epithelial cell Drug Used: Ofloxacin and levofloxacin Results: Sharma *et al*. assessed the effect of ofloxacin and levofloxacin on BKV replication in proximal tubular epithelial cell. Ofloxacin and levofloxacin inhibited BKV load in a dose-dependent manner yielding a ~90% inhibition at 150 μg/ml. Ofloxacin at 150 μg/ml inhibited LT-ag mRNA and protein expression from 24 h postinfection. BKV genome replication was 77% reduced at 48 h postinfection and a similar reduction was found in VP1 and agnoprotein expression. At 72 hours postinfection, the reduction in genome replication and protein expression was less pronounced. A dose-dependent cytostatic effect was noted. In infected cells, 150 μg/ml ofloxacin led to a 26% and 6% inhibition of cellular DNA replication and total metabolic activity, respectively, while 150 μg/ml levofloxacin affected this slightly more, particularly in uninfected cells. They concluded that ofloxacin and levofloxacin inhibit but do not eradicate BKV replication in proximal tubular epithelial cells. At a concentration of ofloxacin giving ~90% inhibition in BKV load, no significant cytotoxicity was observed. This concentration can be achieved in urine and possibly in the kidneys. Their results support a mechanism involving inhibition of LT-ag expression or functions but also suggest inhibition of cellular enzymes
Jeffers-Francis *et al*.[41]	Study: Human salivary gland cells and vero cells were infected with BKV, treated with ciprofloxacin, leflunomide and cidofovir and assessed for BKV gene expression and viral replication for up to 5 days postinfection Drug Used: Ciprofloxacin, cidofovir, leflunomide Results: Ciprofloxacin decreased BKV T Ag and VP1 mRNA expression by at least 50% in both cell types and decreased T Ag protein expression at days 3 and 4 postinfection. A 2.5-4 log decrease in intracellular DNA replication and a 2-3 log decrease in progeny release were detected with ciprofloxacin treatment

SV40: Simian virus 40

hemorrhagic cystitis in hematopoietic stem cell transplant in three cases.[44] Similarly, Umbro *et al*.[45] reported a case of successful treatment of BKV infection with 10 days course of ciprofloxacin in a kidney transplant recipient who also had rejection. They analyzed BKV noncoding control region sequences in all the positive samples. These positive samples showed the presence of archetypal sequences with two single nucleotide substitutions and one nucleotide deletion that interestingly were all representative of the subtype/subgroup I/b-1 as identified by the viral protein 1 sequencing analysis. The changes in genome were accompanied by reduction in BKV both in urine and blood. This was interesting because they successfully eradicated BKV while the patient was taking maximum doses of immunosuppressive medications due to concurrent rejection. Cekmen *et al*. in another case report reported that 6 months therapy with fluoroquinolones treatment reduced the viral load and improved the clinical findings.[46]

Fluoroquinolones have been reported to be effective in three retrospective analyses in kidney transplant recipients. Gabardi *et al*. showed that a 1 month course of levofloxacin or ciprofloxacin significantly reduced BKV viremia at 1 year.[47] In another retrospective analysis, 9 kidney transplant recipients diagnosed with BK viruria $\geq 10^6$ copies/mL and viremia $\geq$500 copies/mL who failed to respond to reduction in immunosuppression were treated with ciprofloxacin 250 mg twice a day for 1 month. Three patients showed complete viral clearance and another 3 had a $\geq$50% decrease in plasma viral load.[47] However, Wojciechowski *et al*. reported that 1 month prophylaxis may not be adequate in preventing BKV on long term.[4] Wojciechowski *et al*. in their retrospective analyses showed that prophylactic use of ciprofloxacin reduces BK virus infection at 3 months but not at 1 year. Unfortunately, most of the literature from both kidney and hematopoietic stem cell transplants were from retrospective studies or case reports. To date, there has been no randomized control study to suggest that fluoroquinolones are effective against BKV infection. Table 2 summarizes the studies in favor of effectiveness against BKV.

Evidence against effectiveness of fluoroquinolones

Not all evidence for fluoroquinolones are favorable. Our literature search showed 8 studies that concluded that fluoroquinolones are not effective. The retrospective analysis by Wojciechowski *et al*. found ciprofloxacin prophylaxis to be effective at 3 month but not at 1 year.[4] In a prospective observational study in hematopoietic stem cell transplant, Phipps *et al*. used ciprofloxacin 500 twice a day from day of the conditioning to day 56. They used the intravenous preparation if patients were unable to tolerate orally and also used levofloxacin in asymptomatic patients with rising BKV titers despite ciprofloxacin. Their analysis showed that ciprofloxacin (or levofloxacin) failed to reduce rates of grades 2–4 hemorrhagic cystitis.[49] In another prospective study, Patel *et al*.[50] used a ciprofloxacin 500 mg twice a day for 3 months. There was 27% reduction in BKV infection. However, it was not statistically significant (P = 0.39) as compared to control group who did not receive ciprofloxacin. Trend of negative results was confirmed in another prospective observational study by Koukoulaki *et al*.[51] They failed to show benefit of ciprofloxacin on BKV reactivation or monthly incidence. Lee *et al*. conducted a multicenter double-blinded randomized controlled trial in 2014 to evaluate the efficacy of levofloxacin in the treatment of BK viremia.[52] The group used levofloxacin 500 mg once a day for 30 days. Levofloxacin was chosen ahead of ciprofloxacin because of its greater bioavailability.[53-54] The study enrolled 46 patients with a diagnosis of BK viremia but only 39 patients were randomly assigned to get either levofloxacin or placebo. A 30-day course of levofloxacin did not significantly reduce BK viral load or improve allograft function at 3 months. This landmark study is important because it was the first study to minimize the confounding factors often seen with observational studies. Unlike other studies, they monitored BKV viremia instead of BKV viruria for initiation of the therapy. However, there were some limitations to this study. There was no uniformization of induction and maintenance protocols used by different centers, and despite randomization, some centers appear to use leflunomide in both arms. The study also did not assess the resistance of BKV strains, which could affect the unfavorable outcome. Another double-blinded randomized control trial was published in 2014 to assess the role of fluoroquinolones in BKV prevention.[32] The primary outcome was time to occurrence of BK viruria (detected using quantitative real-time PCR) within the 1st year of transplantation. Secondary outcomes included BK viremia, peak viral load, rejection, and patient and allograft survival. The trial used levofloxacin 500 mg once a day for 3 months. Moreover, unlike previous trials, all virologic testing was performed centrally at a reference laboratory with a validated assay that was used for clinical purposes. A 3-month course of levofloxacin initiated early following transplantation did not prevent BK viruria. In addition, there was no significant difference between the two groups in regard to any of the secondary end points. There were few limitations in this randomized control trial. Due to resource restrictions, the trial follow-up was terminated prematurely for a subset of 27 patients who had not developed viruria. Second, another potential limitation was the choice of primary outcome (BKV viruria rather than BKV viremia). Viremia rather than viruria will be a good clinical outcome to assess because most monitoring protocols for adjustment of immunosuppression are based on viremia. A recent observational prospective study published in 2016 which used ciprofloxacin as prophylaxis was also found to be negative.[55] We found one meta-analysis by Song *et al*. on fluoroquinolone prophylaxis.[56] The primary outcome of this meta-analysis was BK viremia

Table 2: Studies in favor of use of fluoroquinolones for BKV

Author	Study details
Leung *et al*.[42]	Study Population: Allogeneic hematopoietic stem cell transplant recipient Study Design: Prospective observational study Outcome: Ciprofloxacin recipients developed a significantly lower peak BKV load, compared with cephalosporin recipients (median, 3×10^5 copies/mL vs. 2.6×10^9 copies/mL; P=0.021) Conclusions: Ciprofloxacin decreased urinary BKV reactivation after HSCT
Gabardi *et al*.[47]	Study Population: Kidney transplant recipient Study Design: Retrospective observational study Outcome: A 1-month fluoroquinolone course after transplantation was associated with significantly lower rates of BK viremia at 1 year compared with those with no fluoroquinolone Conclusions: Fluoroquinolones were found effective at preventing BK viremia after renal transplantation
Miller *et al*.[43]	Study Population: Allogeneic HSCT recipients Study Design: Retrospective observational study Outcome: The cumulative incidence of BKV hemorrhagic cystitis was significantly reduced in CP (2.6% vs. 20.9%, P=0.01) Conclusions: Ciprofloxacin prophylaxis appears safe and effective in reducing the incidence of severe BKV hemorrhagic cystitis after allogeneic HSCT
Toptas *et al*.[44]	Study Population: HSCT recipients Study Design: Case report of three patients Outcome: 3 cases of severe hemorrhagic cystitis treated with levofloxacin Conclusions: All cases responded with to treatment with levofloxacin
Umbro *et al*.[45]	Study Population: Kidney transplant recipient Study Design: Case report Outcome: 10 days course of ciprofloxacin Conclusions: Reduction in BKV both in urine and blood despite the fact that they were taking maximum doses of immunosuppressive medications due to concurrent rejection
Cekmen *et al*.[46]	Study Population: Kidney transplant recipient Study Design: Case report Outcome: 6 months therapy with ciprofloxacin Conclusions: Ciprofloxacin reduced the viral load and improved the clinical findings
Arroyo *et al*.[48]	Study Population: Kidney transplant recipient Study Design: Retrospective observational study Outcome: Nine kidney transplant recipients received ciprofloxacin at a median of 130 days following the initial reduction in immunosuppression. Three patients showed complete viral clearance and another 3 had a ≥50% decrease in plasma viral load Conclusions: Ciprofloxacin may be a useful therapy for persistent BKV infection despite conventional treatment
Wojciechowski *et al*.[4]	Study Population: Kidney transplant recipient Study Design: Retrospective observational study Outcome: At 3 months, group without ciprofloxacin had a significantly higher risk of developing BK viremia (0.161 vs. 0.065, P=0.0378) and viruria (0.303 vs. 0.146, P=0.0067) compared with those receiving prophylaxis, but this difference disappeared at 12 months for both viremia (0.297 vs. 0.261, P=0.6061) and viruria (0.437 vs. 0.389, P=0.5363) Conclusions: Ciprofloxacin prophylaxis is effective at 3 months but not at 1 year

HSCT: Hematopoietic stem cell transplantation

and viruria at 1 year post-transplantation. Secondary outcomes were BK virus-associated nephropathy (BKVN), graft failure, and fluoroquinolone-resistant infection. They included 8 comparative studies including randomized control trial and observational studies. A total of 1477 participants with a mean duration of fluoroquinolone prophylaxis of >1 month were analyzed. They concluded that at 1 year, fluoroquinolone prophylaxis was not associated with a decreased incidence of BK viremia.

Despite the limitations observed in these two randomized control studies,[32,52] findings cannot be ignored. Even though there were slight methodological flaws, the double-blinded and randomized nature of the trials arguably provided better evidence than current data that were derived from prospective or retrospective observational studies. Moreover, a recent negative meta-analysis further argues against use of fluoroquinolones against BKV. A new double-blind randomized control trial using ciprofloxacin 250 mg once daily for 3 months has been running since January 2013. The trial primary outcome is BK viremia or the presence of BK viral inclusions on kidney biopsy specimens. The results of the trial are still awaited.[57] It will be interesting to see its result. Table 3 summarizes the studies that reported against the effectiveness of fluoroquinolones in BKV viruria or viremia.

Table 3: Studies against use of fluoroquinolones for BKV

Author	Study Details
Wojciechowski *et al*.[4]	Study Population: Kidney transplant recipient Study design: Retrospective observational study Outcome: At 3 months, group without ciprofloxacin had a significantly higher risk of developing BK viremia (0.161 vs. 0.065, *P*=0.0378) and viruria (0.303 vs. 0.146, *P*=0.0067) compared with those receiving prophylaxis, but this difference disappeared at 12 months for both viremia (0.297 vs. 0.261, *P*=0.6061) and viruria (0.437 vs. 0.389, *P*=0.5363) Conclusions: Despite short-term benefits, prophylaxis was not effective at 1 year
Phipps *et al*.[49]	Study Population: Allogeneic HSCT recipients Study design: Prospective observational study Outcome: Study analysis showed that ciprofloxacin (or levofloxacin) failed to reduce rates of grades 2-4 hemorrhagic cystitis. It developed in 16% of patients receiving prophylaxis and 15% not receiving it (*P*=1.0). Grade 2-4 hemorrhagic cystitis was attributable to BKV in all patients. On univariate analysis, unrelated donor and HLA-mismatched transplants were significantly associated with Grades 2-4 hemorrhagic cystitis (*P*=0.006 and 0.021, respectively) Conclusions: Ciprofloxacin (or levofloxacin) failed to reduce rates of Grades 2-4 hemorrhagic cystitis
Patel *et al*.[50]	Study Population: Kidney transplant recipient Study design: Observational study Outcome: Beginning in March 2012, renal transplant recipients were discharged on ciprofloxacin 500 mg once daily for 90 days. Ciprofloxacin patients were compared to a consecutive cohort of patients transplanted from January 2011 to March 2012 who did not receive ciprofloxacin prophylaxis Conclusions: A 27% reduction in BKV was seen at 6 months, though this did not reach statistical significance (*P*=0.39)
Lee *et al*.[52]	Study Population: Kidney transplant recipient Study design: Randomized control trial Outcome: At the 3-month follow-up, the percentage reductions in BK viral load were 70.3% and 69.1% in the levofloxacin group and the placebo group, respectively (*P*=0.93). The percentage reductions in BK viral load were also equivalent at 1 month (58% vs. and 67.1%; *P*=0.47) and 6 months (82.1% vs. 90.5%; *P*=0.38) Conclusions: A 30-day course of levofloxacin does not significantly improve BK viral load reduction or allograft function when used in addition to overall reduction of immunosuppression
Knoll *et al*.[32]	Study Population: Kidney transplant recipient Study design: Randomized control trial Outcome: BK viruria occurred in 22 patients (29%) in the levofloxacin group and in 26 patients (33.3%) in the placebo group (hazard ratio, 0.91; 95% CI: 0.51-1.63; *P*=0.58). There was no significant difference between the 2 groups in regard to any of the secondary end points. There was significant bacterial resistance and nonsignificant increased tendinitis in levofloxacin group Conclusions: Among kidney transplant recipients, a 3-month course of levofloxacin initiated early following transplantation did not prevent BK viruria. Levofloxacin was associated with an increased risk of adverse events such as bacterial resistance
Lebreton *et al*.[55]	Study Population: Kidney transplant recipient Study design: Prospective observational study Outcome: The rates of BK viruria, BK viremia, and BKV-associated nephropathy did not differ between patients who were given or not given ciprofloxacin prophylaxis. These rates were also identical when patients received quinolones at any time within the first year after transplantation compared to those that had not Conclusions: The use of quinolones seemed to not have any beneficial effect in preventing BKV replication in kidney-transplant patients receiving heavy immunosuppression
Song *et al*.[56]	Study Population: Kidney transplant recipient Study design: Meta-analysis Outcome: At 1 year, fluoroquinolone prophylaxis was not associated with a decreased incidence of BK viremia (RR: 0.84; 95% CI: 0.58-1.20). No significant differences in BKVN (RR: 0.88; 95% CI: 0.37-2.11), risk of graft failure due to BKVN (RR: 0.68; 95% CI: 0.29-1.59), or fluoroquinolone-resistant infection (RR: 1.08; 95% CI: 0.64-1.83) were observed between the fluoroquinolone prophylaxis and control groups Conclusions: Fluoroquinolones are ineffective in preventing BKV infection following renal transplantation
Koukoulaki *et al*.[51]	Study Population: Kidney transplant recipient Study design: Prospective observational study Outcome: Authors studied prospectively 32 *de novo* renal transplant recipients for a period of 12 months with sequential samples of urine and blood tested for BKV with real-time polymerase chain reaction. 9 recipients received ciprofloxacin for 3 weeks and 23 recipients were on treatment with ciprofloxacin for 6 weeks. No effect was found on BK reactivation and monthly incidence Conclusions: Ciprofloxacin did not affect BKV reactivation and monthly incidence

HLA: Human leukocyte antigen, RR: Risk ratio, CO: Confidence interval, BKVN: BK virus nephropathy

Way forward

In our opinion, we believe that fluoroquinolones have anti-BKV activity. The evidence has been demonstrated in various *in vitro* studies. However, its low selectivity index (<3.9) has raised some doubts on its effectiveness against BK virus in the clinical settings. *In vivo* studies which favor fluoroquinolones are mostly retrospective or case reports, but recent prospective evidence by Leung *et al*. has given rise to optimism for a role in prevention of BKVN.[42] However, the recent negative reports in the double-blinded randomized control trial and a negative meta-analysis have added uncertainties in its usefulness in prevention of BKVN. This is further compounded by the relative high cost in using these agents long term and the possibility of complications such as Achilles tendonitis and microbial resistance.[32,52] We believe the current evidence is not favorable enough to warrant the use of fluoroquinolones for long-term prophylaxis. Intermittent screening for BKV viremia and preemptive reduction in immunosuppression on detection remains the best strategy.[3,58] More research is needed to validate current available evidence and investigate the potential of other agents.

Conclusion

Fluoroquinolones have been used *in vitro* and *in vivo* studies for prevention of BKVN. At the moment, it cannot be recommended either as prophylactic or therapeutic option. The only viable option is screening for BKV viremia and preemptive reduction in immunosuppression on detection of the virus. There is a need for an effective and less nephrotoxic drug to prevent or treat BKVN.

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Conflicts of interest

There are no conflicts of interest.

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