Efficacy of Levofloxacin in the Treatment of BK Viremia: A Multicenter, Double-Blinded, Randomized, Placebo-Controlled Trial

Belinda T. Lee, Steven Gabardi, Monica Grafals, R. Michael Hofmann, Enver Akalin, Aws Aljanabi, Didier A. Mandelbrot, Deborah B. Adey, Eliot Heher, Pang-Yen Fan, Sarah Conte, Christine Dyer-Ward, and Anil Chandraker

Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

Correspondence: Dr. Anil Chandraker, Transplantation Research Center, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, MA 02115. Email: achandraker@rics.bwh.harvard.edu

Abstract

Background and objectives BK virus reactivation in kidney transplant recipients can lead to progressive allograft injury. Reduction of immunosuppression remains the cornerstone of treatment for active BK infection. Fluoroquinolone antibiotics are known to have *in vitro* antiviral properties, but the evidence for their use in patients with BK viremia is inconclusive. The objective of the study was to determine the efficacy of levofloxacin in the treatment of BK viremia.

Design, setting, participants, & measurements Enrollment in this prospective, multicenter, double-blinded, placebo-controlled trial occurred from July 2009 to March 2012. Thirty-nine kidney transplant recipients with BK viremia were randomly assigned to receive levofloxacin, 500 mg daily, or placebo for 30 days. Immunosuppression in all patients was adjusted on the basis of standard clinical practices at each institution. Plasma BK viral load and serum creatinine were measured monthly for 3 months and at 6 months.

Results 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% versus and 67.1%; P=0.47) and 6 months (82.1% versus 90.5%; P=0.38). Linear regression analysis of serum creatinine versus time showed no difference in allograft function between the two study groups during the follow-up period.

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.

Clin J Am Soc Nephrol 9: 583–589, 2014. doi: 10.2215/CJN.04230413

Introduction

The BK polyomavirus (BKV), named after the patient from whom the virus was first isolated in 1971, infects up to 90% of the population (1). Primary viral infection generally occurs in childhood and persists in the genitourinary tract, remaining quiescent in most immunocompetent hosts. Transplantation and long-term immunosuppression allows for reactivation of viral replication, causing interstitial nephritis and progressive allograft injury in kidney transplant recipients (2–6).

Routine screening for BKV reactivation after transplantation has been widely recommended and is performed at most transplant centers. The goal of diagnosing and managing BK viremia early in the course of active infection is to prevent the progressive allograft failure that is highly associated with polyomavirus-associated nephropathy (PyVAN).

BK viruria (BKV replication limited to the urogenital tract) can be detected in 30% of the kidney transplant population. BK viremia and BK nephropathy develop in about 11%–13% and 8% of kidney transplant recipients, respectively (7,8). Nearly half of all patients who develop BK nephropathy experience allograft failure (9,10).

Treatment primarily involves reduction of immunosuppression. Definitive evidence for the use of antiviral agents, such as cidofovir, leflunomide, or intravenous immunoglobulin, to treat BK infection is lacking (11,12). Fluoroquinolone antibiotics have also been shown to have antiviral properties, and their efficacy against BKV has been suggested by *in vitro* studies and small, single-center *in vivo* analyses (13–17). No randomized, controlled trials have validated the use of any treatments for BK viremia. To our knowledge, this is the first prospective, double-blind, randomized, placebo-controlled trial to examine the use of levofloxacin in kidney transplant recipients with BK viremia.

Materials and Methods

Trial Design and Study Population

We enrolled adult kidney transplant recipients, age>18 years, with documented BK viremia at eight transplant centers in the United States. Patient enrollment occurred from July 10, 2009, to March 20, 2012.

Baseline characteristics, including age, sex, race, comorbid disease, transplant details, medications, and allograft function, were collected from the patients' medical records. Exclusion criteria are listed in Supplemental Table 1.

Study participants were randomly assigned in a 1:1 ratio to receive levofloxacin, 500 mg, dosed appropriately for renal function (500 mg daily for estimated GFR>50 ml/min per 1.73 m^2, 500 mg every other day for estimated GFR=20–49 ml/min per 1.73 m^2, or 500 mg twice a week for estimated GFR=10–19 ml/min per 1.73 m^2) or a similar-looking placebo for 30 days. Duration of therapy was based on our previous study on the use of levofloxacin in the prevention of BK viremia (14).

After diagnosis of BK viremia, a confirmatory BK viral load was checked before randomization. Plasma BK viral load was then monitored monthly by PCR for 3 months and at 6 months after beginning of treatment or placebo. Renal function was also monitored monthly for 3 months and at 6 months. Each participating center managed changes in immunosuppression according to standard clinical practices at their institution. This design was based on three principal ideas: first, it would be unethical not to reduce immunosuppression after detection of BK viremia given the potentially devastating effect of unchecked BK infection on the transplanted kidney. Second, it would be impractical to dictate how immunosuppression should be reduced in individual patients at different centers, because reduction of immunosuppression very much depends on the individual setting, such as whether or not the patient is receiving a steroid free protocol, and the strength of the viral load. Third, any additional therapy for treatment of BK nephropathy would have to be shown to be significantly better than current management for the benefits of treatment to outweigh any potential adverse effects. We therefore estimated that the treatment group would have to show a 30%–50% further reduction of BK viral load to be clinically worthwhile. To achieve this, a sample size of 16 patients in each group would be necessary to have 80% power to detect a 30% difference in BK viral load reductions, assuming an SD of 30%.

The study protocol was approved by the review boards at all participating institutions and was conducted according to the provisions of the Declaration of Helsinki. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul, as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism (18). All study participants provided written informed consent. The clinical trial was registered with the National Institutes of Health on December 16, 2009 (NCT01034176).

Study Endpoints

The primary endpoint was percentage reduction in plasma BK viral load at 3 months. Secondary endpoints included percentage reduction in BK viral load at 6 months, the number of patients with >50% reduction in BK viral load at 3 and 6 months, the number of patients with sustained BK viremia at 3 and 6 months, and allograft function at 6 months. Percentage BK viral load reduction was calculated by comparing the BK viral load on the confirmatory testing and at 3 months and 6 months after start of study drug or placebo. The use of percentage reduction in our evaluation of BK viral load served a 2-fold purpose. First, it standardized the decrease in BK viral load among the study participants (*e.g.*, one patient may have a BK viral load of 5000 copies/ml, whereas another would present with a BK viral load in the millions; a decrease of 2500 copies/ml has different implications in each case). Second, the percentage reduction of BK viral load was used to adjust for the multiple laboratories performing the PCR assays (Supplemental Table 2). Patients without any decrease in BK viral load or those with an increase in BK viral load during the monitoring period were considered to have 0% reduction in viral load. When a specific BKV copy number was not reported (*e.g.*, when BK viral load was reported as <5000 copies/ml), this was coded as the median value of 2500 copies/ml for data analysis. Allograft function was evaluated by monitoring serum creatinine (sCr) at 1, 2, 3, and 6 months and by analyzing the slope of the line made by sCr versus time.

Statistical Analyses

Baseline descriptive statistics were summarized as percentages. To describe the central location of the continuous variables, the mean of the normally distributed continuous variables and the median of variables not normally distributed were reported. Categorical variables were compared using the Fisher exact test. Continuous variables were analyzed using the *t* test or a chi-squared test (Mood median test). Linear regression analysis was performed to compare the progression of renal function as estimated by sCr versus time in the two study groups. A two-sided P value<0.05 was considered to represent a statistically significant difference. Statistical analyses were conducted using JMP Pro, version 10.0 (SAS Institute, Cary, NC).

Results

Patients

Forty-six patients were initially enrolled in the study (Figure 1). Three patients had undetectable plasma BK viral load on the confirmatory testing and were not included in further analysis. Forty-three patients were randomly assigned, but one was nonadherent with follow-up and another withdrew from the study before the 1-month study visit. Both were in the placebo group, and no data were available regarding these two individuals after enrollment. Two patients in the treatment group developed Achilles tendon pain or injury and were withdrawn from the study after 8 and 16 days. Data were not available to allow us to include these two patients in the outcomes analysis; however, they were included in the analysis of adverse events.

Thus, a total of 39 patients were randomly assigned and completed at least the 3-month study visit. Twenty study participants were allocated to receive levofloxacin and 19 to receive placebo. The baseline characteristics are summarized in Table 1. Age, sex, race, prevalence of diabetes mellitus, history of desensitization, induction therapy, and concomitant cytomegalovirus infection did not significantly differ between the levofloxacin and placebo groups. The only statistically significant difference concerned the number of patients in each group who had had a previous transplant: six patients in the placebo group versus one in the levofloxacin group (P=0.04).

There were also no statistically significant differences in the BK viral load at the start of the study, the peak BK viral load, the time from transplant to diagnosis of BK viremia, the creatinine level at the time of BK diagnosis, or the number of days on levofloxacin or placebo. The number of patients who were treated with leflunomide or who were receiving a steroid-free immunosuppressive regimen was also equivalent between the two study groups. Table 2 summarizes the total daily dose of tacrolimus and mycophenolate mofetil (MMF) for each study group throughout the study period. Dose reductions and medication discontinuation rates were similar between the two study groups.

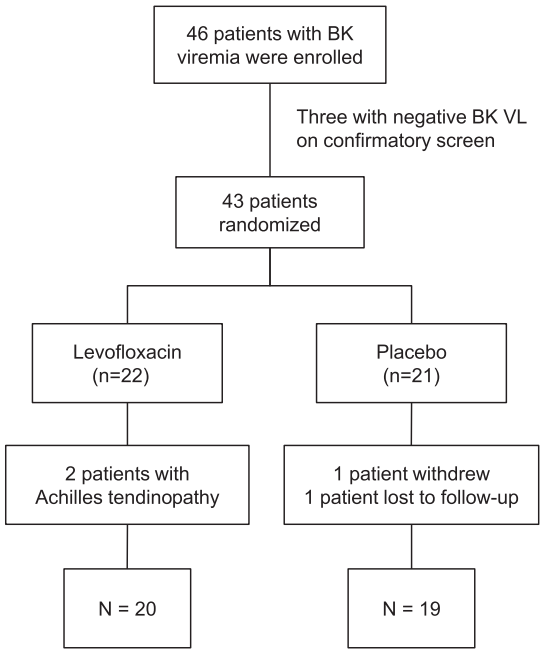


Figure 1. | **Study design.** VL, viral load.

BK Viral Load Reduction

BK viremia developed 28–2555 days after transplant (median, 131 days). One individual did not have a BK viral load checked at 3 months, so the 2-month BK viral load was used for data analysis. One patient died before the 6-month follow-up and was not included in the 6-month analysis of BK viral load or renal function.

There was no statistically significant difference in the median BK viral load for each study group at 0, 1, 2, 3, and 6 months during the study period (Figure 2). Supplemental Figure 1 shows plasma BK viral loads for each patient throughout the study period. At 3 months, the levofloxacin and placebo groups had similar reductions in BK viral load (70.3%±42.5% versus 69.1%±39.5%, respectively; P=0.93), as shown in Table 3. The number of study participants with a ≥50% reduction after 3 months was also equivalent (75% versus 68%; P=0.73). BK viral load reduction and number of patients achieving a ≥50% reduction in BK viral load at 6 months did not differ between the two groups.

BK viral load increased in 25% of the participants in the levofloxacin group compared with 16% in the placebo group (P=0.69). Although most participants had an overall decrease in the number of copies of BKV, only eight patients in the levofloxacin group and six in the placebo group had undetectable plasma levels of BKV at 6 months (P=0.74).

Post hoc analysis of BK viral load reduction and allograft loss excluding patients exposed to leflunomide is reported in Supplemental Table 3.

Table 1. Patient demographic and clinical characteristics

Characteristic	Levofloxacin Group (n=20)	Placebo Group (n=19)	P Value
Mean age at transplant (yr)	54	54.9	0.78
Women	2 (11)	7 (58)	0.06
African American	3 (15)	2 (10.5)	0.69
Diabetes mellitus	8 (40)	9 (47)	0.75
Previous transplant	1 (0.05)	6 (31.6)	0.04
Desensitized	0	3 (15.8)	0.11
Induction regimen			0.11
Thymoglobulin	12 (60)	14 (73.7)	
Simulect	8 (40)	5 (26.3)	
Cytomegalovirus disease	4 (20)	6 (31.6)	0.48
Median onset of BK viremia (IQR) (d)	118 (64–249)	170 (49–344)	0.08
Median BK viral load after consent (IQR) (copies/ml)	24,075 (6,875–65,981)	47,900 (12,500–183,000)	0.27
Median peak BK viral load (IQR) (copies/ml)	74,875 (31,275–255,325)	119,000 (30,200–471,200)	0.64
Mean creatinine at BK diagnosis (mg/dl)	1.6	1.8	0.19
Average duration of treatment (d)	29.9	29.2	0.51
Leflunomide use	4 (20)	2 (11)	0.66
Prednisone free	8 (40)	5 (26)	0.50
Acute rejection after BK diagnosis	1 (5)	0 (0)	>0.99

Unless otherwise noted, values are the number (percentage) of patients. IQR, interquartile range.

Table 2. Immunosuppression medications and average daily doses before BK viremia diagnosis and throughout study period

Variable	Patients Receiving MMF (n)[a]	Average Daily MMF Dosage±SD (mg/d))[b]	Patients Receiving Tacrolimus (n)[c]	Average Daily Tacrolimus Dose±SD (mg/d)
BK viremia diagnosis				
Levofloxacin	16	1531±499	18	6.3±3.6
Placebo	19	1657±443	18	5.9±3.0
P value		0.44		0.73
Study entry				
Levofloxacin	11	1000±316	19	4.6±2.8
Placebo	12	1167±504	17	5.1±3.3
P value		0.35		0.64
3 mo				
Levofloxacin	10	950±369	19	4.2±2.4
Placebo	10	1200±483	17	5.1±3.0
P value		0.21		0.35
6 mo				
Levofloxacin	11	955±270	18	4.1±2.6
Placebo	11	1136±505	16	5.3±3.1
P value		0.31		0.25

MMF, mycophenolate mofetil.
[a]After diagnosis of BK viremia, MMF was discontinued and replaced with sirolimus (n=1), azathioprine (n=3), or leflunomide (n=4) in some study participants. Two patients began receiving leflunomide after BK viremia diagnosis.
[b]Thirteen patients were receiving mycophenolate sodium. The equivalent MMF dose is reported and used for analysis (*e.g.*, mycophenolate sodium, 720 mg twice daily, is reported as 2000 mg total daily dose of MMF).
[c]Cyclosporine was used in one patient. Two other patients not receiving tacrolimus were receiving sirolimus at the time of BK viremia diagnosis.

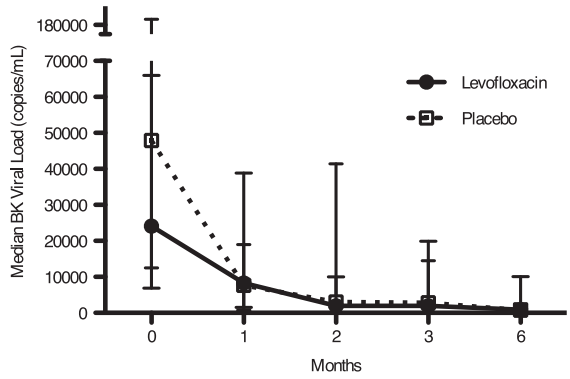


Figure 2. | Median BK viral load throughout the study period. There was no statistically significant difference in the median BK viral load at the onset of the study, or at 1, 2, 3, or 6 months. Error bars represent the interquartile range for each data point.

Allograft Function

sCr at diagnosis of BK viremia and at 1, 2, 3, and 6 months after enrollment in the study is reported in Table 4. The sCr values did not significantly differ at any of these time points. Linear regression analysis of sCr versus time (Figure 3) showed no statistically significant difference in allograft function between the two study groups during the follow-up period. Only two patients had allograft failure and resumed renal replacement therapy; both were in the placebo group. However, this finding was not statistically significant (P=0.49).

Safety Profile

Of the 22 participants initially randomly assigned to the levofloxacin group, two (9%) developed Achilles tendon pain. Levofloxacin was discontinued in both patients, and pain resolved in both. Two individuals in the placebo group reported depression or suicidal ideation. One patient in the levofloxacin group developed biopsy-proven acute rejection.

Two patients in the overall cohort died (one in each group). Both causes of death were determined to be unrelated to the study drug. The cause of death in the patient in the levofloxacin group was disseminated adenocarcinoma of unknown primary. This patient died before the 6-month follow-up and was omitted from the 6-month outcomes analysis.

One participant in the placebo group developed staphylococcal infection after a planned surgery. This patient was unblinded and treated with levofloxacin for 1 week during the second month of follow-up.

Discussion

BK nephropathy is associated with high rates of allograft loss, and, unfortunately, treatment options remain limited. Reduction of immunosuppression is the mainstay of treatment for PyVAN (8,9,11,19,20). Cidofovir, leflunomide, and intravenous immunoglobulin have also been used, but there is no definitive evidence for their efficacy in the treatment of BK viremia (11,12,20–25).

Levofloxacin is a quinolone antibiotic with known activity against bacterial type II topoisomerase (26). Topoisomerase II is an essential enzyme for bacterial DNA replication and is also involved in the DNA replication

Table 3. Outcomes

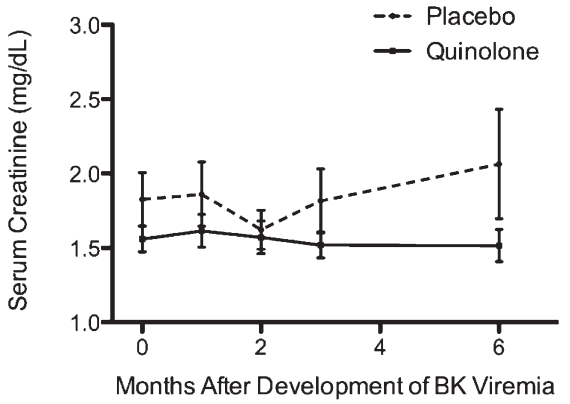
Outcome	Levofloxacin Group (*n*=20)	Placebo Group(*n*=19)	*P* Value
Reduction in BK viral load at 3 mo (%)	70.3±42.5	69.1±39.5	0.93
Patients with >50% reduction in BK viral load at 3 mo	15 (75)	13 (68)	0.73
Reduction in BK viral load at 6 mo (%)	82.1±34.7	90.5±22.2	0.38
Patients with >50% reduction in BK viral load at 6 mo	16 (84) (*n*=19)	17 (89) (*n*=19)	>0.99
Increase in BK viral load at 3 mo	5 (25)	3 (16)	0.69
Sustained BK viremia at 3 mo	13 (65)	14 (74)	0.73
Sustained BK viremia at 6 mo	11 (58)	13 (68)	0.74
Allograft loss	0 (0)	2 (11)	0.49

Unless otherwise noted, values are the number (percentage) of patients. Values expressed with a plus/minus sign are the mean±SD.

Table 4. Mean serum creatinine±SD at BK viremia diagnosis and at 1, 2, 3, and 6 months after start of study

Study Time Point	Levofloxacin Group	Placebo Group	*P* Value
BK viremia diagnosis	1.6±0.4	1.8±0.8	0.19
1 mo	1.6±0.5	1.9±0.9	0.32
2 mo	1.6±0.5	1.6±0.6	0.76
3 mo	1.5±0.4	1.8±0.9	0.21
6 mo	1.5±0.5	2.1±1.6	0.17

Creatinine values are expressed as mg/dl.



	Slope of sCr vs. Time	95% CI
Levofloxacin	-0.01	-0.06 to 0.03
Placebo	0.04	-0.06 to 0.14

Figure 3. | Linear regression analysis of serum creatinine versus time. Allograft function did not significantly differ between the two study groups during the follow-up period. 95% CI, 95% confidence interval; sCr, serum creatinine.

process of simian virus 40, a polyomavirus closely related to BKV (27). Use of quinolone antibiotics inhibits BKV DNA replication and decreases viral growth *in vitro* (13).

In vivo studies of the use of quinolones in BKV reactivation have been small and inconclusive. In 2005, a group in Hong Kong reported decrease of BKV replication in recipients of allogeneic hematopoietic stem cell transplants treated with ciprofloxacin (15). In kidney transplant recipients, a 10-day course of gatifloxacin was shown to decrease BK viremia in 7 of 10 patients after 2 months of follow-up. The effective use of fluoroquinolones as prophylaxis against the development of BK viremia has also been studied in both the hematopoietic stem cell transplant and kidney transplant populations (14,16,17). Gabardi *et al.* showed that a 1-month course of fluoroquinolones after kidney transplantation was associated with significantly lower rates of BK viremia at 1 year (14). A recent analysis also showed the efficacy of a 30-day course of ciprofloxacin in the prevention of BKV reactivation at 3 months, although not at 1 year (17). Both were retrospective studies of patients who had been prescribed a fluoroquinolone for infection prophylaxis (14,17).

To our knowledge, the current study is the only prospective, randomized, controlled trial of any treatment regimen for BK infection. The results of this study show that levofloxacin does not provide further benefit with regard to viral load reduction, clearance of BK viremia, or allograft survival compared with immunosuppression reduction alone. Changes in BK viral load were standardized by calculating percentage reduction for each patient. Efficacy of levofloxacin in the treatment of BK viremia was investigated using both categorical assessments (number of patients achieving 50% reduction in BK viral load, number of patients with sustained viremia, and number of patients with an increase in BK viral load) and numeric assessments of BK viral load.

Both study groups were well matched with regard to demographic and transplant factors, including use of specific induction therapies and steroid-free protocols. Other than immunosuppression, no specific demographic or transplant factor, such as donor age, degree of sensitization, cold ischemic time, or cytomegalovirus disease, has been identified as a risk factor for PyVAN (9). In this one important aspect, more patients in the placebo group had received previous transplants (six versus one; P=0.04) or required desensitization; either situation would, presumably, require a greater degree of immunosuppression. Although this difference in the study groups could insert a confounding effect to increase the appearance of efficacy of levofloxacin, the lack of difference in BK viral load reduction clearly indicates the lack of effect of levofloxacin on BKV reduction and clearance. On 14 other points of comparison, including total daily dose of tacrolimus and MMF, no statistically significant differences between the two study groups were seen.

The dose and duration of drug administration were similar or higher than those in previous retrospective clinical studies of ciprofloxacin, gatifloxacin, and levofloxacin in the prevention or treatment of BK viremia (14,17). Levofloxacin has greater bioavailability than ciprofloxacin, and a 500-mg/d dosage of levofloxacin is probably similar to the slightly higher doses of ciprofloxacin used in other studies (15,16,28,29). Furthermore, a higher dose or longer course of levofloxacin would have increased potential for microbacterial resistance and rates of adverse events in an immunologically vulnerable population.

In our study cohort we observed a high rate of Achilles tendonitis (n=2 [9%]). Although the reported incidence rate of fluoroquinolone-associated tendinopathy is <1% in the general population, the risks of tendonitis and tendon rupture increase with the use of corticosteroids and in kidney transplant recipients (30,31). The US Food and Drug Administration black box warning for the risk of tendonitis and tendon rupture with the use of fluoroquinolones makes the judicious use of this class of antibiotics important in the kidney transplant population (31).

Acute rejection from decreases in immunosuppression or an increase in the immune response due to active viral replication is also associated with BK infection. In this study, one patient had biopsy-proven acute rejection. The patient was in the levofloxacin group and cleared the BK viremia at 3 months. No evidence suggests that fluoroquinolones affect acute rejection rates.

On the basis of the patient cohort that was enrolled, the study was powered to detect a 27% or greater difference in the BK viral load reductions at 3 months. In clinical practice, determining what constitutes a significant reduction of BK viral load is difficult. Although a log reduction of BK viral load is certainly accepted as clinically relevant, it becomes more challenging to determine significance when, for example, a BK viral load of 250,000 copies/ml is reduced to 200,000 copies/ml or when 10 million copies is reduced to 8 million copies. Thus, we estimated that a 30% reduction in BK viral load would be the minimum cutoff for clinical significance, and we designed the study to be powered accordingly.

The strengths of this study include the fairly well randomized study groups, the use of a placebo control group, and the blinding of both the study participants and the health care team. Limitations of the study include the predominance of patients with a previous transplant in the placebo group and the variability in management of immunosuppression at the various transplant centers. Despite this, the study groups were still well balanced in terms in induction medication, steroid withdrawal, need for desensitization, and use of leflunomide. Although statistically nonsignificant, the placebo group did have higher starting and peak BK viral load. Similar to the confounding effect that a higher degree of immunosuppression in the placebo group could have, more severe BK disease in the placebo group would spuriously show efficacy of the study drug. However, this was not the case.

Protocol biopsies were not required as a part of this study, and only five patients had allograft biopsies performed after BK viremia was diagnosed. None had evidence of BK nephropathy. Another limitation of the study was the lack of a central laboratory for BK viral load analysis, potentially introducing variation based on laboratory differences. Regardless of the potential differences in the study groups, in a negative result study such as this one, the likelihood that the various confounders would affect the outcome in an equal and opposite direction would be small. The relatively small number of patients in the study also limited our ability to detect small differences in BK viral load reduction (*e.g.*, <30%).

Finally, we realize that the various fluoroquinolones have inherent differences, and we cannot say with absolute certainty that results would be similar with quinolone antibiotics other than levofloxacin.

In conclusion, we found that use of levofloxacin does not improve BK viral load reduction, BK viral load clearance, or allograft function in the setting of a reduction of immunosuppression. The use of fluoroquinolones in the renal transplant recipient has significant potential adverse effects, including Achilles tendonitis. Although using fluoroquinolones as prophylaxis against BK reactivation may be beneficial, their use in the treatment of already established BK viremia is not warranted.

Acknowledgments

Patients were also recruited from Lahey Clinic Hospital and Fletcher Allen University of Vermont Hospital.

Disclosures

None.

References

1. Hirsch HH, Steiger J: Polyomavirus BK. *Lancet Infect Dis* 3: 611–623, 2003
2. 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* 158: 176–181, 1988
3. Purighalla R, Shapiro R, McCauley J, Randhawa P: BK virus infection in a kidney allograft diagnosed by needle biopsy. *Am J Kidney Dis* 26: 671–673, 1995
4. Pappo O, Demetris AJ, Raikow RB, Randhawa PS: Human polyoma virus infection of renal allografts: Histopathologic diagnosis, clinical significance, and literature review. *Mod Pathol* 9: 105–109, 1996
5. Mathur VS, Olson JL, Darragh TM, Yen TS: Polyomavirus-induced interstitial nephritis in two renal transplant recipients: Case reports and review of the literature. *Am J Kidney Dis* 29: 754–758, 1997

6. Randhawa PS, Finkelstein S, Scantlebury V, Shapiro R, Vivas C, Jordan M, Picken MM, Demetris AJ: Human polyoma virus-associated interstitial nephritis in the allograft kidney. *Transplantation* 67: 103–109, 1999
7. Hirsch HH, Knowles W, Dickenmann M, Passweg J, Klimkait T, Mihatsch MJ, Steiger J: Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. *N Engl J Med* 347: 488–496, 2002
8. Brennan DC, Agha I, Bohl DL, Schnitzler MA, Hardinger KL, Lockwood M, Torrence S, Schuessler R, Roby T, Gaudreault-Keener M, Storch GA: Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. *Am J Transplant* 5: 582–594, 2005
9. Vasudev B, Hariharan S, Hussain SA, Zhu YR, Bresnahan BA, Cohen EP: BK virus nephritis: Risk factors, timing, and outcome in renal transplant recipients. *Kidney Int* 68: 1834–1839, 2005
10. Hirsch HH: Polyomavirus BK nephropathy: A (re-)emerging complication in renal transplantation. *Am J Transplant* 2: 25–30, 2002
11. Bohl DL, Brennan DC: BK virus nephropathy and kidney transplantation. *Clin J Am Soc Nephrol* 2[Suppl 1]: S36–S46, 2007
12. Johnston O, Jaswal D, Gill JS, Doucette S, Fergusson DA, Knoll GA: Treatment of polyomavirus infection in kidney transplant recipients: A systematic review. *Transplantation* 89: 1057–1070, 2010
13. Ferrazzi E, Peracchi M, Biasolo MA, Faggionato O, Stefanelli S, Palù G: Antiviral activity of gyrase inhibitors norfloxacin, coumermycin A1 and nalidixic acid. *Biochem Pharmacol* 37: 1885–1886, 1988
14. Gabardi S, Waikar SS, Martin S, Roberts K, Chen J, Borgi L, Sheashaa H, Dyer C, Malek SK, Tullius SG, Vadivel N, Grafals M, Abdi R, Najafian N, Milford E, Chandraker A: Evaluation of fluoroquinolones for the prevention of BK viremia after renal transplantation. *Clin J Am Soc Nephrol* 5: 1298–1304, 2010
15. Leung AY, Chan MT, Yuen KY, Cheng VC, Chan KH, Wong CL, Liang R, Lie AK, Kwong YL: Ciprofloxacin decreased polyoma BK virus load in patients who underwent allogeneic hematopoietic stem cell transplantation. *Clin Infect Dis* 40: 528–537, 2005
16. Miller AN, Glode A, Hogan KR, Schaub C, Kramer C, Stuart RK, Costa LJ: Efficacy and safety of ciprofloxacin for prophylaxis of polyomavirus BK virus-associated hemorrhagic cystitis in allogeneic hematopoietic stem cell transplantation recipients. *Biol Blood Marrow Transplant* 17: 1176–1181, 2011
17. Wojciechowski D, Chanda R, Chandran S, Lee B, Webber A, Macaraig M, Tomlanovich S, Vincenti F: Ciprofloxacin prophylaxis in kidney transplant recipients reduces BK virus infection at 3 months but not at 1 year. *Transplantation* 94: 1117–1123, 2012
18. Steering Committee of the Istanbul Summit: Organ trafficking and transplant tourism and commercialism: the Declaration of Istanbul. *Lancet* 372: 5–6, 2008
19. Buehrig CK, Lager DJ, Stegall MD, Kreps MA, Kremers WK, Gloor JM, Schwab TR, Velosa JA, Fidler ME, Larson TS, Griffin MD: Influence of surveillance renal allograft biopsy on diagnosis and prognosis of polyomavirus-associated nephropathy. *Kidney Int* 64: 665–673, 2003
20. Sood P, Senanayake S, Sujeet K, Medipalli R, Zhu YR, Johnson CP, Hariharan S: Management and outcome of BK viremia in renal transplant recipients: A prospective single-center study. *Transplantation* 94: 814–821, 2012
21. Pallet N, Burgard M, Quamouss O, Rabant M, Bererhi L, Martinez F, Thervet E, Anglicheau D, Noel LH, Rouzioux C, Legendre C: Cidofovir may be deleterious in BK virus-associated nephropathy. *Transplantation* 89: 1542–1544, 2010
22. Sener A, House AA, Jevnikar AM, Boudville N, McAlister VC, Muirhead N, Rehman F, Luke PP: Intravenous immunoglobulin as a treatment for BK virus associated nephropathy: One-year follow-up of renal allograft recipients. *Transplantation* 81: 117–120, 2006
23. Wadei HM, Rule AD, Lewin M, Mahale AS, Khamash HA, Schwab TR, Gloor JM, Textor SC, Fidler ME, Lager DJ, Larson TS, Stegall MD, Cosio FG, Griffin MD: Kidney transplant function and histological clearance of virus following diagnosis of polyomavirus-associated nephropathy (PVAN). *Am J Transplant* 6: 1025–1032, 2006
24. Guasch A, Roy-Chaudhury P, Woodle ES, Fitzsimmons W, Holman J, First MR; FK778 BK Nephropathy Study Group: Assessment of efficacy and safety of FK778 in comparison with standard care in renal transplant recipients with untreated BK nephropathy. *Transplantation* 90: 891–897, 2010
25. Saad ER, Bresnahan BA, Cohen EP, Lu N, Orentas RJ, Vasudev B, Hariharan S: Successful treatment of BK viremia using reduction in immunosuppression without antiviral therapy. *Transplantation* 85: 850–854, 2008
26. Crumplin GC, Kenwright M, Hirst T. Investigations into the mechanism of action of the antibacterial agent norfloxacin. *J Antimicrob Chemother* 13 Suppl B: 9–23, 1984
27. Yang L, Wold MS, Li JJ, Kelly TJ, Liu LF: Roles of DNA topoisomerases in simian virus 40 DNA replication in vitro. *Proc Natl Acad Sci U S A* 84: 950–954, 1987
28. Garrison MW: Comparative antimicrobial activity of levofloxacin and ciprofloxacin against Streptococcus pneumoniae. *J Antimicrob Chemother* 52: 503–506, 2003
29. Lubasch A, Keller I, Borner K, Koeppe P, Lode H: Comparative pharmacokinetics of ciprofloxacin, gatifloxacin, grepafloxacin, levofloxacin, trovafloxacin, and moxifloxacin after single oral administration in healthy volunteers. *Antimicrob Agents Chemother* 44: 2600–2603, 2000
30. Khaliq Y, Zhanel GG: Fluoroquinolone-associated tendinopathy: A critical review of the literature. *Clin Infect Dis* 36: 1404–1410, 2003
31. U.S. Food and Drug Administration: Levaquin (levofloxacin) Tablets and Oral Solution October 2008. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyRelatedDrugLabelingChanges/ucm121615.htm. Accessed March 3, 2013

Received: April 23, 2013 **Accepted:** November 2, 2013

Published online ahead of print. Publication date available at www.cjasn.org.

This article contains supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.04230413/-/DCSupplemental.

See related editorial, "Treatment of BK Viremia after Renal Transplantation: Are Fluoroquinolones a False Dawn?," on pages 445–447.