Original Investigation

Levofloxacin for BK Virus Prophylaxis Following Kidney Transplantation
A Randomized Clinical Trial

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IMPORTANCE BK virus infection is a significant complication of modern immunosuppression used in kidney transplantation. Viral reactivation occurs first in the urine (BK viruria) and is associated with a high risk of transplant failure. There are currently no therapies to prevent or treat BK virus infection. Quinolone antibiotics have antiviral properties against BK virus but efficacy at preventing this infection has not been shown in prospective controlled studies.

OBJECTIVE To determine if levofloxacin can prevent BK viruria in kidney transplant recipients.

DESIGN, SETTING, AND PARTICIPANTS Double-blind, placebo-controlled randomized trial involving 154 patients who received a living or deceased donor kidney-only transplant in 7 Canadian transplant centers between December 2011 and June 2013.

INTERVENTIONS Participants were randomly assigned to receive a 3-month course of levofloxacin (500 mg/d; n = 76) or placebo (n = 78) starting within 5 days after transplantation.

MAIN OUTCOMES AND MEASURES The primary outcome was time to occurrence of BK viruria (detected using quantitative real-time polymerase chain reaction) within the first year after transplantation. Secondary outcomes included BK viremia, peak viral load, rejection, and patient and allograft survival.

RESULTS The mean follow-up time was 46.5 weeks in the levofloxacin group and 46.3 weeks in the placebo group (27 patients had follow-up terminated before the end of the planned follow-up period or development of viruria because the trial was stopped early owing to lack of funding). 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; $P = .58$). There was no significant difference between the 2 groups in regard to any of the secondary end points. There was an increased risk of resistant infection among isolates usually sensitive to quinolones in the levofloxacin group vs placebo (14/24 [58.3%] vs 15/45 [33.3%], respectively; risk ratio, 1.75; 95% CI, 1.01-2.98) as well as a nonsignificant increased risk of suspected tendinitis (6/76 [7.9%] vs 1/78 [1.3%]; risk ratio, 6.16; 95% CI, 0.76-49.95).

CONCLUSIONS AND RELEVANCE 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. These findings do not support the use of levofloxacin to prevent posttransplant BK virus infection.

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Kidney transplantation is the preferred treatment for end-stage renal disease.[1] The development of potent immunosuppressant medications has reduced the incidence of acute rejection to less than 10%.[2] This improvement has not come without a cost, as BK virus infection has emerged as a major complication of kidney transplantation.

BK virus is a polyomavirus with a prevalence of 60% to 80% in the general population.[3] Immunosuppression leads to viral reactivation. BK virus infection progresses through discrete stages, appearing first in the urine (BK viruria), then in the blood (BK viremia), and ultimately in the allograft (BK virus nephropathy).[4] BK virus nephropathy leads to transplant failure in 10% to 100% of affected patients.[5,6]

There are no proven strategies to treat BK virus infection. Recent guidelines based on nonrandomized data recommend screening followed by a reduction in immunosuppression if BK virus is detected.[6] This approach remains problematic because immunosuppression reduction can lead to acute and chronic rejection,[7,8] patients often remain viremic,[7,9,10] and long-term outcomes are uncertain.[11]

Prophylactic strategies are commonly used in kidney transplantation to prevent infections such as *Cytomegalovirus*[12] and *Pneumocystis* infection.[13] Retrospective studies have shown that use of quinolone antibiotics is associated with less BK viruria, viremia, and nephropathy.[14,15] The purpose of the current study was to assess the efficacy and safety of levofloxacin compared with placebo for the prevention of BK viruria. We hypothesized that levofloxacin given in a sufficient dosage early after kidney transplantation could significantly reduce BK viruria.

Methods

Design

We conducted a multicenter, double-blind, placebo-controlled, parallel-group randomized trial comparing a 3-month course of the quinolone antibiotic levofloxacin with placebo in kidney transplant recipients to reduce the risk of BK viruria (**Figure 1**). A detailed version of the trial design and methods has been published.[16] Eligible patients providing written informed consent were randomly assigned to receive either levofloxacin or placebo in a 1:1 fashion. Allocation was achieved through web-based central randomization in variable blocks stratified by center. An independent statistician prepared the randomization schemes. Physicians, nurses, investigators, and research staff were blinded to the randomization scheme, and active study medication and matching placebo were identical in appearance. The designated research pharmacist at the coordinating center was expressly forbidden to discuss individual treatment allocation with the study team or patients at each participating center. Staff at the central laboratory performing the BK virus measurements were not aware of patients' treatment allocation. This study was approved by the Ottawa Hospital Research Ethics Board, Ottawa, Ontario, Canada (the trial protocol is available in Supplement 1).

Patient Population

Eligible patients were adults aged 18 years or older who received a primary or repeat kidney transplant. We excluded patients who were unable to provide informed consent, had more than 5 days since transplantation, acquired BK virus nephropathy with a previous transplant, had a history of allergic reaction to any quinolone antibiotic or quinolone-associated tendinitis or tendon rupture, had a corrected QT interval of 450 milliseconds or longer, were prescribed concurrent medication known to prolong the QT interval, were pregnant or breastfeeding, required a quinolone antibiotic for more than 14 days (eg, for urinary tract infection prophylaxis), received a multiorgan transplant (eg, kidney-pancreas), enrolled in another interventional trial or had previously enrolled in this study, had a history of rhabdomyolysis, or had significant allergic reactions to 3 or more classes of antibiotics. Randomized patients had a planned follow-up period of 1 year after the time of randomization, with study visits every 4 weeks for the first 24 weeks followed by study visits at 32, 40, and 52 weeks.

Trial Intervention

The target dosage of levofloxacin was 500 mg/d for 3 months administered orally once daily. The 500-mg/d dosage was given as two 250-mg capsules to allow for dosage reductions if required. At each study visit, creatinine clearance was estimated using the Cockcroft-Gault formula[17] and the dosage of levofloxacin was adjusted based on guidelines.[18] The medication was started as soon as the patient was able to take oral medications but within 5 days after transplantation[19] with a goal of preventing early viral replication. Levofloxacin was re-encapsulated by Pharmacy.ca to ensure that placebo was identical in appearance to the study medication.

Other Trial Maneuvers

All participants received prophylaxis against *Cytomegalovirus* and *Pneumocystis* based on established guidelines.[20,21] We collected data on cointerventions such as immunosuppressive strategies. Routine use of quinolones for bacterial prophylaxis was not permitted and investigators agreed to not use quinolones for empirical antibiotic therapy. We developed a set protocol to guide nonstudy use of quinolones. If use of quinolone was deemed to be necessary, the study drug was temporarily withheld and cultures obtained. Once cultures were available, patients were switched to a nonquinolone regimen unless the infection was only quinolone sensitive. During this time, study medication (placebo or levofloxacin) was withheld. All nonstudy use of quinolones was documented.

Outcome Measures

The primary outcome of the study was the time to occurrence of BK viruria within the first year after transplantation.[22] BK viruria was defined as 500 copies/mL or more of BK virus DNA in the urine.[16] BK virus infection was determined at each study visit by testing urine samples using quantitative real-time polymerase chain reaction for the detection of BK virus DNA at a central laboratory at the

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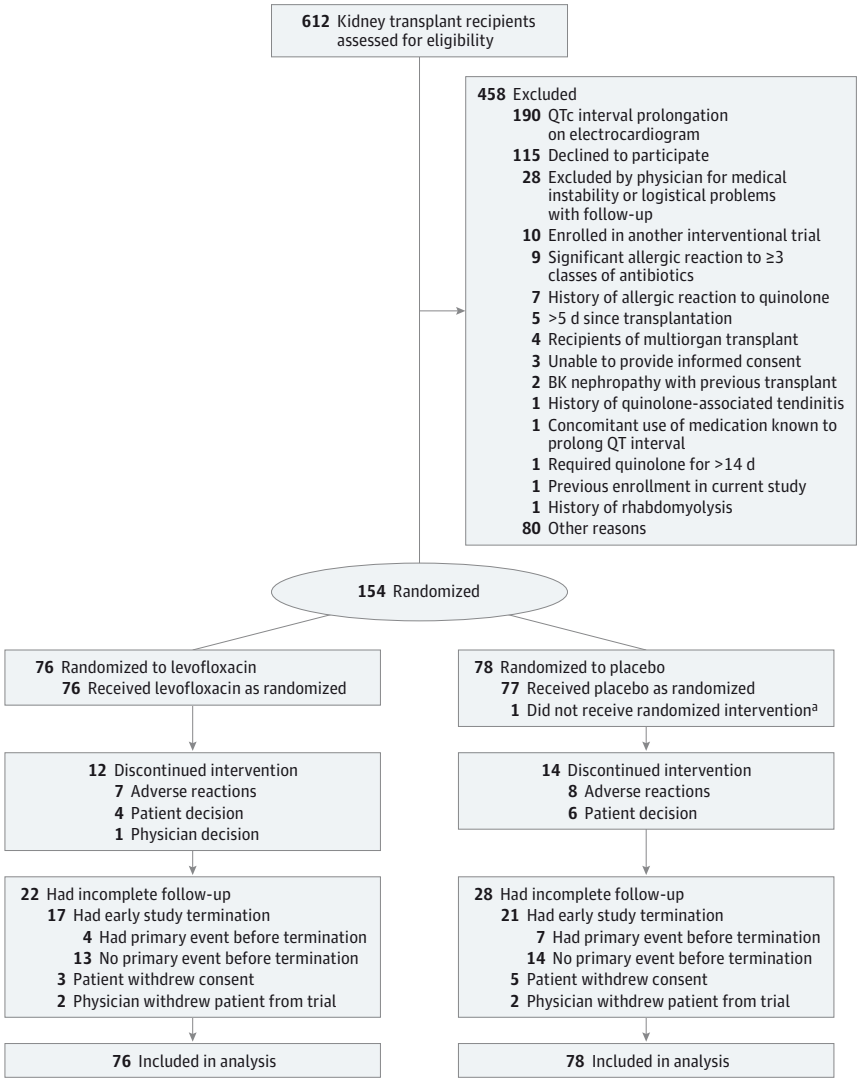
Figure 1. Participant Flow in Randomized Trial of Levofloxacin vs Placebo for BK Viruria in Kidney Transplant Recipients



All 154 patients were analyzed in their assigned treatment group. The study was terminated early because of funding restrictions. Among the 38 patients affected by the early termination (17 in the levofloxacin group and 21 in the placebo group), 11 had developed the primary end point of viruria before termination, leaving 27 at risk of viruria at the time of early study termination. The mean follow-up time for patients affected by the early termination was 37 weeks in the levofloxacin group and 40 weeks in the placebo group.

[a] Patient was prescribed ciprofloxacin for 3 days, never started placebo, and withdrew at first study visit (4 weeks).

University of Alberta, Edmonton. Detailed performance characteristics of the assay have been published.[23] Secondary safety outcomes included the incidence and type of all adverse events including acute rejection, microbiologically confirmed *Clostridium difficile*-associated diarrhea, other infections (viral, bacterial, fungal), positive cultures with quinolone resistance, transplant failure, and mortality. Secondary clinical outcomes included quantitative BK viral load in urine and the occurrence of BK viremia (defined as ≥25 copies/mL of BK virus DNA in the plasma). We also recorded the proportion of randomized participants who took at least 80% of study medication and did not report any episodes of nonadherence (classified as adherent). Medication use was measured by pill count at each study visit as well as by self-reported missed doses. We documented the use of quinolones outside of the protocol and the proportion of patient withdrawals and loss to follow-up.

Statistical Analysis

All analyses were performed by intention to treat. All patients were analyzed in their assigned treatment group with follow-up censored at time of study withdrawal, death or transplant failure, loss to follow-up, end of study (52 weeks), or early study termination. Baseline characteristics of patients in the 2 treatment groups were described with measures of central tendency. For our primary analysis, we performed a nonparametric log-rank test, stratified by center, to compare the time to occurrence of BK viruria between the control and levofloxacin treatment groups. Kaplan-Meier survival curves were plotted to visually assess differences in incidence over time. Although only 46 of 1406 viruria values were missing, we performed a sensitivity analysis with multiple imputation using the Markov chain Monte Carlo method.[24] A sensitivity analysis assessing time to sustained viruria (defined as 2 consecutive epi-

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sodes of positive viruria) was performed using the same statistical strategy.

For secondary and safety outcomes, the proportions of events occurring in each treatment group were compared using mean differences for continuous data and risk ratios for dichotomous variables. Measures of effect are reported with their corresponding 95% confidence intervals. In a secondary analysis performed to account for potential imbalances between groups, a Cox proportional hazards model was fit to adjust for important baseline prognostic risk factors including age, sex, primary or repeat transplant, donor type (living or deceased), and use of immunosuppressant medication. The proportional hazards assumption was met as the interaction of treatment group × time was not significant (P = .47). Exploratory analyses were performed on the following clinically important subgroups: age, sex, type of transplant (primary vs repeat), donor (living vs deceased), and immunosuppression. All tests of statistical inference reflect a 2-sided α=.05. Analyses were performed using SAS software, version 9.4 (SAS Institute Inc).

Sample Size Estimate

Based on data from the literature, we estimated that 35% of patients in the placebo group would develop BK viruria by 1 year after transplantation.[25] To detect a clinically important absolute reduction in BK viruria of 20% (from 35% to 15%) with a 2-sided α=.05, a β=.20, and a 5% loss to follow-up rate, a total of 154 patients (77 per group) was required. The minimal clinically important difference of 20% was justified based on a survey of experts from the Canadian Renal Transplant Study Group and the investigative team.

Results

Patients

The first patient was randomized on December 1, 2011, and recruitment continued until June 25, 2013. The last patient follow-up visit was February 25, 2014. A total of 612 patients received a kidney transplant during the study period in the participating centers and were assessed for eligibility. Of these potentially eligible participants, 154 were randomized (Figure 1). The most common reason for screen failure was a prolonged QT interval (n = 190 patients; 41% of screen failures) followed by patient refusal (n = 115 patients; 25% of screen failures). Patients were randomized an average of 2.4 days after transplantation in the levofloxacin group compared with 2.5 days in the placebo group. Of the 154 randomized patients (100% of the planned sample size), n = 153 received the allocated intervention; 1 patient in the placebo group who was prescribed ciprofloxacin for 3 days starting on the day of randomization never started the allocated intervention and was followed up in the placebo group until the patient withdrew from the trial at 4 weeks. Because of resource constraints, the trial was terminated early, before 38 patients had completed 12 months of follow-up. All patients had completed 8 months of follow-up at the study termination and 11 of the 38 patients had developed viruria, leaving 27 patients at risk of the primary outcome at the time study follow-up was terminated. The mean follow-up time for patients affected by the early termination was 37 weeks in the levofloxacin group and 40 weeks in the placebo group. The overall mean follow-up time was 46.5 weeks in the levofloxacin group and 46.3 weeks in the placebo group.

Table 1. Baseline Participant Characteristics[a]

Characteristics	Levofloxacin Group (n = 76)	Placebo Group (n = 78)
Age, mean (SD), y	47.8 (14.2)	48.2 (12.7)
Female	27 (35.5)	16 (20.5)
Body mass index, mean (SD)[b]	27.0 (4.7)	27.0 (5.2)
Race		
White	49 (64.5)	50 (64.1)
Black	3 (3.9)	7 (9.0)
Asian	3 (3.9)	7 (9.0)
Aboriginal	4 (5.3)	1 (1.3)
Other	14 (18.4)	11 (14.1)
Unknown	3 (3.9)	2 (2.6)
Primary etiology of renal disease		
Glomerulonephritis	18 (23.7)	12 (15.4)
Polycystic kidney disease	14 (18.4)	16 (20.5)
Diabetes mellitus	9 (11.8)	15 (19.2)
Hypertension	4 (5.3)	5 (6.4)
Other	26 (34.2)	25 (32.1)
Unknown	5 (6.6)	5 (6.4)
Comorbidities		
Diabetes	16 (21.1)	19 (24.4)
Previous cancer	7 (9.2)	4 (5.1)
Cardiovascular disease (coronary, cerebral, or peripheral vascular disease)	5 (6.6)	10 (12.8)
Hepatitis C antibody positive	1 (1.3)	1 (1.3)
Hepatitis B surface antigen positive	1 (1.3)	3 (2.0)
Donor type		
Living	46 (60.5)	47 (60.3)
Deceased	30 (39.5)	31 (39.7)
Transplant		
Primary	68 (89.5)	74 (94.9)
Repeat	8 (10.5)	4 (5.1)
Ureteric stent	73 (96.1)	73 (96.6)
Induction immunosuppression	73 (96.1)	75 (96.2)
Basiliximab	48 (63.2)	58 (74.4)
Antithymocyte globulin	25 (32.9)	17 (21.8)
No induction	3(4.0)	3 (3.9)
Maintenance immunosuppression at time of randomization		
Tacrolimus	55 (72.4)	61 (78.2)
Cyclosporine	2 (2.6)	5 (6.4)
Mycophenolate mofetil or sodium	75 (98.7)	75 (96.2)
Corticosteroid	50 (65.8)	48 (61.5)

[a] Data are expressed as No. (%) of participants unless otherwise indicated.

[b] Body mass index was calculated as weight in kilograms divided by height in meters squared.

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Table 2. Clinical Outcomes

Clinical End Points	Levofloxacin Group (n = 76)	Placebo Group (n = 78)	Risk Ratio or Mean Difference (95% CI)
Viruria			
No. (%)	22 (29.0)	26 (33.3)	0.87 (0.54 to 1.39)
Initial BK viral titer, copies/mL			
Mean (SD)	2.1×10^8 (9.2×10^8)	1.9×10^9 (7.5×10^9)	-1.7×10^9 (-4.9×10^9 to 1.6×10^9)
Median (IQR)	1.7×10^4 (1.0×10^4 to 1.1×10^6)	9.8×10^4 (1.0×10^4 to 1.1×10^8)	
Peak BK viral titer, copies/mL			
Mean (SD)	3.4×10^8 (9.4×10^8)	2.8×10^9 (8.1×10^9)	-2.5×10^9 (-6.0×10^9 to 9.9×10^9)
Median (IQR)	6.8×10^6 (1.0×10^4 to 2.2×10^8)	1.3×10^7 (3.5×10^4 to 1.5×10^9)	
Viremia			
No. (%)	6 (7.9)	9 (11.5)	0.68 (0.26 to 1.76)
Initial BK viral titer, copies/mL			
Mean (SD)	7550 (16 542)	4503 (5419)	3046 (−10 430 to 16 522)
Median (IQR)	560 (500 to 1880)	1965 (500 to 7700)	
Death, No. (%)	0	0	
Allograft loss, No. (%)	0	1 (1.3)	
Acute rejection, No. (%)	6 (7.9)	5 (6.4)	1.2 (0.41 to 3.67)

Abbreviation: IQR, interquartile range.

Patient characteristics are reported in **Table 1**. Overall, the 2 study groups were similar. The mean age of included patients was 47.8 years in the levofloxacin group and 48.2 years in the placebo group. A greater number of female patients were randomized to levofloxacin (35.5% to levofloxacin vs 20.5% to placebo). A total of 60% of transplants were from living donors. The use of induction immunosuppression was similar between the groups, as was maintenance immunosuppression at the time of randomization.

In the levofloxacin group, 12 patients (17.1%) discontinued the study drug before the 12-week intervention period was completed (patient decision, n = 4; physician decision, n = 1; adverse events, n = 7) (Figure 1). In the placebo group, 14 patients (17.9%) discontinued the study drug before the 12-week intervention was completed (patient decision, n = 6; physician decision, n = 0; adverse events, n = 8). Adherence to the intervention was excellent, with 90.2% of the levofloxacin group and 90.3% of the placebo group reporting that no study dose was missed. Investigators reduced the dosage of study drug at least once in 55.3% of the levofloxacin group and in 55.1% of the placebo group, usually because of impaired renal function. Off-protocol use of quinolones occurred in 25% of patients in the levofloxacin group (median duration, 7 days; interquartile range, 5-10 days) and in 18% of patients in the placebo group (median duration, 7 days; interquartile range, 3-7 days), mostly for treatment of urinary tract and respiratory tract infections.

Primary End Point

The primary outcome of BK viruria occurred in 22 patients (29.0%) in the levofloxacin group and in 26 patients (33.3%) in the placebo group (risk ratio [RR], 0.87; 95% CI, 0.54-1.39) (**Table 2**). This translates into an absolute reduction of BK viruria by 4.4% (95% CI, −18.9% to 10.3%). The principal prespecified analysis of the primary outcome (time to viruria stratified by study center) was not significantly different between the groups (hazard ratio, 0.91; 95% CI, 0.51-1.63; $P = .58$ by log-rank test) (**Figure 2**). There were negligible quantitative differences between the imputed and nonimputed effect sizes (hazard ratio, 0.88; 95% CI, 0.50-1.56). A Cox proportional hazards model adjusting for age, sex, primary or repeat transplant, donor type, use of corticosteroids, and induction medication demonstrated a similar result (hazard ratio, 0.87; 95% CI, 0.48-1.58). There was also no difference in the occurrence of sustained viruria, defined as 2 consecutive episodes of positive viruria (eFigure 1 in Supplement 2). Our findings were consistent across all analyzed subgroups (eFigure 2 in Supplement 2).

Secondary End Points

There was no difference between the 2 groups with regard to other clinical events. BK viremia occurred in 7.9% of the levofloxacin group and 11.5% of the placebo group (RR, 0.68; 95% CI, 0.26-1.76) (Table 2). There was no difference in either blood or urine BK viral load between the groups (Table 2). Acute rejection occurred in less than 10% in both groups; there were no deaths, and only 1 allograft failed by the end of the study period (Table 2). There were no cases of biopsy-proven BK virus nephropathy.

The safety outcomes are reported in **Table 3**. Infections were similar in both groups, occurring in 59.2% of the levofloxacin group and 44.9% of the placebo group (RR, 1.32; 95% CI, 0.97-1.81). The types of infections were also similar between the groups and, importantly, there were no cases of *C difficile* infection (Table 3). Among the obtained cultures, 14 isolates (46.7%) were reported as quinolone resistant in the le-

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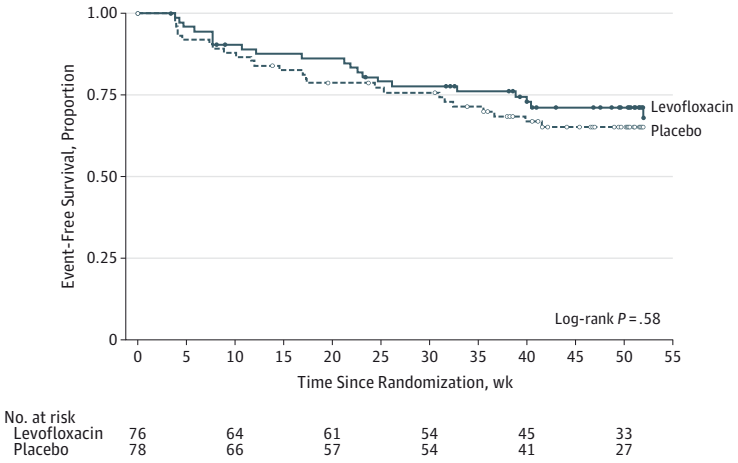
Figure 2. Time to First Episode of Viruria



No. at risk

Levofloxacin	76	64	61	54	45	33
Placebo	78	66	57	54	41	27

Circles indicate when data were censored. There was no significant difference in time to first viruria between patients randomized to levofloxacin vs placebo.

vofloxacin group and 15 (32.6%) in the placebo group (RR, 1.43; 95% CI, 0.81-2.50). When the analysis was restricted to isolates usually sensitive to quinolones, the proportion of resistant isolates was 58.3% (14/24) in the levofloxacin group and 33.3% (15/45) in the placebo group (RR, 1.75; 95% CI, 1.01-2.98). There was a nonsignificant increase in the risk of suspected tendinitis among patients receiving levofloxacin (7.9% vs 1.3%; RR, 6.16; 95% CI, 0.76-49.95) (see case descriptions in eTable 1 in Supplement 2). Other adverse events such as QTc prolongation, hypoglycemia, rash, and diarrhea were similar between the treatment groups (Table 3). Renal function was similar in both groups throughout the study (Table 3).

Discussion

In this multicenter, placebo-controlled randomized trial, a 3-month course of levofloxacin prophylaxis did not prevent the occurrence of BK viruria within the first year after transplantation. Analysis of secondary virologic measures including occurrence of BK viremia, peak urine and blood viral loads, and time to sustained viruria showed that such measures were not significantly different between the levofloxacin and placebo groups. No cases of BK virus nephropathy were observed in either group. Levofloxacin prophylaxis was associated with quinolone resistance and a nonsignificant increase in suspected tendinitis. To our knowledge, this was the first randomized clinical trial of a pharmacologic intervention for the prevention of BK virus infection after kidney transplantation.

Prolonged antimicrobial prophylaxis following organ transplantation has proven very successful for prevention of other opportunistic viral pathogens, most notably *Cytomegalovirus*. No specific antiviral agent for BK virus currently exists. However, quinolone antibiotics have demonstrated in vitro activity against polyomaviruses at concentrations achievable through standard dosing regimens.[26] The mechanism of viral inhibition may be from activity against BK virus large T-antigen helicase activity.[27] There are no prospective clinical studies evaluating quinolone prophylaxis for the prevention of BK virus reactivation following kidney transplantation, although several retrospective studies have suggested a potential clinical benefit. Wojciechowski et al[15] compared quinolone prophylaxis in a cohort of 130 patients (ciprofloxacin, 250 mg twice daily for 30 days) vs a historical control group of 106 patients who did not receive prophylaxis. They observed a significantly lower 3-month risk of BK viruria (14.6% vs 30.3%), although this difference was not present at 12 months. A nonsignificant difference in BK nephropathy was also observed (0.8% vs 4.7%). Gabardi et al[14] retrospectively analyzed 40 patients who received quinolone prophylaxis (duration, 30 days) because of a sulfa allergy. These patients were compared with a control group of patients with no quinolone exposure. A significantly lower rate of viremia was observed at 1 year (4% vs 22.5%) after transplantation. The observed beneficial effects in studies that have compared outcomes with historical control groups may be attributable in part to changes in immunosuppression over time as well as enhanced monitoring and awareness of BK virus infection. Levofloxacin has been evaluated for treatment of established BK viremia in a randomized trial of 39 kidney transplant patients.[28] Percentage reductions in BK viral load were similar at 1, 3, and 6 months following a 30-day course of levofloxacin compared with placebo.

Prolonged prophylaxis with a quinolone antibiotic has the potential for both positive and negative effects unrelated to BK virus. Quinolone prophylaxis has been suggested as a potential method to decrease the incidence of urinary tract infections following kidney transplantation. For example, Rafat et al[29] retrospectively evaluated the incidence of urinary tract infections before and after implementation of a 1-month course of ofloxacin prophylaxis. They observed a substantial reduction in the cumulative 1-year incidence of urinary tract infection. In contrast, our study demonstrates an almost identical incidence of urinary tract infections in the levofloxacin and placebo groups (37.2% and 37.8%, respectively).

Quinolones are one of the main classes of antibiotics used for treatment of common infections after transplantation be-

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Table 3. Safety Outcomes

Outcomes	Levofloxacin Group (n = 76)[a]	Placebo Group (n = 78)[a]	Risk Ratio or Mean Difference (95% CI)
Hospitalization	22 (29.0)	26 (33.3)	0.84 (0.53 to 1.35)
≥1 Infection	45 (59.2)	35 (44.9)	1.32 (0.97 to 1.81)
No. of infections per patient			
Mean (SD)	1.4 (1.6)	1.3 (2.2)	0.1 (−0.5 to 0.7)
Median (interquartile range)	1 (0 to 2)	0 (0 to 2)	
Infections	n = 113	n = 119	
Urinary tract/pyelonephritis	42 (37.2)	45 (37.8)	0.98 (0.70 to 1.37)
Cytomegalovirus	39 (34.5)	39 (32.8)	1.05 (0.73 to 1.51)
Pneumonia	4 (3.5)	2 (1.7)	2.11 (0.46 to 9.71)
Cellulitis	3 (2.7)	1 (0.8)	3.16 (0.46 to 21.9)
Line related	1 (0.9)	0	
Bacteremia	0	1 (0.8)	
Clostridium difficile	0	0	
Other	24 (21.2)	31 (26.1)	0.82 (0.51 to 1.29)
Culture-positive infections	n = 30	n = 46	
Quinolone sensitive	10 (33.3)	26 (56.5)	0.59 (0.33 to 1.00)
Quinolone resistant	14 (46.7)	15 (32.6)	1.43 (0.81 to 2.50)
Quinolone intermediate	0	4 (8.7)	
Quinolone sensitivity not reported by laboratory	6 (20.0)	1 (2.2)	9.2 (1.55 to 56.70)
QTc prolongation on electrocardiogram	3 (4.0)	4 (5.1)	0.77 (0.20 to 2.98)
Suspected tendinitis	6 (7.9)	1 (1.3)	6.16 (0.76 to 49.95)
Significant hypoglycemia	3 (4.0)	5 (6.4)	0.62 (0.17 to 2.25)
Rash	1 (1.3)	1 (1.3)	1.03 (0.11 to 9.70)
Diarrhea	36 (47.4)	30 (38.5)	1.23 (0.86 to 1.79)
Serum creatinine, mean (SD), μmol/L			
At 4 wk	138.3 (70.9)	140.5 (86.2)	−2.1 (−27.3 to 23.1)
At 8 wk	125.2 (115.3)	132.0 (46.6)	−6.8 (−21.4 to 7.7)
At 12 wk	127.0 (49.1)	129.3 (52.9)	−2.3 (−19.0 to 14.3)
At 16 wk	125.0 (49.3)	126.1 (42.6)	−1.2 (−16.4 to 14.1)
At 20 wk	121.5 (42.0)	125.0 (38.1)	−3.4 (−16.8 to 10.0)
At 24 wk	120.8 (44.2)	124.9 (37.3)	−4.2 (−17.7 to 9.4)
At 32 wk	119.1 (40.1)	124.1 (35.6)	−5.0 (−17.8 to 7.8)
At 40 wk	120.4 (41.4)	126.7 (44.5)	−6.3 (−21.2 to 8.6)
At 52 wk	118.2 (40.6)	125.8 (45.6)	−7.5 (−24.0 to 8.9)
Patients with ≥1 other serious adverse event not listed above	22 (28.9)	26 (33.3)	0.85 (0.53 to 1.35)
Total No. of other serious adverse events	27	29	

[a] Data are expressed as No. (%) of participants or events unless otherwise indicated.

cause of their spectrum of activity, tolerability, and low likelihood of clinically relevant interactions with commonly used immunosuppression drugs. For organisms for which a quinolone antibiotic may be effective (eg, Enterobacteriaceae), we observed a nearly 2-fold increased rate of resistance in the levofloxacin group (58.3% vs 33.3%; RR, 1.75; 95% CI, 1.01-2.98). In clinical practice, this would have significant implications for the management of common infections after transplantation. It is encouraging that no cases of *C difficile* colitis were observed despite the prolonged antibiotic exposure. The most serious adverse event in the trial was a nonsignificant increase in suspected tendinitis in the levofloxacin group. A total of 7 cases of tendinitis occurred, of which 6 were in the levofloxacin group. Although no cases of tendon rupture were seen, this may have been due to prompt discontinuation of the study medication in patients in whom tendinitis was suspected. A case of bilateral Achilles tendon rupture was recently reported in a kidney transplant recipient.[30] The patient was given a 1-month course of ciprofloxacin for BK virus prophylaxis because he had lost his first graft because of BK virus nephropathy.[30]

Our study has several limitations. Because of resource restrictions, the trial follow-up was terminated prematurely for a subset of 27 patients who had not developed viruria. Importantly, this decision was made without any analysis of the data. However, it is unlikely that the early termination had a significant influence on the results because all patients completed follow-up to a minimum of 8 months after transplantation, and the onset of viruria after 6 months is known to be infrequent, with more than 85% of cases reported within the

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first 3 months after transplantation.[25] Late-onset viruria was uncommon in either group of the study, with only 3 cases reported after 40 weeks. In a simulation in which we assumed a rate of viruria twice that observed in the study and assigned all events to the placebo group, there was no significant difference in viruria between the groups (eTable 2 in Supplement 2). Another potential limitation was the choice of primary outcome (development of viruria). Although we did not test donor and recipient serostatus in this study, we would expect these factors and other unmeasured potential confounders to be randomly distributed between the treatment and placebo groups in this randomized study. It could be argued that viremia may be a more relevant clinical outcome because monitoring protocols with adjustments to immunosuppression are usually based on viremia.[25,31] However, in the pathogenesis of BK nephropathy, detection of viral reactivation in the urine is the first step and precedes the development of both viremia and nephropathy.[4] Based on our data, a more definitive trial with either viremia or BK nephropathy as an end point would not be indicated because the required sample size would be prohibitive and the accompanying burden of toxicity would be unacceptable to patients and clinicians. Although only levofloxacin was studied, the drug is more consistently active against BK virus than is ciprofloxacin,[26] has greater activity against the closely related SV40 polyomavirus than either ciprofloxacin or ofloxacin,[32] achieves a higher urinary concentration than ciprofloxacin,[33] and requires only once-daily dosing, which may have contributed to the low (<10%) frequency of missed doses in the study.

Our study also has several strengths. Rigorous blinding was maintained, adherence to study medication was very good, and no loss to follow-up occurred. In addition, all virologic testing was performed centrally at a reference laboratory with a validated assay that is used for clinical purposes. Finally, a comprehensive assessment of potential adverse effects was performed, including an analysis of bacterial resistance.

Conclusions

Among kidney transplant recipients, a 3-month course of levofloxacin initiated early after transplantation did not prevent BK viruria. This intervention was associated with an increased risk of adverse events such as bacterial resistance. These findings do not support the use of levofloxacin to prevent posttransplantation BK virus infection.

ARTICLE INFORMATION

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