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# A 3-month course of ciprofloxacin does not prevent BK virus replication in heavily immunosuppressed kidney-transplant patients

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ABSTRACT

*Background:* In vitro and retrospective studies of kidney-transplant patients have shown that quinolones can efficiently prevent BK virus (BKV) replication. However, in a prospective study, a 3 month-course of levofloxacin did not decrease the rate of BK viruria in kidney-transplant patients treated with standard immunosuppression.
*Objectives:* The aim of this study was to assess the effect of a 3-month course of ciprofloxacin prophylaxis on BKV replication in kidney-transplant patients that had received heavy immunosuppression (plasma exchange or immunoadsorption and rituximab) to achieve desensitization before undergoing HLA- and/or ABO-incompatible (ABOi) transplantation.
*Study design:* Twenty-nine patients were given ciprofloxacin (500 mg/d) for 3 months, starting immediately after transplantation. The results were compared with results from a previous study where patients had received a similar immunosuppression regimen without ciprofloxacin prophylaxis ($n = 43$). Around 60% of patients had undergone a retransplantation. After transplantation, all patients were given induction therapy, tacrolimus, mycophenolic acid and steroids. BK viruria and viremia were monitored at months 1, 3, 6 and 12 post-transplantation.
*Results:* 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. The rate of bacterial infection was also similar in patients who had or had not received ciprofloxacin.
*Conclusion:* The use of quinolones seemed to not have any beneficial effect in preventing BKV replication in kidney-transplant patients receiving heavy immunosuppression.


## 1. Background

BK virus (BKV) replication and BKV-associated nephropathy, also called polyomavirus-associated nephropathy (PVAN), are commonly observed after kidney transplantation [1]. They are responsible for impaired kidney function and decreased kidney-allograft survival [1]. Prevention of PVAN relies on systematic screening strategy for decoy cells, BK viruria, and viremia after transplantation, and reduction of immunosuppression once BK virus is detected in the urine or blood [1,2].

Quinolone antibiotics have been shown to have a mild anti-viral activity against polyomavirus [3] [4]. Sharma et al. have found that ofloxacin and levofloxacin inhibit BKV load in primary human renal proximal tubular epithelial cells [5]. Retrospective studies have shown that ciprofloxacin prophylaxis reduces BK virus replication in the urine and blood [6,7]. However, a prospective randomized trial showed that a 3-month course of levofloxacin, given to

*Abbreviations:* ABOi, ABO incompatible; BKV, BK virus; HLAi, human leukocyte antigen incompatible; PVAN, polyoma-virus associated nephropathy.

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**Table 1**
The patients' characteristics.

| | Ciprofloxacin prophylaxis $N = 29$ | No ciprofloxacin prophylaxis $N = 43$ | $p$-value |
|---|---|---|---|
| Recipient age (years) | 49 ± 14 | 46 ± 14 | NS |
| Donor age (years) | 50 ± 14 | 53 ± 12 | NS |
| Recipient gender: Male (%) | 48.3 | 55.8 | NS |
| Donor gender: Male (%) | 55.2 | 34.9 | NS |
| Initial nephropathy | | | NS |
| Glomerular disease | 13 | 17 | NS |
| Interstitial or urological disease | 6 | 9 | NS |
| Vascular disease or diabetes | 5 | 7 | NS |
| Genetic disease | 4 | 9 | NS |
| Other | 1 | 1 | NS |
| First transplantation (%) | 48.3 | 46.5 | NS |
| Preemptive transplantation (%) | 17.2 | 11.6 | NS |
| Duration of dialysis (months) | 29 (0–132) | 25 (0–244) | NS |
| Diuresis at transplantation (%) | 48.3 | 48.8 | NS |
| Living donors (%) | 89.7 | 51.1 | 0.0008 |
| ABOi transplantation (%) | 55.2 | 32.6 | NS |
| HLAi transplantation (%) | 65.5 | 72.1 | NS |
| DGF* (%) | 20.7 | 32.6 | NS |
| Cold ischemia time (min) | 372 ± 357 | 798 ± 601 | 0.001 |
| Warm ischemia time (min) | 59 ± 21 | 59 ± 28 | NS |
| CMV status | | | |
| D+/R+ | 7 | 12 | NS |
| R+ | 15 | 25 | NS |
| D−/R− | 5 | 6 | NS |
| Valganciclovir prophylaxis (%) | 82.8 | 86.0 | NS |
| Duration of CMV prophylaxis (months) | 5.4 ± 1.2 | 6.2 ± 1.8 | NS |

*Abbreviations*: ABOi. ABO incompatible; HLAi. HLA incompatible; DGF. delayed graft function; CMV. cytomegalovirus; D. donor; R. recipient; NS. not significant.
* Delayed graft function was defined as the necessity of at least one dialysis session within the first week after transplantation.

kidney-transplant patients receiving standard immunosuppression, did not prevent BK viruria [8].

## 2. Objectives

The aim of our study was to assess the effect of a 3-month course of ciprofloxacin as prophylaxis on BK viruria and viremia in kidney-transplant patients that had received heavy immunosuppression to achieve desensitization before HLA-incompatible (HLAi) and/or ABO-incompatible (ABOi) transplantation.

## 3. Study design

Between June 2012 and June 2014, patients who had undergone a desensitization protocol for HLAi and/or ABOi kidney transplantation at our center were given ciprofloxacin at a daily dose of 500 mg for 3 months, starting immediately after transplantation, to prevent BK virus replication ($n = 29$). Patients who had lost their previous kidney allograft from PVAN were not included in this study. The results observed in this group were compared with those from a previous study where patients had undergone a desensitization protocol for HLAi and/or ABOi kidney transplantation between January 2010 and May 2012, but had not received ciprofloxacin prophylaxis ($n = 43$). The Toulouse University Hospital's Institutional Review Board approved the present study, and all patients were followed-up until 1 year posttransplant.

Desensitization protocols included apheresis sessions, rituximab, and intravenous immunoglobulins. All patients were given rituximab. The infused dose of rituximab was 375 mg/m$^2$. The number of rituximab infusions and apheresis sessions, as well as the apheresis technique, were chosen according to the number of donor-specific antibodies and their mean immunofluorescence intensities for HLAi transplantation and the isoagglutinin level for ABOi transplantation. At transplantation, all patients were given an induction therapy. After transplantation, all patients were given a triple immunosuppressive regimen based on tacrolimus, mycophenolic acid, and steroids. After transplantation, all patients were given a ureteric stent for 6 weeks.

In the BKV prophylaxis group, patients were given ciprofloxacin at a dose of 250 b.i.d. If kidney function was impaired, ciprofloxacin was reduced to 250 mg/d. Ciprofloxacin prophylaxis was scheduled for 3 months. We have chosen to use ciprofloxacin rather than levofloxacin because, when we have initiated the study, ciprofloxacin was used in all previous reports in kidney-transplant patients that showed that quinolones can efficiently prevent BKV replication [6,7]. All patients from both the BKV prophylaxis and non-BKV prophylaxis groups were given prophylaxis against *Pneumocystis jiroveci* of sulfamethoxazole-trimethoprime for 6 months. Similarly, all patients at risk for cytomegalovirus infection, i.e., donor seropositive/recipient seronegative, or seropositive recipients were given valganciclovir prophylaxis for 3–6 months.

The urine and blood of all kidney-transplant patients were screened for BKV at months 1, 3, 6, 9, and 12 after transplantation, as well as each time they presented with impaired kidney function. BKV infection was defined as viral replication within the urine and/or blood. Patients where BKV replication was detected in the blood twice, at one-month intervals, underwent a kidney biopsy. In addition to microscopy, SV40 staining was done to confirm a diagnosis of PVAN.

### 3.1. Virological analyses

Nucleic acids were extracted from urine and blood samples using a MagNA Pure 96$^{TM}$ instrument and a MagNA Pure 96 DNA and viral NA small-volume kit® (Roche Diagnostics, Meylan, France), according to the manufacturer's instructions (extracted volume: 200 μL, elution volume: 100 μL). The detection limit for BKV was 500 copies/mL (2.7 log copies/mL).

### 3.2. Statistical analyses

Reported values represent the means (±SD) or medians (ranges). Proportions were compared using Fisher's exact test.