Treatment of BK Viremia after Renal Transplantation: Are Fluoroquinolones a False Dawn?

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Fluoroquinolones, DNA gyrase inhibitors, display anti-BK properties through inhibition of DNA topoisomerase and polyomavirus-associated large T-antigen helicase (1,2). An in vitro analysis using older fluoroquinolone compounds, nalidixic acid and oxolinic acid, demonstrated that these agents are capable of inhibiting replication of BK virus (BKV) DNA. Another analysis using contemporary fluoroquinolones (i.e., levofloxacin, trovafloxacin, ciprofloxacin, and ofloxacin) showed that these antibiotics, in vitro, have the ability to inhibit viral DNA replication and T-antigen helicase activity of simian virus 40; this monkey polyomavirus has been associated with FSGS and other human diseases, including polyoma virus–associated nephropathy (3).

Several previous studies have investigated the use of fluoroquinolones in immunosuppressed patients. In a clinical analysis of renal transplant recipients, 2 months after a 10-day course of gatifloxacin, 7 of 10 recipients with urine decoy cells had reduction in viremia or disappearance of urinary decoy cells without any reduction in immunosuppression. In another retrospective analysis, 1-month treatment with ciprofloxacin, 250 mg twice daily, or levofloxacin, 250 mg daily, as part of an antipneumocystis prophylaxis strategy after renal transplantation, was associated with significantly lower rates of BK viremia at 1 year compared with patients without fluoroquinolone exposure (4). A third relevant study retrospectively compared the effect of no BK prophylaxis in 106 patients with that of BK prophylaxis with ciprofloxacin, 250 mg twice daily, for 30 days on the rate of BKV infection during the first 12 months after kidney transplantation. Ciprofloxacin prophylaxis was associated with less BK viremia at 3 months but not at 1 year (5).

All three studies have significant limitations. Nevertheless, the findings were provocative and suggest that fluoroquinolones may prevent BK reactivation in kidney transplantation.

In a related study of allogeneic hematopoietic stem cell transplant (HSCT) recipients, 90 days of prophylaxis with ciprofloxacin, 500 mg twice daily, was associated with a reduction in the incidence of BK-associated hemorrhagic cystitis, from 20.9% to 2.6% (6). However, in a different study in HSCT recipients (7), ciprofloxacin reduced the reactivation of BK viremia but did not decrease the incidence of hemorrhagic cystitis. The authors surmised that ciprofloxacin resistance might have been a contributing factor because four of the seven BKV isolates were ciprofloxacin resistant in vitro. Inadequate dosing may have contributed to poor efficacy because the antibiotic dosing was not consistent in this partly retrospective study. Patients in this study received continuous oral (500 mg twice daily) or intravenous (200 mg twice daily) ciprofloxacin, but of 51 patients who initially received ciprofloxacin, 13 had their therapy interrupted and data from these patients were excluded from analysis. In addition, 7 patients were switched to ceftibuten after 1 week of therapy. Urinary ciprofloxacin levels were measured in 20 ciprofloxacin recipients, and 1 ciprofloxacin recipient was excluded from analysis because of an indefinite BKV viruria pattern. The mean urinary concentration of ciprofloxacin was 23–152.9 μg/ml compared with a level of 350 μg/ml, which would be expected after a single oral dose of 500 mg (8).

In this issue of the CJASN, Lee et al. report on a prospective, multicenter, double-blinded, placebo-controlled trial performed to determine whether fluoroquinolones can effectively treat BK viremia (9). Initially, 46 patients were enrolled after diagnosis of BK viremia, but only 39 patients were randomly assigned: 20 to receive levofloxacin and 19 to receive placebo. Study patients received levofloxacin, 500 mg daily, for 30 days after detection of BK viremia, with the dose adjusted for GFR. Levofloxacin levels were not measured, and the duration of therapy was chosen on the basis of the earlier work by the authors (4). The two groups were fairly well matched except that more patients in the placebo group (n=6) had received previous transplants compared with the levofloxacin group (n=1).

Despite a variety of nonstandardized secondary interventions, the percentage reduction in BK viral load at 1, 2, 3, or 6 months did not differ between groups. There was also no difference in the number of patients who achieved at least a 50% reduction in BK viral load at 3 and 6 months.

The authors should be commended on several aspects of their study. First, by conducting a prospective, multicenter, double-blinded, placebo-controlled trial, they minimized the confounding associated with observational studies. Second, they used BK viremia, rather than BK viruria, to initiate treatment because BK
viruria is relatively benign as long as it does not progress to viremia (10). Third, the study’s simplified intervention and surveillance procedures made participant recruitment and retention relatively easy.

Several important limitations exist for the study, however. First, each participating center managed changes in immunosuppression according to their standard institutional practices. The different induction and maintenance immunosuppression protocols can affect the incidence of BK viremia and response to intervention. Second, as the authors mention, no single assay was used to assess BK level, and results from different laboratories typically vary by 1–2 logs (11). The authors believe they overcame this limitation by looking at the percentage reduction in viral load. Third, the duration of therapy might have been too short or the dose too low; both were concerns from previous clinical studies. Fourth, although the use of leflunomide was equal in both groups (20%), its use confounds the study. The reported efficacy of leflunomide to treat BK infection may actually be through immunosuppression reduction rather than a direct antiviral effect. Recently, the putative anti-BK properties have been challenged (12,13). It also would have been informative to know the practice of participating centers on the use of ureteral stents, which have been associated with increased BK nephropathy and inferior outcomes (14). Finally, the study did not assess the presence of levofloxacin-resistant BK strains, and their presence could have affected the study.

Further studies are being performed to provide additional information regarding the use of fluoroquinolones after transplantation. An ongoing Canadian trial is evaluating the use of 3 months of levofloxacin, 500 mg daily, to reduce the incidence of BK viruria, viremia, or nephropathy while avoiding unintended consequences (15). Another agent, CMX001 (a mimic of a naturally occurring lipid, lyssolecithin, formed by linking 3-hexadecyloxy-1-propanol to the phosphonate group of cidofovir) is under investigation for prevention or treatment of BK infection. CMX001 has already been shown to inhibit BK replication in human renal tubular epithelial cells (16), to be safe and well tolerated in renal transplant recipients with BK viruria, and to reduce the incidence of cytomegalovirus in recipients of HSCTs without myelosuppression or nephrotoxicity (17).

So, what can we gain from this study? One month of levofloxacin adjusted for renal function does not appear to help clear BK viremia after renal transplantation. Maybe it was too little, too late, and for too short of time. However, higher doses, earlier initiation, or extended duration might lead to unintended consequences, such as adverse drug reactions, development of drug-resistant infections, and Clostridium difficile infections. Overall, this is an important negative study regarding the use of fluoroquinolones to treat BK viremia in renal transplant recipients.

For now, screening for BK viremia and preemptive reduction in immunosuppression upon detection remain the best strategy to prevent progression from BK viremia to nephropathy (18,19). Unfortunately, the use of fluoroquinolones to prevent or treat BK viremia does not appear to be a viable therapeutic option, and there is an urgent need for development of a safe and efficacious antiviral agent against BK virus, as well as a prophylactic vaccine.

Disclosures
None.

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