Treatment of Polyomavirus-Associated Nephropathy With the Association of Sirolimus and Leflunomide

Caroline Lamarche, Anne Boucher, Raymond Dandavino, Lynne Senécal, Suzon Collette, Duy Tran, Michel Vallée

Dear Editor:

Polyomavirus-associated nephropathy (PVAN) is an important cause of graft failure, affecting up to 10% of renal transplant patients. Fifty percent of polyomavirus viremia occur in the first 3 months, and 95% in the first 2 years after transplant. In the early reports, up to 50% of viremia resulted in graft loss. Polymerase chain reaction (PCR) BK virus viremia is a sensitive and specific method to predict viral nephropathy, as it precedes PVAN by a median of 8 weeks. Systematic screening followed by preemptive reduction of immunosuppression is now widely recognized to prevent and treat PVAN. However, this strategy may increase the risk of acute graft rejection. The study was approved by the Ethical Review Committee of the Institute. All of the protocols conformed to the ethical guidelines of the 1975 Helsinki Declaration.

Clinicians are now looking for drugs with antiviral activity allowing a decrease in viral replication without affecting the overall level of immunosuppression. In addition to its immunosuppressive property, leflunomide significantly inhibits BK virus DNA replication in vitro. Sirolimus also is an interesting option because inhibition of the mTOR pathway can impair BK virus large T protein expression. In 2010, Liacini and associates reported the use of leflunomide in combination with sirolimus to inhibit the protein kinase pathway in vivo.

In this retrospective cohort study, we reviewed the clinical data of all renal allograft recipients transplanted from June 2006 to December 2010 at Maisonneuve-Rosemont Hospital to analyze the incidence, treatment, and prognosis of BK viremia. Patients were routinely screened for BK viremia by real time PCR. Before June 2010, screening was every 3 months for a 2-year period. After June 2010, PCR was obtained monthly for the first 6 months after transplant, every 2 months for the following 6-month period, and every 3 months for the second year. A graft biopsy was performed if BK viremia was significant (≥ 10⁴ copies/mL) and persistent or if it was associated with graft dysfunction. Every patient with PVAN had a diminution of immunosuppression level, but it was left to each clinician’s discretion.

In our cohort 43 patients (24.9%) developed BK viremia of more than 100 copies/mL and 18 patients (10.4%) had biopsy-proven PVAN. In the PVAN cohort, mean age at transplant was 49 years old, all were a first graft, 13/18 were men, 15/18 were white, 17/18 had a cadaveric graft, and 6 patients had simultaneous JC viremia. The induction consisted of IL-2 receptor antagonists in 16 recipients and antithymocyte globulin in 2 recipients. The sirolimus-leflunomide combination was used in 8 out of 18 patients. In the 10 others, 2 were on a leflunomide and tacrolimus combination, 2 were on sirolimus and a reduced dose of mycophenolate mofetil (MMF), and 6 were on a reduced dose of MMF with tacrolimus (Table 1). Duration of viremia was significantly longer with the sirolimus-leflunomide combination compared to other strategies (Table 1). Mean leflunomide blood level was 36 µg/mL.

Why was the outcome of patients treated with the combination of sirolimus and leflunomide for PVAN so poor? A771726, the active metabolite of leflunomide, has antiviral effect by inhibiting pyrimidine synthesis at a low level (10 µg/mL) and tyrosine kinase at high level. The effect on BK virus replication can be reversed by the addition of uridine at a leflunomide level of 10 µg/mL. With...
leflunomide levels ≥ 40 μg/mL, the effect on BK virus replication cannot be reversed in vitro. Nevertheless, the effect of high leflunomide level on BK virus replication remains controversial in vivo. Therefore, mean leflunomide level, although slightly low in our cohort, should not explain the failure of viremia clearance. There are even less data to support the use of sirolimus in PV AN patients. Sirolimus can decrease BK virus large T protein expression but has no effect on BK virus DNA replication. Although sirolimus does not inhibit BK virus specific T-cell activation, it may inhibit its proliferation and expansion in a dose-dependent manner. In our study, the poor efficacy of the combined sirolimus-leflunomide therapy in PVAN patients might be explained by the ineffectiveness of sirolimus in vivo. Also, there was a potential selection bias as the combination of leflunomide and sirolimus was reserved for those not responding to the usual diminution of immunosuppression.

In conclusion, this is the first study relating the use of the combination of sirolimus and leflunomide for the treatment of PVAN. In this retrospective study, clearance of BK virus viremia was not improved by this combination. However, it is not a case-control study and groups were not equivalent Therefore, the efficacy of the combination of sirolimus and leflunomide must be confirmed by a randomized, controlled, multicenter clinical trial, which is already going on (the BK: KIDNI Trial; BK Viremia: kinase Inhibition to Decrease Nephropathy Intervention Trial; ISRCTN40228609).

**Key words:** Renal transplant, BK virus, Antirejection therapy

**References**