BK Virus and Nephropathy in Kidney Transplant Recipients

DEAR EDITOR

Polyomavirus-associated nephropathy (PVAN) remains an important cause of allograft dysfunction and graft loss after kidney transplantation [1, 2]. Furthermore, up to 10% of renal transplant recipients show a viral reactivation that can lead to PVAN and delayed treatment results in high risk of graft loss (up to 80%) [3]. We read with interest the article published by Pakfetrat, *et al* [2], and would like to comment on that.

BKV infection can be detected by viral serology, urine cytology, or nucleic acid testing methods such as quantitative PCR (Q-PCR) analysis of urine, plasma or blood samples [1, 2]. Viral load monitoring in urine and plasma by real-time PCR after transplantation is the most common diagnostic tool to detect viral reactivation [3]. Based on the results of large cross-sectional and prospective longitudinal studies using nucleic acid testing for the detection of BKV reactivation after renal transplantation, it seems that, with time, approximately 5%–15% of patients become BKV-positive in their plasma and 20%–40% of patients become BKV-positive in their urine [1]. Progression of BK viruria to PVAN without concomitant viremia is exceptionally rare [1]. There are some protocols for screening BKV. Several investigators suggest to first check the viremia, while others recommend checking viruria [1, 4]; however, all experts agree on the need to combine both plasma and urine determinations of the BKV DNA load in order to identify renal transplant patients at high risk of BKV-associated nephropathy [5]. In addition, the screening of kidney transplant recipients with nucleic acid testing of plasma or urine, has been controversial still [4].

In the lack of standardized Q-PCR assays for BKV, clinical and research laboratories have developed their own in-house Q-PCR methods using various primers, probes and standards. As a result, making comparisons of BKV loads among laboratories is difficult and guidelines for quantitative cut-off values for viral load in urine and plasma are only of limited use in screening strategies or monitoring protocols [1].

In 2005, guidelines for BKV screening using nucleic acid testing were formulated and included quantitative cut-off values for viral loads as a threshold for performing additional testing. The guidelines stated that if urine viral loads exceeded 10^7 copies/mL or if plasma viral loads were higher than 10^4 copies/mL for more than three consecutive weeks, a renal biopsy should be considered [1].

Diagnostic cut-off values for PVAN in urine samples varying between 7.9×10^6 and 2.5×10^7 copies/mL, and plasma cut-off values between 3.0×10^3 and 3.2×10^4 copies/mL, clearly illustrate the inter-assay variability [1]. The observed substantial inter-assay variability occurs for a number of reasons—differences in sample type (urine, serum, plasma, and blood), differences in DNA extraction methods, different features of primer and probe design (including effects of BKV subtype-associated polymorphisms), different amplification conditions, and different choices of reference material (*e.g.*, mixed-patient standard *vs* Dunlop strain genome plasmid) [1].

Finally, we completely agree that screening methods and detection of BK virus and BKVN are different and further studies to standardize and uniform the protocols are needed.

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Authors' Reply

DEAR EDITOR,

Polyomavirus BK and its related clinical complications, especially BKVAN, are among the important viral complications with roles in the pathogenesis of nephropathy in kidney transplant recipients. Our center has focused on this subject to evaluate and study different basic and clinical aspects of BK virus pathogenesis. Our article is the first report on this issue. In our report, we only evaluated a small group of transplant recipients who suspected with BKVAN by evaluating BK viral load in plasma and FFPE tissue samples taken from the patients. In our report, the presented cut-off value for plasma and tissue load of BK viral genome were not used to confirm direct correlation between BK viral active infection and BKVAN. The cut-off value was used as a predictive value to screen the suspected patients from others for future follow-up. However, the results need to be confirmed and standardized in further studies.

Before introduction of noninvasive diagnostic tests for polyomavirus BK replication, BKVAN was mostly diagnosed in advanced stages based on histological examination of the kidney biopsy specimens [1]. In these years, molecular methods including PCR and real-time PCR have significantly contributed to rapid accurate diagnosis of polyomavirus BK [2], and targeted reduction of immunosuppression to resolve infection and improve renal function [3, 4]. Screening for BK virus infection in urine or plasma samples taken from patients, is a matter of debate; controversy exists on importance of each of them in evaluation of viral pathogenesis. The importance of molecular analysis of BK viruria and urine cytology for the diagnosis of BKVAN is clearly mentioned in earlier reports. A negative test result in BK viruria and cytology has a very high negative predictive value (almost 100%). However, a positive test in urine is not associated with an increased risk of BKVAN and requires evaluation of BK viremia in those recipients whose BK viruria exceeds the established thresholds. In addition, Molecular analysis of BK viruria is expensive and time-consuming and needs more follow-up as BK viremia [5]. There is also a direct correlation between BK viremia load, degree of graft dysfunction, severity of histological BKVAN tissue patterns, and number of infected renal cells in histological slides [6]. Such correlation suggests that viremia occurs mainly, if not entirely, from the viral replication started in the kidney. This is the reason why the amount of viremia is more predictive for BKVAN than presence of viruria [7-10]. Therefore, use of real-time PCR protocols to detect BK virus in plasma is now recommended by Kidney Disease: Improving Global Outcomes (KDIGO) [11].

On the hand, researchers recently reported marked variability between commonly used polyomavirus BK load assays related to rearrangements occurred in different loci of BK virus genome sequences, especially in NCCR [12, 13]. Therefore, neither polyomavirus BK real-time PCR protocol nor the cut-off value for significant viral replication has so far been completely standardized [1, 14-16]. Few data have been published on the specificity and sen-

sitivity of blood BK virus load measurement for BKVAN screening. In 2005, preliminary recommendations were published proposing that a threshold value of 1.0×104 copies/mL for presumptive BKVAN should be followed by an allograft biopsy [17, 18]. However, Hoffman, et al, and others recently reported marked variability between commonly used BK viral load assays and diagnostic cut-off values [8, 19, 20]. Based on these results, we believe that in the absence of standardization for measurement of blood BK virus load, a threshold value for BKVAN screening should be established for each different molecular assay protocols.

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