Viremia Negativization After BK Virus Infection in Kidney Transplantation: A National Bicentric Study

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ABSTRACT

Background. BK virus (BKV) infection represents a potentially dreadful complication after kidney transplantation (KT). When BK viremia is detected, the best therapeutic approach remains not entirely clarified. Critical elements of BK viremia treatment are immunosuppression minimization and introduction of drugs like leflunomide, everolimus, and fluoroquinolones. The study aimed to analyze the results of the BK viremia management in 2 collaborative Italian centers.

Methods. Ten patients undergoing KT in the 2 collaborative Italian centers of Sapienza University of Rome and University of L'Aquila from January 2013 to December 2017 and showing a post-KT diagnosis of BK viremia were retrospectively investigated.

Results. Mean time from KT to BKV positivity was 7 months (range: 1-19 months). At diagnosis, the mean viral load was 683,842 copies/mL (range: 5800-4,052,415 copies/mL), with an average zenith of 2,428,410 copies/mL (range: 6762-18,022,500 copies/mL). In the 5 patients with BKV nephropathy, we observed a switch from antimetabolite to leflunomide (n = 5), a switch from tacrolimus to everolimus (n = 3), or an introduction of fluoroquinolones (n = 3). BKV clearance was achieved in 3 patients.

Conclusions. Early BKV diagnosis and stepwise minimization of immunosuppression remain the first-line approach in patients with BK viremia. In the presence of BKV nephropathy, a combination of antiviral drugs like leflunomide and fluoroquinolones/everolimus should favor viremia clearance.

BK virus (BKV) infection represents a potentially dreadful complication after kidney transplantation (KT), mainly in the case of BKV nephropathy (BKVN) [1]. The prevalence of BK viremia in the KT population ranges from 7% to 27%, evolving into BKVN in 1% to 27% of patients [2]. The peak of BKV infection incidence is observed 2 to 6 months post KT. If the diagnosis is not rapidly assessed, this infection eventually results in permanent graft dysfunction or loss. Therefore, a preventive strategy with active surveillance has been improved [1,2]. However, when BK viremia is detected, the best therapeutic approach remains not entirely clarified.

The critical element of BK viremia treatment is immunosuppression minimization. However, this strategy is not free of risks, possibly being associated with increased rates of acute rejection, eventually worsening the BKV infection after the use of antirejection therapy. Several pharmacologic strategies have also been proposed for treating the BKV infection, such as cidofovir, leflunomide, intravenous immunoglobulin, and fluoroquinolones [1,2].

The study aimed to analyze the results of the BK viremia management after KT in 2 collaborative Italian centers.

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MATERIALS AND METHODS

A retrospective analysis was carried out on 318 patients undergoing a KT in the 2 collaborative Italian centers of Sapienza University of Rome and University of L'Aquila from January 2013 to December 2017. We started the present study from 2013 because all the patients with a BKV diagnosis before this specific period were managed only with an immunosuppression reduction approach, without any specific drug used with a curative intent against the virus.

In accordance with the Kidney Disease: Improving Global Outcomes guidelines, BK viremia was routinely searched 1. every 2 weeks during the first post-KT month; 2. monthly during the first 6 months; 3. every 3 months during the first 2 years; 4. annually after the first 2 years; and 5. in all patients with renal function impairment [3]. In patients with a positive result, BK viremia was investigated biweekly until undetectable. When BKV plasma viral load was >10,000 copies/mL, we adopted an immunosuppression minimization protocol based on 1. antimetabolite agent dose reduction by 50% and subsequent discontinuation, if necessary; 2. steroid dose reduction by 25% to 50% in one or more steps; and 3. calcineurin inhibitor (CNI) dose reduction by 25% to 50% in 1 or more steps. Graft biopsy was always performed in patients with 1. viremia >100,000 copies/mL or 2. allograft dysfunction, with the intent to confirm the possible diagnosis of BKVN. In patients with BKVN, apart from the immunosuppression minimization, we 1. switched CNI with mammalian target of rapamycin inhibitors or 2. introduced leflunomide and/or fluoroquinolones.

RESULTS

Ten (3.1%) patients showed BK viremia. Demographic and BKV characteristics are shown in Table 1. Nine patients were men, with a mean age at transplant of 49 ± 10.7 years. One living donation and retransplant were observed. Five patients had 4 HLA mismatches, 3 had 3 mismatches, and 2 had 5 mismatches. In 3 patients, induction with antithymocyte globulin was performed. In all the patients, immunosuppression maintenance was done using tacrolimus, mycophenolate mofetil, and prednisone. Two episodes of acute cellular rejection (Banff Grade 1B and 2A) treated with steroid pulses were observed before BK viremia detection.

The mean time from KT to a BKV positive PCR was 7 months (range: 1-19 months). In the 2 patients previously treated for the acute rejection, viremia was found 19 months after KT but 3 and 5 months after the antirejection therapy, possibly because of the new immunosuppression peak. At diagnosis, mean viral load was 683,842 copies/mL (range: 5800-4,052,415), with an average zenith of 2,428,410 copies/mL (range: 6762-18,022,500). BKVN was histologically confirmed in 5 patients: in 2 patients, an acute contextual rejection (Banff Grade 1A and 1B) was detected. During the infection period, serum creatinine achieved an average increase of 101% (range: 7%-580%) compared with pre-BKV values. Immunosuppression was always reduced. In 5 patients, mycophenolate mofetil was substituted by leflunomide 40.0 mg daily; adverse effects associated with leflunomide use were anemia (1 patient) and pruritus (2 patients). In 3 patients, fluoroquinolones 500.0 mg daily were added. In 3 patients, a switch from CNI to everolimus was observed. In 2 patients, tacrolimus was withdrawn. BKV clearance was achieved in 3 patients after 6 months (ranges: 3-11 months) from the diagnosis.

Table 1. Demographic and Treatment Variables

Variables	Mean ± SD or n (%)
Mean age, y	49 ± 10.7
Sex, male	7 (70.0)
Deceased donor	9 (90.0)
HLA mismatch	
5	2 (20.0)
4	5 (50.0)
3	3 (30.0)
Retransplant	1 (10.0)
Induction therapy	
Basiliximab	7 (70.0)
ATG	3 (30.0)
Initial maintenance therapy	
TAC + MMF + steroid	10 (100.0)
ACR episodes before BKV infection	
Banff 1B	2 (20.0)
Banff 2A	1 (10.0)
BKV therapy	
IS minimization	10 (100.0)
Switch TAC/EVE	1 (10.0)
Switch MMF/quinolone	1 (10.0)
Switch MMF/leflunomide	2 (20.0)
Switch MMF/leflunomide + quinolone	1 (10.0)
Switch MMF/leflunomide + quinolone and switch TAC/EVE	2 (20.0)

ACR, acute cellular rejection; ATG, anti-thymocyte globulin; BKV, BK virus; EVE, everolimus; IS, immunosuppression; MMF, mycophenolate mofetil; SD, standard deviation; TAC, tacrolimus.

Interestingly, all the patients showing BK viremia clearance received leflunomide. In 2 of these 3 patients, a biopsy-proven BKVN was detected before the treatment, also requiring CNI withdrawal for the treatment. Patient and graft survival were 100% after a mean follow up of 17 months from the diagnosis of positive BK viremia (range: 6-41 months).

DISCUSSION

BKV infection represents a challenge in the KT setting. Several donor- and recipient-related features have been identified as risk factors for the BKV activation, like the immunosuppressive regimens, the type of donor (deceased vs living), the recipient's male sex, the history of re-KT, the recipient's age, the use of ureteral stents, the delayed graft function, and the acute rejection episodes [4]. BKV should be carefully managed, mainly because of the risk of its evolution to BKVN [1,5]. Preemptive monitoring represents the current standard approach with the intent to prevent BKV infection. We adopted in the present series the Kidney Disease: Improving Global Outcomes recommendations [3], observing a BK viremia incidence in approximately 3% of patients, with a peak within 6 months from KT. Our data are in line with previously reported series [6].

The cornerstone of treatment of BKV infection is the immunosuppression minimization [7,8], but the best management, mainly in patients with BKVN, is still unclear. In our experience, we initially adopted a hybrid immunosuppressive minimization approach in patients with less severe

viremia rates. We performed a combined reduction of steroids, CNI, and antiproliferative drugs in 1 or 2 steps, showing a good viremia control in 3 patients without the need for further therapeutic strategies.

The drugs commonly used for the treatment of patients with more severe BK viremia are cidofovir, intravenous immunoglobulin, everolimus, fluoroquinolones, and leflunomide [9–14].

The cidofovir treatment should be considered a second-line choice in BKVN because of its high renal and medullar toxicity. Similar consideration should be made for immunoglobulin therapy, potentially using it only in patients with simultaneous acute rejection [9–11]. In our experience, we did not use these drugs, so we cannot give final comments on their utility.

In our experience, we used a combination of everolimus, fluoroquinolones, and leflunomide for the management of the 5 patients showing a BKVN.

As for the everolimus, international literature demonstrated a trend toward improved viral clearance after the switch from CNI [12,13]. Nevertheless, in one-third of the reported patients, the viremia persisted or even increased, and higher rates of concomitant acute rejection were reported [14].

Fluoroquinolones should inhibit but do not wholly eradicate BKV replication in renal proximal tubular epithelial cells [10]. Therefore, there is not enough evidence to support the use of fluoroquinolones in the treatment of BKV, mainly in light of the possible side effects [15].

Leflunomide contextually presents immunosuppressant and antiviral properties, theoretically being able to limit the virus replication and to avoid the risk of acute rejection [16]. As an example, we used the leflunomide in 1 patient with a pre-KT panel reactive antibody (PRA) $> 90\%$ and 2 patients with a previous episode of acute rejection. Interestingly, we observed a viremia clearance in 50% of patients treated with leflunomide, a higher percentage in respect to the previously reported studies [17,18].

We can only assume that the combination of the approaches (minimization and leflunomide + everolimus or fluoroquinolones) should explain for this result. Unfortunately, the smallness of the cohort does not give us the opportunity to report more robust results.

CONCLUSION

Our study reinforces the concept that early diagnosis with monitoring reduces the damage caused by BKV and its evolution in BKVN. A stepwise minimization of immunosuppressive therapy remains the first-line approach in patients with low-to-moderate BK viremia. In patients with BKVN, a combination of antiviral drugs like leflunomide + fluoroquinolones/everolimus seems to be useful in favoring the viremia clearance and in avoiding graft loss. Further more extensive studies are necessary with the intent to better guide therapy and improve outcomes for BKVN.

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