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Increasing net immunosuppression after BK polyoma virus infection

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Abstract

Background: Reducing immunosuppression can effectively treat BK viremia (BKV) and BK nephropathy, but has been associated with increased risks for acute rejection and development of donor-specific antibodies (DSA). To date there have been no systematic evaluations of re-escalating immunosuppression in transplant patients with resolving BKV. Importantly, the safety of this approach and impact on graft survival is unclear.

Methods: We performed a single-center retrospective review of kidney transplant recipients between July 2011 and June 2013 who had immunosuppression reduction after developing BKV (plasma PCR ≥ 1000 copies/ml). Changes in immunosuppression and patient outcomes were tracked until occurrence of a complication event: biopsy-proven acute rejection (BPAR), detection of de novo DSA, or recurrent BKV. Patients were grouped according to whether or not net immunosuppression was eventually increased.

Results: Out of 88 patients with BKV, 44 (50%) had net immunosuppression increased while the other 44 did not. Duration of viremia, peak viremia, induction, and sensitization status were similar between the two groups. In a Kaplan-Meier analysis, increasing immunosuppression was associated with less BPAR ($P = .001$) and a trend toward less de novo DSA development ($P = .06$). Death-censored graft survival ($P = .27$) was not different between the two groups. In the net immunosuppression increase group, recurrent BKV occurred in 22.7% without any BKV-related graft losses.

Conclusion: These findings support potential benefits of increasing immunosuppression in patients with low-level or resolved BKV, but prospective trials are needed to better understand such an approach.

KEYWORDS

BK polyoma virus, graft survival, immunosuppressive regimens, infectious complication, kidney transplant, rejection: T-cell–mediated (TCMR)

Abbreviations: AMR, antibody-mediated rejection; BKV, BK viremia; BKVN, BK virus nephropathy; BPAR, biopsy-proven acute rejection; CNI, calcineurin inhibitor; DSA, donor-specific antibodies; IQR, interquartile range; ISx, immunosuppression; IVIG, intravenous immune globulin; MFI, mean fluorescence intensity; PCR, polymerase chain reaction; PRA, panel reactive antibody; rATG, rabbit anti-thymocyte globulin; SD, standard deviation; TCMR, T-cell–mediated rejection.

1 | INTRODUCTION

BK polyomavirus resides latent in the renourinary epithelium and can reactivate after kidney transplant to cause irreversible renal tubular damage and progressive graft dysfunction.[1] BK viremia (BKV) occurs in 10%-30% of kidney transplant recipients while 1%-10% of patients develop BK virus nephropathy (BKVN).[2,3] BK infection is considered a sequela of over-immunosuppression, and given the lack of effective anti-viral therapies, reducing immunosuppression has emerged as the primary management strategy for BKV.[4,5]

Accumulating data suggest that BKV and BKVN are associated with the development of de novo donor-specific antibodies (DSA) as well as acute rejection.[6–12] In biopsy series documenting the histologic evolution of definite and/or presumptive BKVN, approximately 40% of graft losses were compounded by rejection and Drachenberg et al reported that rejection increased the risk of graft loss by fourfold.[6,7] Rejection may be explained through cytokine release and by T cells directed at BK virus thereby triggering an alloreactive immune response.[13,14] Another hypothesis is that reduced immunosuppression as part of BKV treatment elicits immune reactivation and subsequent rejection. Given the threat to graft survival after insults from BKVN and successive rejection ensue, immunosuppression management in these patients needs to be critically evaluated.[15,16]

To the best of our knowledge, the impact of re-escalating immunosuppression in patients with resolving BKV has not been systematically studied. Furthermore, the safety of this approach and the effects on rejection and graft survival have not been explored. At our institution, a variety of approaches existed amongst transplant nephrologists' immunosuppressive medication adjustments in patients with improving BKV, enabling a retrospective comparison between different management approaches. In this study, patients' immunosuppressive medications were initially decreased to treat BKV. We then compared outcomes between patients who subsequently had a net increase in their immunosuppression regimen and patients whose immunosuppression was not increased.

2 | MATERIALS AND METHODS

2.1 | Immunosuppression

Protocol induction therapy included rabbit anti-thymocyte globulin (rATG) 5 mg/kg cumulative dose for high-immunologic risk patients (panel reactive antibody [PRA] >20%, African-American, living-unrelated donor transplant, ABO incompatible transplant, positive crossmatch, delayed graft function, presence of DSA, or history of de-sensitization therapy) while all other patients received no induction. Basiliximab could be substituted for rATG in individuals deemed to be at excessive infectious risk. Triple-drug therapy with tacrolimus, mycophenolate mofetil, and prednisone were used for maintenance immunosuppression. Tacrolimus trough targets were 8-12 ng/mL (0-90 days), 6-10 ng/mL (91-120 days), and 4-8 ng/mL (>120 days), and all patients were discharged on mycophenolate mofetil 2000 mg/day or mycophenolate sodium 1440 mg/day. Prednisone was decreased to 5-10 mg/d within 6 months of transplant.

2.2 | BKV screening and management

Institution protocol required plasma BK PCR screening (Viracor™ assay, Viracor Eurofins, Lee's Summit, MO) at 1, 3, 6, 9, 12, 18, and 24 months, and patients underwent protocol biopsies at 3, 6, and 12 months post-transplant. Additionally, a plasma BK PCR was ordered when an indication biopsy was performed for graft dysfunction.

Immunosuppression was generally modified in patients with a plasma BK PCR ≥ 1000 copies/mL and involved a stepwise approach of holding or dose reducing mycophenolate by 50% followed by a reduction in the tacrolimus target trough to 3-5 ng/mL. Tacrolimus trough was adjusted if patients did not achieve a 50% reduction in viral load or a plasma BK PCR value < 5000 copies/mL after 8 weeks of reduced mycophenolate dosing. If biopsy-proven BKVN occurred, mycophenolate was discontinued. Leflunomide and intravenous immune globulin (IVIG) could be used at clinician discretion.

2.3 | Donor-specific antibody screening

Donor-specific antibody screening was performed at 12 months and yearly thereafter for 5 years total as well as at the time of indication biopsy using the Luminex® single antigen bead assay (One Lambda, Inc, West Hills, CA). Patients at high immunological risk (positive crossmatch, preformed DSA, history of antibody-mediated rejection [AMR] or desensitization) or intermediate immunological risk (peak PRA > 20%, re-transplant, African American, T-cell–mediated rejection [TCMR] ≥Banff 2A) underwent additional DSA screening either monthly for the first 6 months or at months 3 and 6, per the high and intermediate immunological risk protocols, respectively.

2.4 | Study design

This single-center study was completed by retrospective chart review of kidney and combined-kidney transplant recipients transplanted between July 2011 and June 2013. Patients with less than one year of BK PCR screening from transplant were excluded. The index event for study inclusion was defined as post-transplant BKV with a peak PCR of ≥1000 copies/mL which was generally managed initially by net immunosuppression reduction. Each immunosuppression dose adjustment after the index event was tracked to determine if immunosuppression doses were eventually re-escalated and patients were divided into two groups: net immunosuppression increase or no net immunosuppression increase. Patients were included in the net immunosuppression increase group if their

mycophenolate dose was increased and/or the tacrolimus target trough was increased compared to the initial reduction made at the time of the index event.

All charts were screened for two complications indicative of under-immunosuppression, including biopsy-proven acute rejection (BPAR: TCMR ≥Banff 1A or AMR) and de novo DSA with ≥700 mean fluorescence intensity (MFI). Biopsies were read according to the 2007 Banff scoring.[17] In the group of patients whose net immunosuppression was eventually increased after BKV improved, charts were also screened for recurrent BKV, a complication suggestive of over-immunosuppression. Study definition of recurrent BKV was met if a net increase in immunosuppression was followed by a rising viral load that prompted the clinician to subsequently decrease the level of immunosuppression.

Study follow-up ended when the first of any three complication events occurred, treating them as competing endpoints: BPAR, de novo DSA, or recurrent BKV. Immunosuppressant dosing at least 4 weeks prior to one of these complications, or at the date of last lab if no complication occurred, was used to classify patients into either the net immunosuppression increase group or no net immunosuppression increase group. The two groups were compared for all-cause graft failure and composite complication comprised of BPAR and de novo DSA. Recurrent BKV was reviewed separately to evaluate safety of increasing net immunosuppression in patients with improving BKV.

2.5 | Statistical analysis

For statistical comparison of the demographic data, the chi-square or Fisher's exact test were used for categorical variables while the Student's *T* test or Mann-Whitney *U* tests were used for continuous variables as appropriate. Mean ± standard deviation (SD) was calculated for normally distributed continuous data. For non-normally distributed data, median and interquartile range (IQR) were reported. Kaplan-Meier survival analyses with log-rank test were conducted to compare the two groups for time to BPAR, de novo DSA and composite complication events.

3 | RESULTS

Out of 422 kidney transplant recipients that were screened, 88 had BKV with a peak PCR ≥ 1000 copies/mL. Patients were mostly Caucasian (62.5%), male (68.1%), received a deceased donor transplant (54.5%), and rATG (71.6%) for induction. The median viral load that prompted initial reduction in immunosuppression was 7200 copies/mL (IQR: 2300-33 000 copies/mL) in the no net immunosuppression increase group and 7100 copies/mL (IQR: 3400-14 350 copies/mL) in the net increase group ($P = .58$). BKV was managed by either reduction or discontinuation of mycophenolate in 86 (97.7%) patients and 15 patients in each group had target tacrolimus troughs decreased. Net immunosuppression was reduced for a second time in 36 patients after the viral load increased in 24 (66.7%) patients or due to insufficient viral load decline in 12 (33.3%) patients. Of these 12 patients, 11 (91.7%) patients had immunosuppression reduced again after the plasma BK PCR decreased by less than 0.5 $\log_{10}$ copies/mL after a median of 46 days (IQR: 27-82.3 days) from when immunosuppression was first reduced.

There were 44 patients who had an eventual net increase in immunosuppression after the index BKV event. Immunosuppression was increased in 18 (40.9%) patients after the virus was no longer detected by plasma PCR, and in 26 (59.1%) patients who had low-level viremia, with a median viral burden of 1000 copies/mL (IQR: 300-1725 copies/mL). Patient characteristics were well matched between patients with and without a net increase in immunosuppression (Table 1). Importantly, the median of the peak viral load in the group with no increase in net immunosuppression was 7200 copies/mL (IQR: 2375-38 350 copies/mL) and was comparable to 10 200 copies/mL (IQR: 4400-50 025 copies/mL) in the group with an increase in net immunosuppression ($P = .23$). Likewise, near-equal proportions of patients in the no net increase (45.5%) or net increase (50.0%) groups had a peak PCR ≥ 10 000 copies/mL ($P = .67$). The median time from transplant to BKV onset was similar ($P = .47$), 160.5 days (IQR: 55.8-240.5 days) in the group without a net increase and 101.5 days (IQR: 58.3-198.8 days) in the group with a net increase in immunosuppression.

Patients had a median follow-up of 3.4 years (IQR: 1.1-5.0 years), which concluded when they had the first complication event (BPAR, de novo DSA or recurrent BKV) or at last lab follow-up if no complications occurred. Patients in the net increase group were more likely to achieve initial BK viral clearance (77.3% vs 52.3%, $P = .01$). However, the median times from index event to BK clearance were similar between the net increase group and the no net increase group (176 days [IQR: 99-376 days] vs 126 days [IQR: 72-175 days], respectively; $P = .10$). Numerically more patients in the no net increase group experienced a complication event (63.6% vs 50%, $P = .20$), which resulted in a shorter time from index event to complication event of 1.2 years (IQR: 0.4-3.6 years) in the no net increase group compared to 3.5 years (IQR: 1.1-5.0 years) in the net increase group ($P = .001$). One patient in each group received leflunomide, and there was no significant difference in frequency of IVIG administration between the net immunosuppression increase (11 of 44 patients, 25%) and no net increase (5 of 44 patients, 11.4%) groups ($P = .10$). Mean estimated glomerular filtration at 12 and 24 months after transplant were not significantly different between the groups.

3.1 | Graft survival

Overall graft survival was better when net immunosuppression was increased although there was no difference in death-censored graft failure between the groups (Figure 1A,B). Of the seven patients with death-censored graft failure in the group without a net increase in immunosuppression, 5 (71.4%) graft losses were attributed to chronic rejection, and one graft loss was related to acute AMR and

TABLE 1 Demographics and baseline characteristics

	Net ISx not increased (n = 44)	Net ISx increased (n = 44)	*P*-value
Mean age, year (SD)	52 (15.7)	51 (14.6)	.65
Male, n (%)	30 (68.1)	30 (68.1)	1
Race, n (%)			
Caucasian	27 (61.4)	28 (63.6)	.85
Black	12 (27.2)	9 (20.5)	
Asian	1 (2.3)	2 (4.5)	
Other	4 (9.1)	5 (11.4)	
Cause of ESRD, n (%)			
Hypertension	6 (13.6)	7 (15.9)	.57
Diabetes mellitus	13 (29.6)	18 (40.9)	
Polycystic kidney disease	3 (6.8)	6 (13.6)	
Glomerulonephritis	6 (13.6)	3 (6.8)	
FSGS	2 (4.6)	1 (2.3)	
Other	14 (31.8)	9 (20.5)	
Re-transplant, n (%)	3 (6.8)	2 (4.5)	1
Simultaneous pancreas-kidney transplant, n (%)	2 (4.5)	2 (4.5)	1
Heart-kidney transplant, n (%)	1 (2.3)	0	1
Liver-kidney transplant, n (%)	1 (2.3)	0	1
Mean PRA, % (SD)			
Class I peak	17.6 (27.3)	17.0 (30.8)	.93
Class II peak	19.5 (32.0)	10.0 (23.5)	.12
Donor characteristics, n (%)			
Deceased	23 (52.3)	25 (56.8)	.5
Living related	9 (20.4)	5 (11.4)	
Living unrelated	12 (27.3)	14 (31.8)	
Induction, n (%)			
rATG	30 (68.2)	33 (75.0)	.72
Basiliximab	2 (4.5)	1 (2.3)	
None	12 (27.3)	10 (22.7)	
Leflunomide use, n (%)	1 (2.3)	1 (2.3)	1
IVIG use, n (%)	5 (11.4)	11 (25.0%)	.1
Delayed graft function, n (%)	5 (11.4)	7 (15.9)	.76
Mean creatinine, mg/dL (SD)			
3 month	1.5 (0.6)	1.4 (0.4)	.37
6 month	1.4 (0.5)	1.4 (0.8)	.93
12 month	1.5 (0.5)	1.3 (0.4)	.07
24 month	1.5 (0.7)	1.4 (0.5)	.29
Mean eGFR[a], ml/min per 1.73 m^2 (SD)			
12 month	53.3 (16.4)	59 (16.2)	.11
24 month	53.7 (18.6)	56.8 (18.5)	.45

Abbreviations: ESRD, end stage renal disease; FSGS, focal segmental glomerulosclerosis; ISx, immunosuppression; IVIG, intravenous immune globulin; PRA, panel reactive antibody; rATG, rabbit anti-thymocyte globulin; SD, standard deviation.

[a]Calculated by Modification of Diet in Renal Disease (MDRD) equation.

BKVN each. In the group with a net increase in immunosuppression, 2 of 3 (66.7%) death-censored graft failures were from chronic rejection and one graft loss was related to cardiorenal disease. Cardiovascular events were the most common cause of death: two

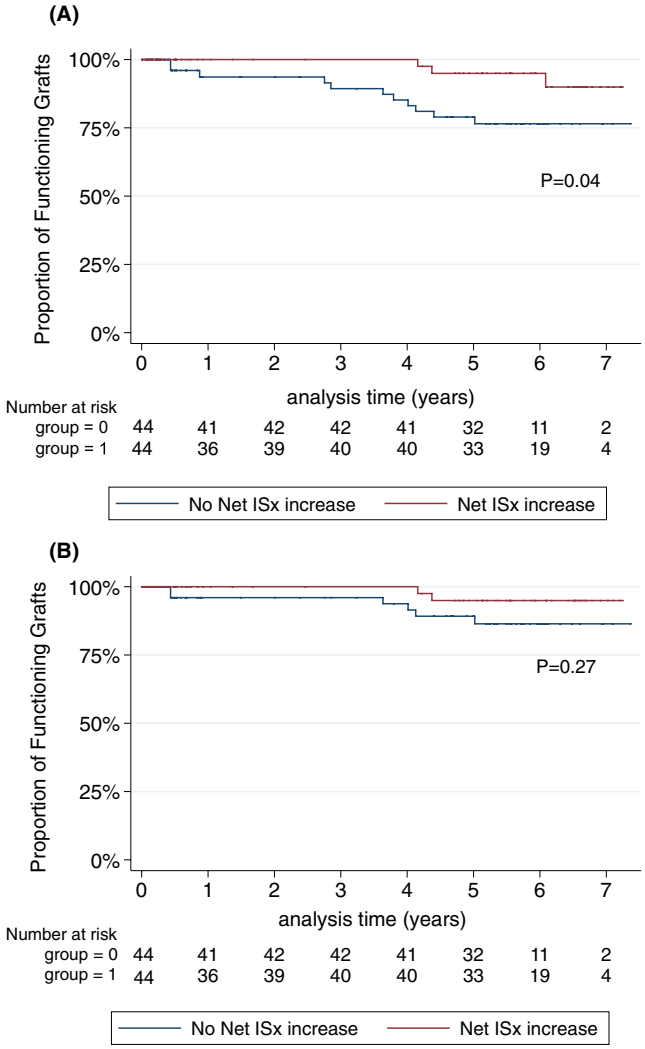

FIGURE 1 Graft Survival. (A) Overall graft survival (non-censored for death; $P = .04$) but not (B) death-censored graft survival ($P = .27$) was worse when the net immunosuppression was not increased

patients in the net increase group, one of whom was a heart-kidney transplant recipient, and one patient in the group without a net increase. An additional three patients whose net immunosuppression was not increased died, one from infection and two deaths from unknown causes.

3.2 | Biopsy-proven acute rejection and de novo DSA

Biopsy-proven acute rejection episodes before the onset of index BKV as well as rejection episodes that occurred after index BKV up to the first complication event/last lab follow-up (if no complication event occurred) are recorded in Table 2. Rates of BPAR before index BKV were not significantly different between groups ($P = .33$). Of the 19 patients who developed BPAR after BKV, only one had a previous BPAR (Banff 1A) episode, and this patient was in the no net increase group. Overall, there were 19 (21.6%) patients in the entire cohort with BPAR that occurred after the development of BKV, of which 14 (73.7%) patients were in the no net increase group. The majority (89.5%) of BPAR episodes after BKV were T-cell–mediated rejections.

The SV40 staining was negative in 16/19 (84.2%) patients and not tested in 2/19 (10.5%) patients diagnosed with BPAR. Although one patient with BPAR (Banff 1B) also had scattered weak nuclear SV40 positivity of unclear significance on biopsy, the diagnosis of rejection was strengthened by the diffuse inflammation and tubulitis in many areas away from the positive signal. Of all patients with BPAR after BKV, only the two patients diagnosed with AMR had positive C4d staining. As assessed by survival estimates, significantly more patients without a net increase in immunosuppression developed BPAR ($P = .001$), with each of these episodes except for one occurring within one year of BKV (Figure 2A).

Between the index BKV event and the first complication event (or last lab follow-up if no complication event occurred), an average of 3.5 ± 2.3 DSA tests per patient were checked in the no net increase group and an average of 5.1 ± 4.4 DSA tests per patient were ordered in the net increase group ($P = .04$). More DSA screenings were likely ordered in the net increase group as these patients were less likely to develop de novo DSA and BPAR, and were therefore followed for longer according to study design. Although risk of developing de novo DSA was not statistically different between the two groups ($P = .06$), de novo DSA formation was numerically higher in patients without a net increase in immunosuppression, 34.1% vs 15.9% (Figure 2B). Adjustment in net immunosuppression was associated with a significant difference in the composite complication events of BPAR and de novo DSA ($P = .0004$, Figure 2C). Median time to de novo DSA after BKV was 335 days (IQR: 96.5-718 days) in patients with no net immunosuppression increase. Of the 21 patients with de novo DSA, 19% had class I DSA, 61.9% had class II DSA, and 19% had both class I and II DSA. The median MFI of the immunodominant de novo DSA was higher for class II compared to class I DSA (1,978 MFI [IQR: 1,015-2,105 MFI] vs 5,134 MFI [IQR: 2,853-11,006 MFI], $P = .01$). Of the six patients with a combined kidney transplant, none developed de novo DSA in either group and one simultaneous pancreas-kidney transplant recipient in the no net increase group experienced TCMR.

3.3 | Recurrent BK viremia after immunosuppression re-escalation

An average of 3.1 ± 2.0 quantitative BKV PCRs per patient were ordered within the first three months after increasing net immunosuppression, and an average of 27.2 ± 21.0 quantitative BK PCRs per patient were ordered between the time of increasing net immunosuppression to last lab follow-up. After the net immunosuppression was increased, 10 (22.7%) patients experienced recurrent BKV that prompted the clinician to subsequently decrease maintenance immunosuppression. In patients with recurrent BKV, the

TABLE 2 Biopsy-proven acute rejection characteristics

	Net ISx, not increased (n = 44)	Net ISx Increased (n = 44)	
Rejection events before the index event of BKV			
Any rejection, n (%)	7 (15.9%)	4 (9.1%)	.33
T-cell–mediated rejection, n (%)	7 (15.9%)	4 (9.1%)	
Banff 1A[a]	4 (57.1%)	0	
Banff 1B[a]	2 (28.6%)	2 (50%)	
Banff 2A[a]	1 (14.3%)	1 (25%)	
Banff 2B[a]	0	1 (25%)	
Antibody-mediated rejection, n (%)	0	1 (25%)	
Median days from BPAR to index BKV, days (IQR)	100 (55.5-374.5)	114 (42.5-255)	.53
Rejection events after the index event of BKV[b]			
Any rejection, n (%)	14 (31.8%)	5 (11.4%)	.02
T-cell–mediated rejection, n (%)	12 (27.3%)	5 (11.4%)	
Banff 1A[a]	4 (33.3%)	3 (60.0%)	
Banff 1B[a]	4 (33.3%)	2 (40.0%)	
Banff 2A[a]	4 (33.3%)	0	
Antibody-mediated rejection, n (%)	2 (4.5%)	0	
Median days from index BKV to BPAR, days (IQR)	146 (79.8-156)	203 (188-437)	.003

[a]Out of composite cases.

[b]Includes rejection events occurring after index BKV up to the first complication event (ie BPAR, de-novo DSA, recurrent BKV) or last lab follow-up if no complication event occurred.

clinician elected to decrease immunosuppression after quantitative viral load doubled compared to the PCR value when immunosuppression was first increased (6 of 10 patients, 60%) or after the viral load rose to ≥1000 copies/mL after previously being undetected (2 of 10 patients, 20%). In the other two (20%) patients, immunosuppression was decreased after less than a twofold rise in the quantitative viral load, but reached 2100 copies/mL in one patient and 12 300 copies/mL in the other case. There were no graft losses due to BKVN in patients with recurrent BKV at the time of last lab follow-up.

4 | DISCUSSION

Based on the philosophy that BKV occurs due to excessive immunosuppression, providers at our center traditionally maintained a minimized immunosuppression regimen after BKV improved or resolved. However, the increasing reports of late rejection or de novo DSA development after BKV prompted some nephrologists to attempt an increase in net immunosuppression, and recurrent BKV was often not observed. As a result, a competing philosophy emerged that it may be possible to increase immunosuppression especially as patients are farther away from the intensive immunosuppression administered early after transplant. This was a proof-of-concept study evaluating the overall impact of increasing net immunosuppression in patients with resolving BKV. The major finding was that this approach appeared to improve rejection-free survival and numerically fewer patients developed de novo DSA compared to the control group whose net immunosuppression was not increased. The 21.6% incidence of BKV observed was consistent with other reports where similar immunosuppression protocols were used.[8,12] In addition, the rates of BPAR and de novo DSA were within the ranges referenced in the literature, 12%-50% and 3.3%-79%, respectively.[8–12,16] The incidence of antibody-medication rejection may have been underestimated by our study since the 2007 Banff schema were applied, and current classification no longer requires positive C4d staining or detection of DSA.[18]

The two groups were remarkably well matched for the degree of patient sensitization, median peak BK viral load, proportion of patients with a peak PCR ≥ 10 000 copies/mL, median time to BK viral clearance and the rATG induction use. Despite being a retrospective evaluation, the comparable distribution of immunologic and viral characteristics between the two groups suggest nephrologists had similar information at the time net immunosuppression was evaluated; thus, a natural experiment comparing immunosuppression adjustments in patients with BKV was possible. The

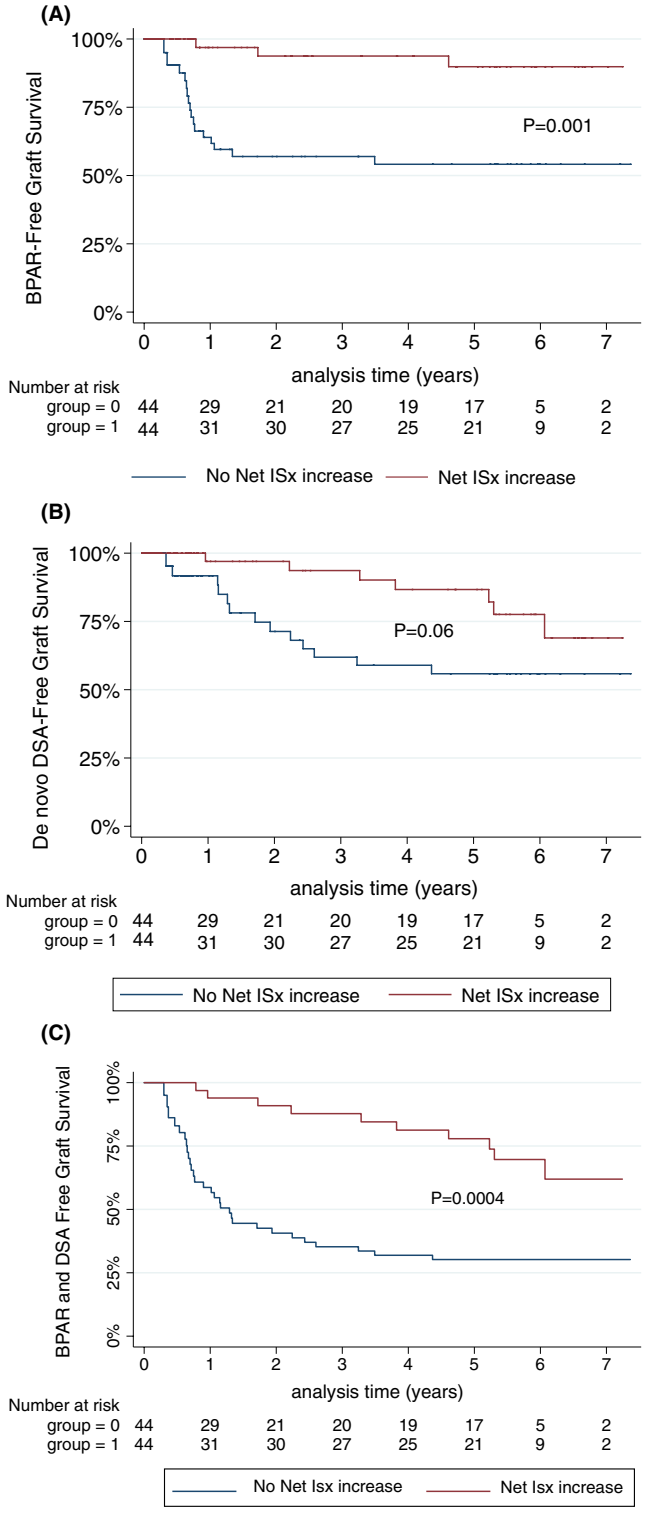

FIGURE 2 Individual and Composite Complications: BPAR and de novo DSA. Increasing net immunosuppression was associated with less (A) BPAR ($P = .001$), but had no significant effect on (B) de novo DSA development ($P = .06$). Escalating net immunosuppression had protective effect on (C) composite BPAR and de novo DSA development ($P = .0004$)

protocol-driven post-transplant management of BK PCR screening, surveillance biopsies, DSA monitoring, and use of the same Viracor assay in all patients for the duration of the study period provided rich data from the usual patient care and enabled studying BKV and complications.

Our findings could be impactful as patients developing acute rejection and de novo DSA are more likely to experience premature graft loss, especially when rejection occurs after BKV.[15,16,19,20] Although a statistical difference in death-censored graft failure was not observed in our study (in part due to low event rates in both groups during follow-up period), graft losses due to acute or chronic rejection occurred in three-times the number of patients whose net immunosuppression was not increased. Increasing immunosuppression after BKV improved was associated with recurrent BKV in less than 25% of patients, and none of these patients experienced graft loss related to BKVN at the end of last lab follow-up. These results suggest that in patients with resolving BKV, net immunosuppression may be safely increased in some patients.

Outcomes of immunosuppression reduction strategies during BKV treatment have been extensively studied.[8,10,21–24] In patients with BKV, tacrolimus reduction by ≥20% within 1 month of BKV diagnosis was recently associated with acute rejection rates of 34.2% compared to 7.9% in patients with less aggressive modifications ($P = .008$).[16] Meanwhile, gradual immunosuppression tapering has been protective against DSA development when dosing modifications were made at slower 4-week intervals compared to 2-week intervals.[10] Bischof et al demonstrated BKV clearance in 96% of patients and low rates of TCMR (7%) and AMR (4%) when the calcineurin inhibitor (CNI) was reduced first, and secondarily the anti-metabolite dose was decreased if BKV did not improve; investigators hypothesized decreasing the CNI first may allow for a stronger T-cell response towards BK virus, while continuing mycophenolate may be protective against AMR since B-cell proliferation remains inhibited.[24] These findings aid the clinician in minimizing immunosuppression. In contrast, studies comparing approaches to re-escalating net immunosuppression after BKV resolution are not available.

Various practices have been reported regarding adjusting net immunosuppression after BKV. For example, Hardinger et al described that 10 of 11 (91%) patients with sustained BKV (>1 month) did not have an antimetabolite restarted 5 years after transplant despite 95% of patients achieving BKV resolution within 1 year post-transplant.[21] It should be noted that 5-year rejection rates were not different in patients with or without BKV (11% vs 22%, $P = .164$) despite not routinely increasing net immunosuppression.[21] However, this study did not employ surveillance DSA testing or protocol biopsies, which is a strength of our study. In more recent studies, increasing net immunosuppression appears to have been practiced by some clinicians. For example, the institution protocol in the Sawinski et al study allowed for re-introduction of the anti-metabolite after BKV clearance according to clinician judgment.[12] In the Elfadawy et al study, only patients with persistent high BKV (peak viral ≥ 10 000 copies/mL and BKV duration of >3 months), but not patients with low or transient BKV, were maintained on a regimen with significantly reduced mean mycophenolate or tacrolimus levels after BKV compared to levels from aviremic controls.[8] Although these studies suggest net

immunosuppression may have been increased in some patients, it is not possible to determine whether escalation of the CNI or mycophenolate dosing should be prioritized in patients with improving BKV.

Given the retrospective nature of this study, the data was not granular enough to determine the impact of specific interventions. For example, patients with a minor increase in the total daily mycophenolate dose by 25% were categorized in the same net increase cohort as patients with a more clinically significant change, such as both a 50% mycophenolate dose increase and tacrolimus trough increase. Additionally, changes in immunosuppression were according to physician discretion rather than an enforced study protocol. As a result, all variables influencing immunosuppression modifications may not have been captured by retrospective review such as comorbid infections or adverse drug side effects, which may explain why patients without a net increase in immunosuppression were at increased risk for all-cause graft failure. However, the similar patient demographics at baseline, peak BK viral load, and use of leflunomide and IVIG between groups were reassuring.

Although current guidelines recommend reducing immunosuppression in patients with sustained viremia of >1000 copies/mL, some studies have historically applied thresholds of ≥10 000 copies/mL, and caution is thus warranted generalizing our study results to patients with a high viral burden.[5] Another limitation is the absence of a standardized BK assay, which contributes to the variation in viral quantification between assays and across studies, and in turn may affect the reproducibility of our findings at an outside center. Whether complete BK clearance or stable, low-level viremia should be achieved prior to immunosuppression dose increases also cannot be determined by the results of the study, and a rigorous, prospective study is necessary to answer several of these unknowns.

5 | CONCLUSION

In conclusion, increasing net immunosuppression after BKV appeared to reduce rates of acute rejection without adversely impacting graft or patient survival, and was associated with numerically fewer graft losses due to chronic rejection. A prospective study is needed to determine if these results can be replicated in a larger cohort and to evaluate the impact of specific interventions for management of immunosuppression after BKV resolution.

DISCLOSURES

No conflicts of interest to disclose.

AUTHORS CONTRIBUTIONS

LC: data collection, data analysis/interpretation, drafting article, critical revision of article; AM: concept/design, data collection, data analysis/interpretation, critical revision of article; JMP: concept/design, data analysis/interpretation, critical revision of article; MDSP: concept/design, critical revision of article; DRK: data analysis/interpretation, critical revision of article; ASN: concept/design, data collection, data analysis/interpretation, drafting article, critical revision of article.

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REFERENCES

1. Mbianda C, El-Meanawy A, Sorokin A. Mechanisms of BK virus infection of renal cells and therapeutic implications. *J Clin Virol*. 2015;71: 59-62.
2. Hirsch HH, Brennan DC, Drachenberg CB, et al. Polyomavirus-associated nephropathy in renal transplantation: interdisciplinary analyses and recommendations. *Transplantation*. 2005;79:1277-1286.
3. Bohl DL, Brennan DC. BK virus nephropathy and kidney transplantation. *Clin J Am Soc Nephrol*. 2007;2:S36-S46.
4. Johnston O, Jaswal D, Gill JS, et al. Treatment of polyomavirus infection in kidney transplant recipients: a systematic review. *Transplantation*. 2010;89:1057-1070.
5. Hirsch HH, Randhawa PS, AST Infectious Diseases Community of Practice. BK polyomavirus in solid organ transplantation—Guidelines from the American Society of Transplantation Infectious Disease Community of Practice. *Clin Transplant*. 2019;e13528.
6. Drachenberg CB, Papadimitriou JC, Chaudhry MR, et al. Histological evolution of BK virus-associated nephropathy: importance of integrating clinical and pathological findings. *Am J Transplant*. 2017;17:2078-2091.
7. Nankivell BJ, Renthawa J, Sharma RN, et al. BK virus nephropathy: histological evolution by sequential pathology. *Am J Transplant*. 2017;17:2065-2077.
8. Elfadawy N, Flechner SM, Schold JD, et al. Transient versus persistent BK viremia and long-term outcomes after kidney and kidney-pancreas transplantation. *Clin J Am Soc Nephrol*. 2014;9(3):553-561.
9. Dieplinger G, Everly MJ, Briley KP, et al. Onset and progression of de novo donor-specific anti-human leukocyte antigen antibodies after BK polyomavirus and preemptive immunosuppression reduction. *Transpl Infect Dis*. 2015;17:848-858.
10. Devresse A, Tinel C, Vermorel A, et al. No clinical benefit of rapid versus gradual tapering of immunosuppression to treat sustained BK virus viremia after kidney transplantation: a single-center experience. *Transpl Int*. 2019;32:481-492.
11. Cheungpasitporn W, Kremers WK, Lorenz E, et al. De novo donor-specific antibody following BK nephropathy: the incidence and association with antibody-mediated rejection. *Clin Transplant*. 2018;32(3):e13194.
12. Sawinski D, Forde KA, Trofe-Clark J, et al. Persistent BK viremia does not increase intermediate-term graft loss but is associated with de novo donor-specific antibodies. *J Am Soc Nephrol*. 2015;26:966-975.
13. Zhou W, Sharma M, Martinez J, et al. Functional characterization of BK virus-specific CD4+ T cells with cytotoxic potential in seropositive adults. *Viral Immunol*. 2007;20:379-388.
14. Chen Y, Trofe J, Gordon J, et al. Interplay of cellular and humoral immune responses against BK virus in kidney transplant recipients with polyomavirus nephropathy. *J Virol*. 2006;80(7):3495-3505.

15. Schold JD, Rehman S, Kayler LK, et al. Treatment for BK virus: incidence, risk factors and outcomes for kidney transplant recipients in the United States. *Transpl Int*. 2009;22:626-634.
16. Baek CH, Kim H, Yu H, et al. Risk factors of acute rejection in patients with BK nephropathy after reduction of immunosuppression. *Ann Transplant*. 2018;23:704-712.
17. Solez K, Colvin RB, Racusen LC, et al. Banff 07 Classification of renal allograft pathology: updates and future directions. *Am J Transplant*. 2008;8:753-760.
18. Haas M, Loupy A, Lefaucheur C, et al. The Banff 2017 Kidney Meeting Report: revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials. *Am J Transplant*. 2018;18:293-307.
19. Everly MJ, Rebellato LM, Haisch CE, et al. Incidence and impact of de novo donor-specific alloantibody in primary renal allografts. *Transplantation*. 2013;95:410-417.
20. Kasiske BL, Gaston RS, Gourishankar S, et al. Long-term deterioration of kidney allograft function. *Am J Transplant*. 2005;5:1405-1414.
21. Hardinger KL, Koch MJ, Bohl DJ, et al. BK-virus and the impact of pre-emptive immunosuppression reduction: 5-year results. *Am J Transplant*. 2010;10:407-415.
22. Saad ER, Bresnahan BA, Cohen EP, et al. Successful treatment of BK viremia using reduction in immunosuppression without antiviral therapy. *Transplantation*. 2008;85:850.
23. Ginevri F, Azzi A, Hirsch HH, et al. Prospective monitoring of polyomavirus BK replication and impact of pre-emptive intervention in pediatric kidney recipients. *Am J Transplant*. 2007;7:2727-2735.
24. Bischof N, Hirsch HH, Wehmeier C, et al. Reducing calcineurin inhibitor first for treating BK polyomavirus replication after kidney transplantation: long-term outcomes. *Nephrol Dial Transplant*. 2019;34:1240-1250.

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