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ORIGINAL ARTICLE

Intravenous immunoglobulins do not prove beneficial to reduce alloimmunity among kidney transplant recipients with BKV-associated nephropathy

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SUMMARY

Reduced immunosuppression during BKV-DNAemia has been associated with T-cell mediated rejection (TCMR), *de novo* donor-specific antibodies (DSA) and antibody-mediated rejection (ABMR). Intravenous immunoglobulins (IVIG) may reduce alloimmunity. We studied 860 kidney transplant recipients (KTRs) for the development of BKV-DNAuria and BKV-DNAemia (low-level <10 000 IE/ml, high-level >10 000 IE/ml). 52/131 KTRs with high-level BKV-DNAemia received IVIG. The HLA-related immunological risk was stratified by the Predicted Indirectly Recognizable HLA Epitopes (PIRCHE) algorithm. BKV-DNAuria only was observed in 86 KTRs (10.0%), low-level BKV-DNAemia in 180 KTRs (20.9%) and high-level BKV-DNAemia in 131 KTRs (15.2%). KTRs with low-level BKV-DNAemia showed significantly less TCMR compared to KTRs with high-level BKV-DNAemia (5.2% vs. 25.5%; $P < 0.001$) and no BKV-replication (13.2%; $P = 0.014$), lowest rates of *de novo* DSA (21.3%), ABMR (9.2%) and flattest glomerular filtration rate (GFR) slope (−0.8 ml/min). KTRs with low-level BKV-DNAemia showed significantly higher median (interquartile range) total PIRCHE if they developed TCMR [100.22 (72.6) vs. 69.52 (49.97); $P = 0.020$] or ABMR [128.86 (52.99) vs. 69.52 (49.96); $P = 0.005$]. Administration of IVIG did not shorten duration of BKV-DNAemia ($P = 0.798$) or reduce TCMR, *de novo* DSA and ABMR ($P > 0.05$). KTRs with low-level BKV-DNAemia showed best protection against alloimmunity, with a high number of PIRCHE co-determining the remaining risk. The administration of IVIG, however, was not beneficial in reducing alloimmunity.

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Introduction

Polyomavirus BK (BKV) DNAemia can be observed in up to 30% of kidney transplant recipients (KTRs), mostly within the first 6 months of post-transplantation, and proceeds to BKV-associated nephropathy (BKVN) in 1–2% [1]. Potent immunosuppressive agents, especially tacrolimus plus mycophenolate, lymphocyte depletion [2-5], and the associated lack of BKV-specific immunity have been described as main risk factors [6-11].

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Since no effective antivirals exists, the only established therapy remains pre-emptive reduction of immunosuppression [12-15], but entails increased risks of alloimmunity. Previous data suggest a significantly higher risk for the development of T-cell mediated rejection (TCMR), *de novo* donor-specific antibodies (DSA) and antibody-mediated rejection (ABMR) in KTRs with BKV-DNAemia [16-18].

Very recently, intravenous Immunoglobulins (IVIG), that have been shown to contain high amounts of neutralizing BKV-specific antibodies *in vitro* [19], have been suggested for BKV prophylaxis in KTRs with low neutralizing BKV-specific antibody titres [20]. However, using intravenous Immunoglobulins (IVIG) to treat active BKV-replication remains controversial and showed limited impact on BKV-clearance [21-23]. The rationale for IVIG during reduced immunosuppression, however, is based on their immunomodulatory properties. The main immunomodulatory effect is mediated by the fragment crystallizable fragment (Fc): (i) direct inhibition of antigen-presenting cells and monocyte activation, (ii) inhibition of the complement cascade by binding on complement factors, and (iii) inhibition of anti-HLA antibody production by upregulation of the B-memory-cell inhibiting FcγII2b [24-26]. Nevertheless, there is a lack of clinical data regarding the ability of IVIG to reduce alloimmunity.

Although the risk of alloimmunity has been convincingly linked to the number of HLA mismatches, it is well known that immune responses directed towards allo-HLA proteins are dependent on the number of mismatched HLA amino acids and their immunogenicity [27-29]. Different strategies to better quantify the immunogenicity of specific HLA mismatches have been developed. The Predicted Indirectly ReCognizable HLA Epitopes (PIRCHE) algorithm is one of such algorithms, which counts the number of immunogenic allo-HLA peptides that are able to be presented on recipients HLA [30,31]. A high PIRCHE score has been associated with increased development of *de novo* DSA and allograft failure in recently published studies [32].

Based on recent findings we hypothesize, that a level of immunosuppression, that results in low-level but controlled BKV-replication, may provide sufficient protection from alloimmunity for KTRs at an increased individual risk. Therefore, we attempted to address the following questions:

1. Does the severity of BKV-DNAemia impact the development of TCMR, *de novo* DSA and ABMR?
2. Does epitope matching using the PIRCHE algorithm further stratify the risk of TCMR, *de novo* DSA and ABMR among KTRs with BKV-DNAemia?
3. Does the administration of IVIG in KTRs with high-level BKV-DNAemia contribute to control and BKV-clearance?
4. Does the administration of IVIG during the period of reduced immunosuppression prevent alloimmunity with development of TCMR, *de novo* DSA and ABMR?

Materials and methods

Patients

The study was approved by the cantonal ethic commission review board of Zurich, Switzerland (KEK-ZH-Number 2019-01274) and has been conducted in compliance with the declaration of Helsinki.

We studied 860 KTRs, transplanted between January 1, 2009 and March 31, 2019 at the University Hospital Zurich. All KTRs were monitored for the development of BKV-DNAuria (defined as decoy-cell shedding), low-level BKV-DNAemia (<10 000 IE/ml) and high-level BKV-DNAemia (>10 000 IE/ml).

After the initial hospital stay, all KTRs received follow-up visits at the following timepoints: weekly at week 2–12, monthly at month 4–12. Thereafter, quarterly aftercare is provided in collaboration with local nephrologists and at least yearly in our outpatient clinic. At each visit, KTRs were screened for decoy-cell shedding in the urine. Screening for BKV-DNAemia was conducted at months 1–6, 8, 10, 12 and 18 and at any unclear deterioration of kidney function.

Immunosuppression

IL2-receptor blockade or anti-thymocyte globulin (ATG) was administered for induction with respect to immunological risk. Primary Immunosuppression consisted of a triple-drug immunosuppression with calcineurin Inhibitor (CNI, tacrolimus or ciclosporine), mycophenolate mofetil (MMF) or mycophenolic acid (MPA) and steroids. Initial tacrolimus trough levels were maintained at 10–15 μg/l until week 6, at 8–12 μg/l until week 12, at 7–10 μg/l until month 12, at 6–8 μg/l until month 24 and at 4–6 μg/l thereafter. Initial ciclosporine trough levels were at 200–250 μg/l until week 6, at 180–220 μg/l until week 12, at 150–200 μg/l until months 12, at 80–120 μg/l until months 24 and at 60–100 μg/l thereafter. Dosage of MMF was 2000 mg/day and dosage of MPA was 1440 mg/day. Steroid tapering was performed over 12 weeks to a dose of 5 mg prednisone/day and withdrawn according to the immunological risk.

Transplant International 2021; 34: 1481–1493

Rejection was diagnosed histologically. KTRs with TCMR received intravenous steroid pulses and individual tapering. If rejection persisted, additional lymphocyte depletion was administered. An immunosuppression intensity score was developed for analysis of the degree of immunosuppression among as shown in Table S1.

Kidney allograft function and biopsies

As BKV-DNAemia predominantly occurred within the first 6 months of post-transplantation, we used serum-creatinine and estimated glomerular filtration rate (eGFR) values at 1-year post-transplantation to compare kidney allograft function. eGFR was calculated using the CKD-EPI equation. The eGFR slope was calculated according to the Mitch formula in KTRs with at least 24-month follow-up, starting at 12 months of post-transplantation [32].

Serum-creatinine baseline before, during and after BKV-DNAemia was calculated using the mean of the three lowest serum-creatinine values before BKV-DNAemia, the mean of the three highest values during BKV-DNAemia, and the mean of the three lowest values within 1 year after BKV-clearance.

HLA antibody testing was performed by bead-based Luminex technology at transplantation, at month 3, 6, 12 and annually thereafter.

During the post-transplant follow-up, 404 KTRs received a total of 727 for cause kidney allograft biopsies, evaluated according to the Banff-classification [34]. Kidney allograft biopsies to confirm the diagnosis of BKVN was performed in KTRs with unexplained deterioration of kidney function of ≥30% from baseline, persistent BKV-DNAemia >3 months or suspected rejection.

Decoy cells and quantification of BKV-DNAemia

Urinary sediment cytology was used to detect viral inclusion in urothelial cells (decoy cells) and distinguished into scant, moderate and plenty. Quantification of BKV-DNAemia was performed by quantitative real-time PCR conducted by the TaqMan platform. The lower detection limit of BKV-load was 200 IE/ml.

Treatment of BKV-DNAemia and BKV-associated nephropathy

Treatment of BKV-DNAemia consisted of a stepwise reduction of immunosuppression with respect to the severity of BKV-DNAemia. MMF/MPA was reduced by 25%, 50%, 75% or completely discontinued (Table 1B). CNI trough levels were reduced to target trough levels. In case of no response to reduction of MMF/MPA, CNI trough levels were reduced to target trough levels of 5–7 μg/l, target ciclosporine trough level of 50–80 μg/l. In KTRs with high-level BKV-DNAemia and no response to reduction, CNI was switched to mTOR inhibitor.

Starting on January 1, 2014, IVIG was implemented in the treatment of KTRs with high-level BKV-DNAemia in addition to reduction of immunosuppression. 0.5 mg/kg bodyweight IVIG was administered biweekly during high-level BKV-DNAemia. We therefore obtained two groups among KTRs with high-level BKV-DNAemia: 79 KTRs (transplanted before 2014) treated with reduction of immunosuppression alone, and 52 KTRs (transplanted after 2014) treated with biweekly IVIG in addition to reduction of immunosuppression.

Predicted Indirectly ReCognizable HLA Epitopes

The HLA-derived mismatched allo-peptides that could potentially be presented by a KTR's HLA-class II proteins were calculated using the PIRCHE algorithm [30,31]. Presentation of both HLA-class I derived peptides (HLA-A, B, C) and HLA-class II derived peptides (HLA-DR, DQ) were calculated for each recipient HLA-locus and designated as PIRCHE-A, B, C, DQ and DR. HLA typing of KTRs and donors was achieved by serological and DNA-based techniques and corresponding likely high-resolution results were imputed by the PIRCHE algorithm. The PIRCHE algorithm is available online (https://www.pirche.org).

Statistical methods

Statistical analysis was performed using IBM SPSS Version 25 (SPSS, Chicago, IL, USA).

For comparisons of study groups, two-sided Kruskal–Wallis Test and Mann–Whitney *U*-Test were used for nonparametric independent samples. For comparisons between paired samples, a two-sided Wilcoxon signed-rank test for nonparametric dependent samples was used. Outcomes were measured with Kaplan–Meier models and measured by logrank tests. Clinical characteristics were compared across groups using Fisher's exact test for categorical variables.

Results

Clinical characteristics

During a median follow-up of 50 months (range: 0–129 month) we identified 463 KTRs (53.8%) without

Table 1. (A) Clinical characteristics of different BKV groups. (B) Viral characteristics and BKV therapy of different BKV groups.

	Total (*n* = 860)	BKV-DNAuria only (*n* = 86)	Low-level BKV-DNAemia (*n* = 180)	High-level BKV-DNAemia (*n* = 131)	No BKV-replication (*n* = 463)	*P* value
(A)						
Recipient age, years*	53 (17–80)	49 (18–75)	49 (17–75)	56 (17–80)	53 (17–76)	0.012*
Recipient male sex, *n* (%)	521 (60.6)	63 (73.3)	108 (60.0)	93 (71.0)	257 (55.5)	0.001*
Kidney–pancreas transplantation, *n* (%)	71 (8.3)	5 (5.8)	16 (8.9)	10 (7.6)	40 (8.6)	0.818
Retransplantation, *n* (%)	129 (15.0)	16 (18.6)	21 (11.7)	25 (19.1)	67 (14.5)	0.235
Donor age, years*	52 (0–88)	54 (13–78)	53 (2–79)	54 (3–88)	51 (0–58)	0.121
Donor male sex, *n* (%)	459 (53.4)	46 (53.5)	105 (58.3)	53 (40.5)	255 (55.1)	0.011*
Deceased donation, *n* (%)	616 (71.6)	57 (66.3)	119 (66.1)	95 (72.5)	345 (74.5)	0.119
Donation after cardiac death (CDC), *n* (%)	69 (8.0)	8 (9.3)	12 (6.7)	12 (9.2)	37 (7.8)	0.829
Extended Criteria Donor (ECD), *n* (%)	43 (5.0)	7 (8.1)	10 (5.6)	8 (6.1)	18 (3.9)	0.188
Living donation, *n* (%)	244 (28.4)	29 (33.7)	61 (33.9)	36 (27.5)	118 (25.5)	0.203
Induction immunosuppression, *n* (%)						
Lymphocyte depletion	344 (40.0)	30 (34.9)	62 (34.4)	61 (46.6)	191 (41.3)	0.073
IL-2 receptor blockade	474 (55.1)	48 (55.8)	110 (61.1)	63 (48.1)	253 (54.6)	
ABO desensitization	38 (4.4)	8 (9.3)	8 (4.4)	7 (5.3)	15 (3.2)	
Maintenance immunosuppression, *n* (%)						
Tacrolimus	725 (84.3)	75 (87.2)	146 (81.1)	110 (84.0)	394 (85.1)	0.365
Ciclosporine	128 (14.9)	11 (12.8)	34 (18.9)	20 (15.3)	63 (13.6)	
MMF/MPA	849 (98.7)	86 (100.0)	176 (97.8)	130 (99.2)	457 (98.7)	0.447
AZA	11 (1.3)	0 (0.0)	4 (2.2)	1 (0.8)	6 (1.3)	
Immunosuppression intensity score, *n* (%)						
<2	83 (20.9)	21 (24.4)	44 (24.4)	18 (13.7)	–	0.008*
2	117 (29.5)	27 (31.4)	59 (32.8)	31 (23.7)	–	
>2	197 (49.6)	38 (44.2)	77 (42.8)	82 (62.6)	–	
Steroid free at 1 year, *n* (%)	382 (44.4)	36 (41.9)	91 (50.6)	60 (45.8)	195 (42.1)	0.534
Total HLA mismatches*	5 (0–10)	5 (1–10)	5 (0–10)	5 (0–10)	5 (0–10)	0.393
Total PIRCHE score*	72.00 (0–286.78)	72.50 (0–208.09)	73.47 (0–199.35)	72.79 (1.37–233.55)	71.48 (0.14–286.78)	0.742
PIRCHE-A	14.53 (0–69.37)	17.52 (0–61.15)	14.12 (0–46.79)	14.72 (0–69.37)	13.57 (0–69.22)	0.096
PIRCHE-B	14.35 (0–72.72)	15.96 (0–54.19)	14.89 (0–60.56)	12.92 (0–53.40)	13.52 (0–72.72)	0.452
PIRCHE-C	12.96 (0–75.06)	16.28 (0–51.36)	13.41 (0–50.00)	12.57 (0–75.06)	12.39 (0–60.00)	0.079
PIRCHE-DQ	19.00 (0–82.55)	14.29 (0–59.11)	24.42 (0–67.00)	20.63 (0–71.00)	19.00 (0–82.55)	0.232
PIRCHE-DR	12.58 (0–74.78)	10.09 (0–58.58)	12.43 (0–46.00)	11.76 (0–42.64)	13.22 (0–74.78)	0.839
Delayed graft function, *n* (%)	203 (23.6)	21 (24.4)	32 (17.8)	29 (22.1)	91 (19.7)	0.572

	Total (n = 397)	BKV-DNAuria only (n = 86)	Low-level BKV-DNAemia (n = 180)	High-level BKV-DNAemia (n = 131)	P value
(B)					
Time to BKV-DNAuria, months*	2 (0–86)	3 (0–86)	3 (0–83)	2 (0–64)	0.130
Duration of BKV-DNAuria, weeks*	5 (0–314)	0 (0–216)	2 (0–240)	14 (0–314)	<0.001*
Time to BKV-DNAemia, months*	2 (0–89)	–	5 (0–89)	2 (0–48)	<0.001*
Duration of BKV-DNAemia, weeks*	14 (0–353)	–	0 (0–207)	55 (0–353)	<0.001*
BKV-load at diagnosis, IE/ml*	860 (200–3.8×10^5)	–	385 (200–9.3×10^3)	2.6×10^3 (200–3.8×10^5)	<0.001*
Peak BKV-load, IE/ml*	1.9×10^4 (231–2.0×10^7)	–	1.4×10^3 (231–9.6×10^3)	7.3×10^4 (1.0×10^3–2.0×10^7)	<0.001*
Below detection limit, n (%)	94 (10.9)	–	94 (52.2)	–	
Biopsy-proven BKVN, n (%)	30 (7.6)	–	–	30 (22.9)	–
Recurrence of BKV-DNAemia, n (%)	49 (12.3)	–	17 (9.4)	32 (24.4)	0.001*
Reduction of MMF/MPA, n (%)					
No reduction	–	–	130 (72.2)	13 (9.9)	<0.001*
50% reduction	–	–	41 (22.8)	66 (50.4)	
More than 50% reduction	–	–	8 (4.4)	45 (34.4)	
Discontinuation	–	–	1 (0.6)	7 (5.3)	
Switch from CNI to mTOR inhibitor, n (%)	–	–	0 (0.0)	11 (8.4)	<0.001*

*Median (range).

BKV-replication, 86 KTRs (10.0%) with BKV-DNAuria only, 180 KTRs (20.9 %) with low-level BKV-DNAemia and 131 KTRs (15.2%) with high-level BKV-DNAemia. 41 KTRs (4.8%) showed kidney allograft loss, and 101 KTRs (11.7%) died. Clinical and viral characteristics are shown in Tables 1A,B and S2A.

These 52 KTRs treated with IVIG received a median of 4 IVIG doses (range: 1–43 doses). Clinical characteristics are shown in Tables 2A,B and S2B.

Impact of BKV-replication on kidney allograft outcomes

Kidney transplant recipients with low-level BKV-DNAemia showed the lowest incidence of TCMR (5.2% at 24 months), significantly lower compared to KTRs with high-level BKV-DNAemia (25.5%; $P < 0.001$) and no BKV-replication (13.2%; $P = 0.014$; Fig. 1). Whereas 10/86 KTRs with BKV-DNAuria only (11.6%) and 15/131 KTRs with high-level BKV-DNAemia (11.5%) showed TCMR prior to BKV-DNAemia, only 6/180 KTRs with low-level BKV-DNAemia (3.3%) did ($P = 0.010$). KTRs with low-level BKV-DNAemia showed the lowest incidence of *de novo* DSA (21.3% at 10 years) compared to 30.3% in KTRs with high-level BKV-DNAemia and 33.3% in KTRs with no BKV-replication (Fig. S1a). Similarly, KTRs with low-level BKV-DNAemia showed the lowest incidence of ABMR (9.5% at 10 years) compared to 18.6% in KTRs with high-level BKV-DNAemia and 15.4% in KTRs with no BKV-replication (Fig. S1b).

Kidney transplant recipients with low-level BKV-DNAemia showed the highest eGFR (56 ml/min at 1 year) and flattest median eGFR slope (−0.1 ml/min/year), compared to KTRs with high-level BKV-DNAemia (eGFR 48 ml/min; eGFR slope −0.9 ml/min/year), KTRs with BKV-DNAuria only (eGFR 54 ml/min, eGFR slope −0.9 ml/min/year) and KTRs with no BKV-replication (eGFR 55 ml/min; eGFR slope −0.5 ml/min/year). KTRs with high-level DNAemia showed a significant increase in baseline serum-creatinine values after BKV-DNAemia ($P < 0.001$; Fig. S1c).

No differences were observed for death-censored kidney allograft survival between the different groups (Fig. S3a).

Impact of PIRCHE on alloimmunity

PIRCHE-A, -B, -C, -DQ and -DR scores as well as the number of HLA mismatches did not differ between the different groups (Table 1A, $P > 0.05$).

Kidney transplant recipients with low-level BKV-DNAemia who developed TCMR showed significantly higher PIRCHE-DR and total PIRCHE scores compared to KTRs with low-level BKV-DNAemia who did not develop TCMR ($P = 0.034$; $P = 0.020$; Fig. 2a–c). KTRs with low-level BKV-DNAemia who developed *de novo* DSA showed significantly higher PIRCHE-DR and total PIRCHE scores compared to KTRs with low-level BKV-DNAemia where *de novo* DSA could not be detected ($P = 0.004$; $P = 0.043$; Fig. 2a–c). KTRs with low-level BKV-DNAemia who developed ABMR showed significantly higher PIRCHE-DQ, PIRCHE-DR and total PIRCHE score compared to KTRs with low-level BKV-DNAemia without evidence of ABMR ($P = 0.002$; $P = 0.015$; $P = 0.005$; Fig. 2a–c).

Among KTRs with no BKV-replication, BKV-DNAuria only and high-level BKV-DNAemia, no differences in PIRCHE scores were observed concerning TCMR, *de novo* DSA or ABMR.

Impact of IVIG on BKV-replication

The median duration of BKV-DNAemia among KTRs with IVIG was 47 weeks (range: 15–271 weeks), but not significantly lower compared with KTRs without IVIG, that showed a median duration of BKV-DNAemia of 56 weeks (range: 0–315 weeks; $P = 0.798$; Table 2B).

Impact of IVIG on kidney allograft outcomes

Kidney transplant recipients with IVIG showed a significantly higher incidence of TCMR at 24 months (35.0%) compared to KTRs without IVIG (19.5%; $P < 0.001$; Fig. 3a). In total 6 of 52 KTRs receiving IVIG (11.5%) and 9 of 79 KTRs without IVIG therapy (11.4%) showed TCMR prior to detection of BKV-DNAemia ($P = 1$). The higher rate of TCMR in the IVIG compared to the non-IVIG group occurred during/after BKV-DNAemia. Although no statistical significant difference was observed between the two study groups, KTRs with IVIG therapy showed a higher incidence of *de novo* DSA with 32.3% at 5 years compared to KTRs without IVIG therapy (27.5% at 5 years and 36.0% at 10 years; Fig. S2a). Similarly, KTRs with IVIG showed a significantly higher incidence of ABMR with 28.4% at 5 years of post-transplantation as compared to 4.4% in KTRs without IVIG therapy ($P = 0.012$; Fig. 3b).

Kidney transplant recipients with IVIG therapy showed lower eGFR with 44 ml/min at 1 year and a steeper median eGFR slope decline with −2.3 ml/min, compared to KTRs without IVIG therapy (eGFR 52 ml/

min; $P = 0.132$; eGFR slope −0.8 ml/min; $P = 0.017$). KTRs with and without IVIG therapy showed a significant increase in baseline serum-creatinine values during BKV-replication ($P < 0.001$). While baseline serum-creatinine values normalized widely after BKV-clearance in KTRs without IVIG ($P = 0.111$), baseline serum-creatinine values remained increased in KTRs with IVIG treatment ($P < 0.001$; Fig. S2b).

Kidney transplant recipients with IVIG therapy showed a trend towards inferior death-censored kidney allograft survival ($P = 0.100$, Fig. S2b) and KTRs with IVIG showed a reduced 5-year death-censored kidney allograft survival of 89.5%, compared with 97.4% in KTRs without IVIG (Fig. S3b).

Discussion

The efficacy of IVIG therapy on BKV-DNAemia and potential suppression of alloimmunity remains poorly studied. To our knowledge, this is the largest study to investigate the impact of IVIG therapy on high-level BKV-DNAemia and the first to examine the impact on post-transplant alloimmunity.

It is a crucial but challenging task to find the balance of a sufficient level of immunosuppression to prevent allosensitization while avoiding over-immunosuppression with the risk of BKVN. In our study, we observed the lowest incidence of TCMR, *de novo* DSA and ABMR, highest eGFR at 1-year and flat-test eGFR slope among KTRs with self-limited low-level BKV-DNAemia. This finding suggests that low-level BKV-DNAemia is an indicator of sufficient but not excessive immunosuppression in the early post-transplantation period. Low-level BKV-DNAemia could potentially be used as a surrogate marker of optimal immunosuppression early after kidney transplantation. To apply these results in clinical practice, the dynamics of BKV-DNAemia need to be evaluated in the initial period of BKV-replication. Here, for example, an increased sampling density of 1–2 weeks can be used to estimate if a KTR is sufficiently controlling low-level BKV-DNAemia or a progression from low-level to high-level BKV-DNAemia is occurring. Our findings suggest that immunosuppression should be reduced more restrainedly in KTRs controlling low-level BKV-DNAemia. This may be of particular interest in KTRs with an increased risk of developing rejection. Nevertheless, transition from low-level BKV-DNAemia to high-level BKV-DNAemia can occur rapidly and at any time, complicating clinical applicability. In this scenario, immunosuppression should be reduced more rapidly.

High-level BKV-DNAemia was in our study associated with inferior kidney allograft function at 1-year post-transplant, with high-level BKV-DNAemia patients having higher serum-creatinine levels and lower eGFR compared to KTRs with low-level or no BKV-DNAemia [14,35,36]. These findings are supported by previous studies showing that BKVN results in destruction of tubular epithelial cells, tubular atrophy and fibrosis with a subsequent decline in kidney function [18,37–39]. In contrast to previous results [17], our results did not show an increased risk for the development of *de novo* DSAs among KTRs with high-level BKV-DNAemia, but did show a higher risk of TCMR, which is likely explained by the profound reduction of immunosuppression.

Elevated alloimmune risk of an individual donor/recipient HLA constellation as expressed by a high PIRCHE score has been previously linked to an increased risk for the development of *de novo* DSA and allograft failure [32,33]. However, the risk of a high PIRCHE score in the setting of post-transplant BK viraemia and the associated reduction in immunosuppression has not been previously investigated. Interestingly, we found that the PIRCHE-DR and total PIRCHE score was associated with the development of TCMR, *de novo* DSA development and ABMR among KTRs with low-level BKV-DNAemia, the group of KTRs that we considered adequately immunosuppressed. Our data could suggest, that among perceived adequately immunosuppressed KTRs a high PIRCHE score may identify individuals where a potential reduction of immunosuppression should be carefully balanced with the elevated risk for rejection. Among KTRs with less intense immunosuppression, that is those with no BKV-replication or KTRs with pronounced reduction in immunosuppression during high-level BKV-DNAemia, an elevated risk for alloimmunity as calculated by a high PIRCHE score may add less to the immunological risk calculation in this already high-risk setting.

In our study, KTRs with high-level BKV-DNAemia receiving IVIG did not show improved kidney allograft function compared to KTRs without IVIG therapy. In contrast, we observed a steeper decline of eGFR slope in the IVIG group. As it has been previously shown, kidney allograft injury and BKVN is highly dependent on the duration of BKV-DNAemia [41]. To prevent a decrease in kidney allograft function, fast BKV-clearance seems to be of crucial importance. Although IVIG has been shown to contain BKV-specific neutralizing antibodies [19,23,42] and showed beneficial effects in BKV-control [43,44], our study could neither confirm

Table 2. (A) Clinical characteristics in KTRs with IVIG compared to KTRs without IVIG. (B) Viral characteristics in KTRs with IVIG compared to KTRs without IVIG.

	High-level BKV-DNAemia		
	IVIG (n = 52)	No IVIG (n = 79)	P value
(A)			
Recipient age, years*	59 (23–75)	55 (17–80)	0.131
Recipient male sex, *n* (%)	41 (78.8)	52 (65.8)	0.158
Kidney–pancreas transplantation, *n* (%)	3 (5.8)	7 (8.9)	0.752
Retransplantation, *n* (%)	10 (19.2)	15 (19.0)	1.000
Donor age, years*	56 (3–76)	53 (7–88)	0.227
Donor male sex, *n* (%)	19 (36.5)	34 (43.0)	0.576
Deceased donation, *n* (%)	39 (75.0)	56 (70.9)	0.752
Donation after cardiac death (CDC), *n* (%)	8 (15.4)	4 (5.1)	0.106
Extended Criteria Donor (ECD), *n* (%)	3 (5.8)	5 (6.3)	1.000
Living donation, *n* (%)	13 (25.0)	23 (29.1)	0.368
Induction immunosuppression, *n* (%)			
Lymphocyte depletion	24 (46.2)	37 (46.8)	0.341
IL-2 receptor blockade	27 (51.9)	36 (45.6)	
ABO desensitization	1 (1.9)	6 (7.6)	
Maintenance immunosuppression, *n* (%)			
Tacrolimus	48 (92.3)	62 (78.5)	0.100
Ciclosporine	4 (7.7)	16 (20.3)	
MMF/MPA	52 (100.0)	78 (98.7)	1.000
AZA	0 (0.0)	1 (1.3)	
Steroid free at 1 year, *n* (%)	13 (26.0)	47 (60.3)	<0.001*
Total HLA mismatches*	6 (0–10)	5 (0–9)	0.610
Total PIRCHE score*	81.83 (9.14–233.55)	67.26 (1.37–170.15)	0.064
PIRCHE-A	16.48 (0–69.37)	12.83 (0–43.53)	0.135
PIRCHE-B	15.56 (0–53.40)	11.04 (0–51.18)	0.119
PIRCHE-C	12.90 (0–75.06)	11.17 (0–38.86)	0.428
PIRCHE-DQ	22.49 (0–71.00)	17.60 (0–48.27)	0.228
PIRCHE-DR	13.43 (0–42.64)	11.00 (0–26.80)	0.434
Delayed graft function, *n* (%)	12 (23.1)	17 (21.5)	0.833
(B)			
Time to BKV-DNAemia, months*	2 (0–48)	2 (0–35)	0.944
Duration of BKV-DNAemia, weeks*	47 (15–271)	56 (0–353)	0.798
BKV-load at diagnosis, IE/ml*	1.6×10^3 (200–1.6×10^5)	3.7×10^3 (200–3.8×10^5)	0.674
Peak BKV-load, IE/ml*	9.2×10^4 (1.0×10^4–2.0×10^7)	6.3×10^4 (1.0×10^4–2.0×10^6)	0.055
Biopsy-proven BKVN, *n* (%)	15 (28.9)	15 (19.0)	0.208
Recurrence of BKV-DNAemia, *n* (%)	12 (23.1)	20 (25.3)	0.933
Reduction of MMF/MPA, *n* (%)			
No reduction	3 (5.8)	10 (12.8)	0.023*
50% reduction	20 (38.5)	46 (58.2)	
More than 50% reduction	25 (48.1)	20 (25.6)	
Discontinuation	4 (7.7)	3 (3.8)	
Switch from CNI to mTOR inhibitor, *n* (%)	10 (19.2)	1 (1.3)	<0.001*
Indication biopsies during BKV-DNAemia, *n* (%)	33 (63.5)	52 (65.8)	0.852

*Median (range).

shortened BKV-DNAemia, nor a reduced risk for recurrence. These findings may explain the lack of improved kidney allograft outcomes in the IVIG-treated KTRs. Our findings are not contradictory to very recent findings on the successful use of IVIG for BKV-prophylaxis [20], since BKV-specific neutralizing antibodies and B-

Transplant International 2021; 34: 1481–1493

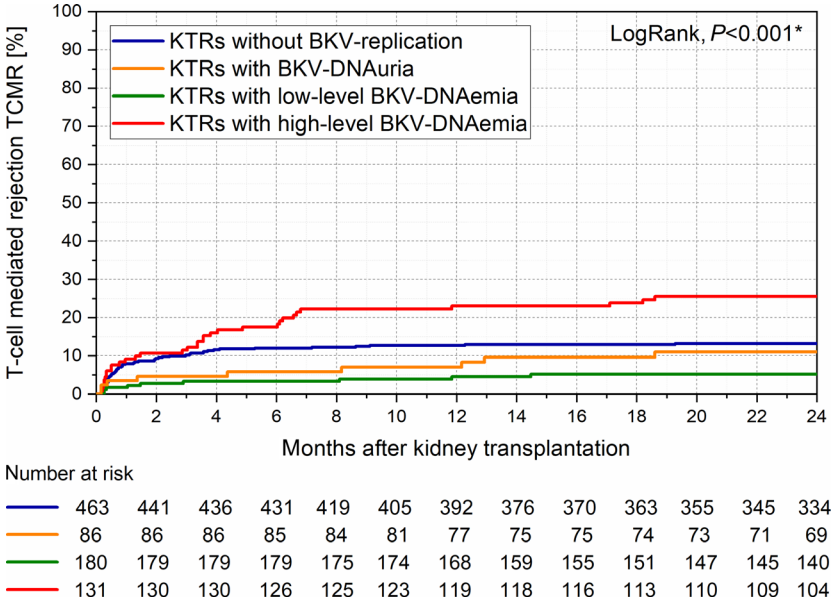

Figure 1 Kaplan–Meier plot of the development of TCMR in different BKV groups. The incidence TCMR is significantly higher among KTRs with high-level BKV-DNAemia compared to KTRs without BKV-replication ($P < 0.001$). The lowest incidence of TCMR, however, was observed in KTRs with low-level BKV-DNAemia and was significantly lower compared to KTRs without BKV-replication (LogRank, $P = 0.014$). KTRs, kidney transplant recipients; TCMR, T-cell mediated rejection.

cell immunity have been associated with prevention of BKV-replication, but BKV-specific T-cell immunity has been associated with the control of BKV-replication [6,7,21]. There are two recent studies investigating IVIG treatment for BKV-DNAemia. Vu *et al.* [43] followed 53 patients with BKV-DNAemia, whereof 30 patients had BKVN and received IVIG 1 g/kg bodyweight. As no control group was established, only qualitative statement could be obtained. Kable *et al.* [44] included 50 KTRs with BKVN, that were treated with a combination of reduced immunosuppression and cidofovir, whereof 22 received IVIG 1 g/kg bodyweight and showed faster BKV-clearance compared to 28 control KTRs. A major difference to our study was the amount of IVIG given, as our dosage was only 0.5 g/kg bodyweight. Randhawa *et al.* estimated in their *in vitro* study a total dose of 5 g IVIG to contain enough BKV-specific antibodies to inactivate a virus load of 1.9×10^6 c/ml in a patient with circulation blood volume of 5000 ml [19]. The mean dose of IVIG administrated in our study was 40 g and thus containing enough BKV-specific antibodies to clear even the highest detected viral load of 2.0×10^7 IE/ml. However, we have to take into account that IVIG was mainly administrated to KTRs in a late-stage of BKV-DNAemia, where tissue injury may already have occurred.

Due to its immunomodulatory properties, IVIG has been postulated to prevent development of alloimmunity during reduced immunosuppression [43–49]. However, we could not observe a risk reduction with respect to development of TCMR, *de novo* DSA and ABMR. Interestingly, the risk for TCMR and ABMR in KTRs with high-level BKV-DNAemia receiving IVIG was even higher than in those without IVIG therapy. This might be due to several reasons: Reduction of MMF/MPA was remarkably higher in the IVIG group, possibly due to the presumed protective effect of IVIG. Thus, the protective effect of IVIG did not appear to be sufficient to compensate for the marked reduction in immunosuppression. There have been previous reports of reduced risk of rejection associated with IVIG therapy [43,48] these studies, however, did not include a control group. There is also no generally accepted consensus about the dose of IVIG that should be used. According to Lachman *et al.*, low dose IVIG (0.1–0.2 g/kg bodyweight) is usually used for substitution of hypogammaglobulinemia, whereas higher doses (1–2 g/kg bodyweight) are required for treatment of ABMR [25]. The dose used in our study was only 0.5 g/kg bodyweight, however, in biweekly intervals, and therefore reach a cumulative dose of 1 g/kg bodyweight/month. Nevertheless, a dosage increase to 1–2 g/kg bodyweight biweekly might have led to different results.

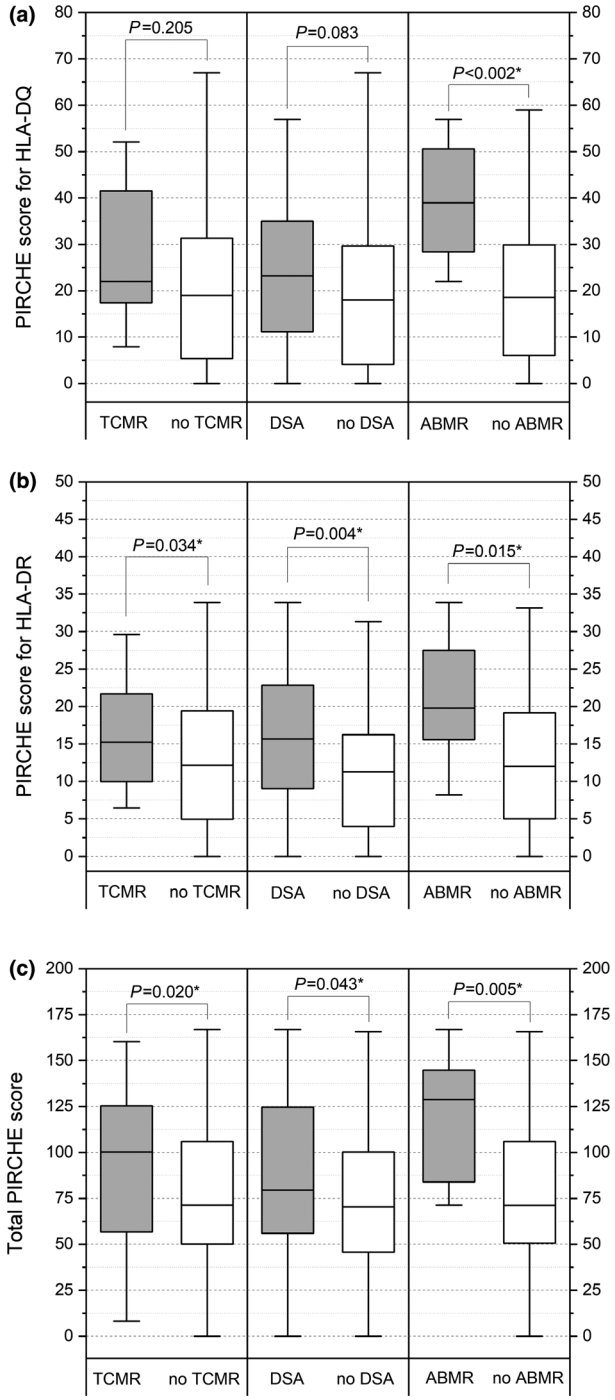

Figure 2 (a) Boxplot of PIRCHE score for HLA-DQ in KTRs with low-level BKV-DNAemia with respect to the development of TCMR, *de novo* DSA and ABMR. KTRs with low-level BKV-DNAemia who developed *de novo* DSA and ABMR showed significantly higher PIRCHE-DQ score as compared to KTRs with low-level BKV-DNAemia who did not. (b) Boxplot of PIRCHE score for HLA-DR score in KTRs with low-level BKV-DNAemia with respect to the development of TCMR, *de novo* DSA and ABMR. KTRs with low-level BKV-DNAemia who developed TCMR, *de novo* DSA and ABMR showed significantly higher PIRCHE-DR score compared to KTRs with low-level BKV-DNAemia who did not. (c) Boxplot of total PIRCHE score in KTRs with low-level BKV-DNAemia with respect to the development of TCMR, *de novo* DSA and ABMR. KTRs with low-level BKV-DNAemia who developed TCMR, *de novo* DSA and ABMR showed significantly higher total PIRCHE score compared to KTRs with low-level BKV-DNAemia who did not. ABMR, antibody-mediated rejection; DSA, donor-specific antibodies; KTRs, kidney transplant recipients; TCMR, T-cell mediated rejection.

Our study had several strengths. We managed to include a large number of clinically and virologically very well characterized KTRs over a 10 years period. A careful post-transplantation follow-up care and our routine BKV-screening enabled us to obtain a very high data density. Further, sensitivity of BKV-PCR was high, with a detection limit of 200 IE/ml. Due to the standardized therapy protocol of BKV-DNAemia, outcomes were highly comparable during the whole study period. IVIG was implemented in the management of high-level BKV-DNAemia starting in 2014 and has been administrated in a unique large number of KTRs to date.

The central limitation of our study is the retrospective design with several potential biases, that should remind not to overstate the role of IVIG. Particularly, IVIG-treated KTRs received more distinctive reduction of immunosuppression, which could limit the comparability with respect to the development of alloimmunity between the IVIG and non-IVIG-treated groups. Overall, we observed a high incidence and early-onset of BKV-DNAemia that may be attributed to our intense immunosuppressive regimen that may exceed dosages and trough levels at other centres. Since we did not perform protocol biopsies in our cohort, our analysis regarding rejection may be impacted by selection bias.

In conclusion, we could demonstrate that KTRs with self-limited low-level BKV-DNAemia showed best protection against allosensitization. Among these KTRs a high PIRCHE score is strongly associated with the risk of *de novo* DSA development and rejection. The administration of IVIG, however, did not prove beneficial to clear BKV-DNAemia or prevent alloimmunity during the period of reduced immunosuppression in our study. Our study has important implications for the management of immunosuppressive therapy in KTRs with BKV-DNAemia.

Authorship

BN: participated in data collection, participated in data analysis, participated in writing of the paper. JN: participated in data collection, participated in writing

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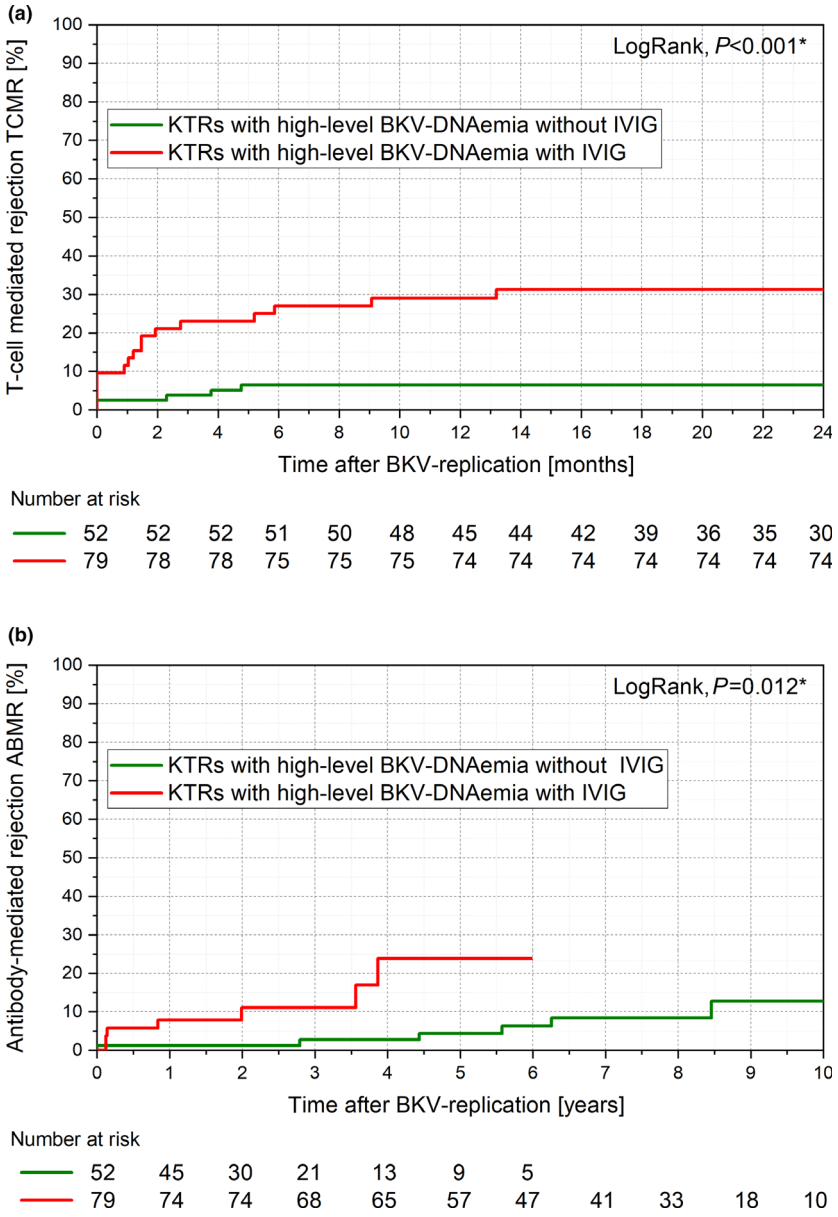

Figure 3 (a) Kaplan–Meier plot of TCMR by IVIG therapy in KTRs with high-level BKV-DNAemia. The incidence of TCMR was significantly higher among KTRs receiving IVIG compared to KTRs without IVIG therapy (LogRank, $P < 0.001$). (b) Kaplan–Meier plot of ABMR by IVIG therapy in KTRs with high-level BKV-DNAemia. The incidence of ABMR was significantly higher among KTRs receiving IVIG compared to KTRs without IVIG therapy (LogRank, $P = 0.012$). ABMR, antibody-mediated rejection; IVIG, intravenous immunoglobulins; KTRs, kidney transplant recipients; TCMR, T-cell mediated rejection.

of the paper. RPW: participated in writing of the paper. TFM: participated in research design, participated in writing of the paper. TS: participated in research design, participated in data collection, participated in data analysis, participated in writing of the paper.

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Conflict of interest

The authors have declared no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. (a) Kaplan–Meier plot of *de novo* DSA development by different BKV groups. (b) Kaplan–

Meier plot of ABMR development in different BKV groups. (c) Boxplots of baseline serum-creatinine values before BKV-replication (grey) and after BKV-replication (replication).

Figure S2. (a) Kaplan–Meier plot of *de novo DSA* development by IVIG therapy in KTRs with high-level BKV-DNAemia. (b) Boxplots of baseline serum-creatinine values before BKV-replication (white), during BKV-replication (grey) and after BKV-replication (dark grey) in KTRs with and without IVIG therapy.

Figure S3. (a) Kaplan–Meier plot of death-censored kidney allograft survival by different BKV groups. (b) Kaplan–Meier plot of death-censored kidney allograft survival by IVIG therapy in KTRs with high-level BKV-DNAemia.

Table S1. Immunosuppression intensity score.

Table S2. (A) Additional clinical characteristics and outcomes of different BKV groups. (B) Additional clinical characteristics and outcomes in KTRs with IVIG compared to KTRs without IVIG.

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