Scandinavian Journal of Urology and Nephrology

ISSN: 0036-5599 (Print) 1651-2065 (Online) Journal homepage: https://www.tandfonline.com/loi/isju19

Risk factors and interventional strategies for BK polyomavirus infection after renal transplantation

Dominik Steubl, Marcus Baumann, Tibor Schuster, MichaeL Fischereder, Bernhard K. Krämer, Uwe Heemann & Jens Lutz

To cite this article: Dominik Steubl, Marcus Baumann, Tibor Schuster, MichaeL Fischereder, Bernhard K. Krämer, Uwe Heemann & Jens Lutz (2012) Risk factors and interventional strategies for BK polyomavirus infection after renal transplantation, Scandinavian Journal of Urology and Nephrology, 46:6, 466-474, DOI: 10.3109/00365599.2012.726643

To link to this article: https://doi.org/10.3109/00365599.2012.726643

Scandinavian Journal of Urology and Nephrology, 2012; 46: 466–474

informa
healthcare

ORIGINAL ARTICLE

Risk factors and interventional strategies for BK polyomavirus infection after renal transplantation

DOMINIK STEUBL[1], MARCUS BAUMANN[1], TIBOR SCHUSTER[2], MICHAEL FISCHEREDER[3], BERNHARD K. KRÄMER[4], UWE HEEMANN[1] & JENS LUTZ[1,5]

[1]Abteilung für Nephrologie, [2]Institut für medizinische Statistik und Epidemiologie, Klinikum rechts der Isar der Technischen Universität München, München, Germany, [3]Medizinische Poliklinik Innenstadt, Klinikum der LMU, München, Germany, [4]V Medizinische Klinik, Universitätsklinikum Mannheim, Mannheim, Germany, and [5]Schwerpunkt Nephrologie, I Medizinische Klinik und Poliklinik, Universitätsmedizin Mainz der Johannis Gutenberg Universität, Mainz, Germany

Abstract

Objective. BK virus (BKV)-induced viraemia after renal transplantation can be associated with severe impairment of graft function. This study evaluated possible risk factors for BKV replication and examined the outcomes following various currently used treatment approaches. *Material and methods.* Fifty-seven renal transplant recipients with BKV viraemia were retrospectively compared with 71 BKV-negative recipients to identify risk factors for BKV viraemia. Furthermore, outcome and graft function in 14 patients with BKV replication, in whom mycophenolate mofetil (MMF) was discontinued with a dose reduction of the remaining immunosuppressants, were compared with 32 patients in whom both MMF and the additional immunosuppressants were reduced. *Results.* Patients with BKV viraemia received MMF ($p < 0.01$) and triple immunosuppression ($p < 0.01$) significantly more often, and displayed tacrolimus ($p = 0.034$) at higher blood concentrations ($p = 0.002$), a lower lymphocyte count ($p = 0.006$) and a longer warm ischaemic time ($p = 0.019$), and were more often male ($p = 0.026$). Patients in whom MMF was stopped had a higher chance of clearance of BKV viraemia ($p = 0.022$), which was achieved more rapidly ($p = 0.048$). Graft function improved during treatment and no graft losses occurred, compared with eight graft losses in the MMF-treated group ($p = 0.04$). *Conclusions.* MMF and tacrolimus could promote BKV viraemia after renal transplantation. Discontinuation of MMF together with a reduction of calcineurin inhibitors and glucocorticoids could be an option to reduce BKV replication after renal transplantation.

Key Words: *BK polyomavirus, immunosuppression, nephrology, renal allograft, transplantation*

Introduction

Acute and chronic graft failure is an important clinical problem in recipients of renal allografts. The main reasons for graft failure include rejections, toxic effects and infections related to immunosuppressive therapy. Among the infectious diseases complicating the course after renal transplantation, BK polyomavirus (BKV) nephropathy has gained interest in recent years, as it has been associated with graft dysfunction and even graft loss [1], although it was documented for the first time as early as 1970 [2]. The primary infection usually occurs in childhood, which leads to a seroprevalence of up to 90% in adults [3]. The virus remains latent in the uroepithelial cells and replication seems to be initiated under immunosuppressive therapy. The prevalence of viral replication in the blood of renal transplant recipients is between 7.5% and 29% [3–6]. BKV nephropathy develops in approximately 1–10% of patients with BKV replication in the blood [3,7–9], of whom 10–80% develop chronic graft dysfunction due to BKV nephropathy [9].

Correspondence: D. Steubl, Department of Nephrology, Klinikum rechts der Isar, Technische Universität München, Ismaninger Str. 22, 81675 München, Germany. Tel: +49 89 4140 5048. Fax: +49 89 4140 4909. E-mail: dominik.steubl@lrz.tum.de

(Received 19 March 2012; revised 2 July 2012; accepted 13 August 2012)

ISSN 0036-5599 print/ISSN 1651-2065 online
DOI: 10.3109/00365599.2012.726643

Risk factors associated with the development of BKV reactivation have been partially identified [9,10]. So far, no specific therapy is available. Most centres follow the recommendations in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines and reduce the dose of immunosuppressants [11].

This study assessed the risk factors associated with BKV replication and whether stopping mycophenolate mofetil (MMF) would have a different outcome in terms of BKV replication and graft function compared with only reducing immunosuppression but continuing MMF.

Material and methods

Study design

This retrospective analysis, conducted at three university hospital centres, evaluated 57 kidney allograft recipients (14 female, 43 male) who underwent transplantation between 2000 and 2006. In all patients BKV viraemia (>500 copies/ml blood) was detected at least once during follow-up (mean ± SD 225 ± 218 days) after transplantation. The threshold of >500 copies/ml was chosen as an inclusion criterion since it has been shown in earlier studies that patients with low levels of BKV replication levels (<10 000 copies/ml) may already suffer from BKV nephropathy or are at least at risk of developing BKV nephropathy [3,12–14]. In addition, outcomes in patients already treated at low viraemia levels, regarding BKV replication and nephropathy as well as graft function, have been demonstrated to be safe without an increased risk of graft failure [3,12–14]. Therefore, every case of viraemia exceeding that threshold is presumed to be of clinical significance, has to be monitored and eventually will require therapeutic action.

To analyse risk factors for the development of BKV replication, this group of patients was compared with a control group of 71 patients (32 female, 39 male) without BKV replication who were randomly selected from 194 patients (age >16 years) who underwent kidney allograft transplantation between 2000 and 2006. These patients were checked for BKV viraemia roughly every 4 weeks during the first 3 months after transplantation; after that time they were checked if a rise in creatinine levels was present. They were not matched for any parameters since they were used to evaluate possible risk factors. Evaluated parameters were gender of recipient, age of recipient/donor, cadaveric versus living transplantation, underlying disease, cytomegalovirus (CMV)–immunoglobulin G (IgG) status of recipient/donor, time of cold/warm ischaemia, number of biopsy-proven rejection episodes, and the immunosuppressive regimen at the time of first detection of BKV replication using serum concentrations of tacrolimus, cyclosporine A and sirolimus or daily dose of MMF and prednisolone, as well as leucocyte and differential blood count. Continuous risk factors and creatinine levels were assessed at 219 ± 66 days (mean ± SD) after transplantation, matched for the mean time of BKV replication detection in the BKV-positive group. To evaluate the graft function in the two groups MMFex and IMMUNred after therapeutic adaption of immunosuppression, creatinine levels were assessed 470 days after transplantation, matched for the mean time of follow-up in the group MMFex. (See below for a description of the two groups.)

To investigate the impact of modifying immunosuppression after BKV replication had been detected, the following endpoints were defined. Primary endpoints were sustained freedom from BKV replication at the end of follow-up, defined as two consecutive measurements within 2 weeks, and the time-course until this target was reached. As secondary endpoints, graft function and graft survival were compared in both groups at the end of follow-up.

Patients were included for this analysis in the case of sustained viraemia, defined by detection of BKV replication in the blood on at least two consecutive measurements. In addition, immunosuppression of the patients had to be reduced in order to treat the viraemia. The use of agents with possible antiviral activity to the pharmacological regimen (e.g. leflunomide) led to the exclusion of the patient.

According to these criteria, 46 of the initial 57 patients were included in the analysis. Five patients had to be excluded because of single, low BKV replication levels that vanished without changes in immunosuppression at the next visit to the outpatient clinic. Three patients were lost to follow-up. A further three patients received leflunomide to treat BKV replication. These patients already initially presented with high BKV replication levels (>1 000 000 copies/ml); a short course of reduced immunosuppression did not lead to a significant improvement in replication levels, so leflunomide was added to the immunosuppressive regimen.

The 46 included patients were split into two groups. Group MMFex patients had discontinuation of MMF and reduction of the remaining immunosuppression after BKV replication was detected in the blood for the first time ($n = 14$, Table I). In this group BKV replication was detected 190 ± 189 days (mean ± SD) after transplantation. The second group, IMMUNred, consisted of 32 patients (Table II), in whom the dosage of immunosuppressive therapy was also reduced, but MMF was not discontinued at the

Table I. Description of immunosuppression schemes at the time of first BK virus (BKV) replication detection, first follow-up and last control in the group MMFex (first follow-up/last control at a mean of 18.8/280 days after first BKV replication).

	First replication		First follow-up		Last control	
	n	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD
Cyclosporine A (ng/ml)	4	172.0 ± 54.0	4	151.0 ± 35.5	4	132.9 ± 44.2
Tacrolimus (µg/l)	10	9.7 ± 3.8*	10	8.2 ± 3.0	10	6.9 ± 1.9
MMF (mg/day)	14	914.3 ± 500	–	–	–	–
Prednisolone (mg/day)	14	13.1 ± 10.0**	13	8.6 ± 5.2	12	6.1 ± 4.2

Data are shown as number of patients (*n*) and mean ± standard deviation.
MMF = mycophenolate mofetil.
*$p = 0.008$ vs mean of first follow-up of tacrolimus; **$p = 0.031$ vs mean of first follow-up of prednisolone.

time of first detection of BKV replication. In this group BKV replication was detected 173 ± 157 days after transplantation. Therefore, in both groups the mean time of BKV replication was comparable, but earlier than in the whole group of patients with BKV replication (225 days). Three patients in whom MMF was discontinued very late in the observation period were also assigned to this group, since it could be assumed that the impact of discontinuing MMF on BKV replication at that point in time was not significant. One patient did not receive MMF at all, since he was on triple immunosuppression consisting of tacrolimus–sirolimus–prednisolone. Since this was a post-hoc analysis of a heterogeneous patient group from three different centres, the decision as to which modification of immunosuppression to perform was up to the physician in charge and did not follow a predefined protocol.

Data collection began when BKV replication was detected. First follow-up was defined as the patient's next visit to the outpatient clinic when BKV replication in the blood was measured. Follow-up was continued until no further BKV replication could be detected, the patient lost the graft or the end of the observation period was reached and viraemia was sustained. This time-point was defined as last control. During follow-up, blood concentrations of tacrolimus, cyclosporine A and sirolimus, doses of MMF and prednisolone, and creatinine levels were evaluated. In addition, all tests for BKV replication in the blood (in copies/ml) were recorded. The mean observation period from the first BKV replication was 280 ± 231 days in the group MMFex and 356 ± 351 days in the group IMMUNred ($p < 0.05$). Creatinine levels, number of graft losses, persisting BKV replication at the end of follow-up and the time until BKV replication was no longer detected were compared between the two groups.

Detection of BK virus replication

Real-time polymerase chain reaction for the detection of viral DNA was performed to quantify the level of BKV replication in the patients' blood samples.

Statistics

Statistical analysis was performed with Excel (Microsoft, Redmond, WA, USA) and SPSS (SPSS, Chicago, IL, USA). Excel was used to generate the control group and SPSS was used for tests of statistical significance.

Unless specified otherwise, continuous parameters were described as mean and standard deviation (SD) for normal distributions and as median and range for skewed distributions. Discrete parameters were assessed by univariate analysis with cross-tables, odds

Table II. Description of immunosuppression schemes at the time of first BK virus (BKV) replication detection, first follow-up and last control in the group IMMUNred (first follow-up/last control at a mean of 25.9/356 days after first BKV replication).

	First replication		First follow-up		Last control	
	n	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD
Cyclosporine A (ng/ml)	5	113.0 ± 54.1*	5	178.2 ± 124.7	2	107.0 ± 25.5
Tacrolimus (g/l)	27	9.2 ± 3.1	27	8.9 ± 3.7‡	28	6.4 ± 2.4
MMF (mg/day)	31	865.5 ± 361.0**	31	762.6 ± 296.8	28	623.0 ± 474.9
Prednisolone (mg/day)	31||	6.4 ± 4.5†	27	5.1 ± 2.5	19	4.3 ± 2.7

Data are shown as number of patients (*n*) and mean ± standard deviation.
*$p = 0.043$ vs mean of first follow-up of cyclosporine A; **$p = 0.024$ vs mean of first follow-up of mycophenolate mofetil (MMF); †$p = 0.002$ vs mean of first follow-up of prednisolone; ‡$p = 0.002$ vs mean of last control of tacrolimus; ||$p < 0.001$ vs *n* at first follow-up of prednisolone.

Table III. Summary of continuous risk factors.

	Case group		Control group	
	n (%)	Mean ± SD	*n* (%)	Mean ± SD
MMF dose (mg/day)	54 (94.7)	858.8 ± 392.1*	40 (56.3)	1505 ± 348.3
Tacrolimus blood concentration (g/l)	44 (77.2)	9.0 ± 3.2**	43 (60.6)	7.1 ± 1.7
Lymphocyte count (cells/l)	44 (77.2)	1213.2 ± 830.6†	53 (74.6)	1634.7 ± 896.2
Warm ischaemic time (min)	53 (93.0)	29.6 ± 13.3‡	71 (100)	26.6 ± 9.7
Cold ischaemic time (min)	54 (94.7)	600.4 ± 452.9	71 (100)	498.7 ± 325.1
Prednisolone dose (mg/day)	53 (93.0)	8.1 ± 6.9	70 (98.6)	7.9 ± 4,7
Cyclosporine A blood concentration (ng/ml)	13 (22.8)	158.4 ± 95.0	28 (39.4)	131.1 ± 26.1
Age donor (years)	46 (80.7)	49.0 ± 17.0	71 (100)	50.3 ± 14.2
Age recipient (years)	57 (100)	47.3 ± 14.5	71 (100)	47.5 ± 16.2
Leucocyte count (cells/l)	56 (98.2)	7400 ± 3100	71 (100)	7700 ± 2800

Case group = patients with detected BK virus (BKV) replication; control group = patients without BKV replication; *n* = number of patients; SD = standard deviation; MMF = mycophenolate mofetil.
*$p < 0.001$ vs mean of control group; **$p = 0.002$ vs mean of control group; †$p = 0.006$ vs mean of control group; ‡$p = 0.019$ vs mean of control group.

ratio (OR) and confidence interval (CI). For independent continuous parameters, the Mann–Whitney test was used for univariate testing of significance, whereas for dependent samples the Wilcoxon test was used. The log-rank test and Kaplan–Meier estimator were used to evaluate the time-course for sustained negative BKV replication. A p value of less than 0.05 was considered significant.

Results

Risk factors for BK virus replication

Patients of male gender ($p = 0.026$) with triple immunosuppression, consisting of calcineurin inhibitor, MMF and prednisolone, were at increased risk of BKV replication ($p < 0.001$). In the whole cohort, tacrolimus and MMF were both risk factors for BKV replication in univariate analysis ($p = 0.034$, $p < 0.001$), as were high serum tacrolimus concentrations ($p = 0.002$). Furthermore, the lymphocyte count was significantly lower in patients with BKV replication ($p = 0.006$), who also had a longer warm ischaemic time ($p = 0.019$) (Table III, Figure 1).

Change of immunosuppression and BK virus replication

Before the first detection of BKV replication, four patients (28.6%) in the group MMFex received triple immunosuppression consisting of cyclosporine A–MMF–prednisolone, whereas 10 patients (71.4%) received tacrolimus–MMF–prednisolone (Table I).

In the group IMMUNred, five patients (15.6%) were on cyclosporine A–MMF–prednisolone, while 25 patients (78.1%) received tacrolimus–MMF–prednisolone. One patient (3.1%) received tacrolimus–MMF and one patient tacrolimus–sirolimus–prednisolone (Table II).

Median BKV replication levels did not differ significantly between the two groups. First median BKV replication was 5105 (range 600–396 000) copies/ml in the group MMFex and 3950 (1000–2 950 000) copies/ml in the group IMMUNred ($p = 0.611$). The number of patients with replication levels greater than 10 000 copies/ml did not differ significantly between the two groups (four patients in group MMFex, eight in group IMMUNred, $p = 1.000$).

After detection of BKV replication, the immunosuppression regimen was adapted. MMF was discontinued in the group MMFex; in one patient prednisolone was also discontinued. Furthermore, serum concentrations of tacrolimus and the dose of prednisolone were significantly reduced ($p = 0.008$, $p = 0.031$). The serum concentration of cyclosporine A also was reduced non-significantly. At the end of the observation period (mean 280 days after first BKV replication), two patients received tacrolimus monotherapy, while the remaining 12 patients still received a calcineurin-inhibitor–prednisolone combination. The concentrations/doses of immunosuppressive agents were not reduced significantly any further after the first control visit (Table I). At the end of the observation period 13 out of 14 patients no longer showed BKV replication. One patient still had low BKV replication levels (<500 copies/ml). This is mentioned here since, in contrast to the inclusion criteria for BKV replication (>500 copies/ml) indicated above, it is important for patients with sustained viraemia to achieve completely negative BKV replication results (replication level of 0 copies/ml); in the authors' clinical experience, relapses may still

occur at this stage. This is in contrast to initial BKV replication levels of less than 500 copies/ml, which often become negative at the next control.

In the group IMMUNred prednisolone was discontinued in four patients with tacrolimus–MMF–prednisolone at the time of first detection of BKV replication. Serum concentrations of cyclosporine A were increased (p = 0.043), whereas the doses of MMF and prednisolone were reduced significantly (p = 0.024, p = 0.002). Tacrolimus serum concentrations tended to be lower (Table II). Until the end of the observation period, 17 patients still received triple immunosuppression, eight patients received tacrolimus–MMF and two patients received tacrolimus monotherapy. The remaining five patients received individual regimens. Overall, 28 patients received MMF until the end of the observation period. Three patients were assigned to the group IMMUNred as MMF was discontinued very late in the time-course. From the first follow-up to the last control concentrations/doses of all immunosuppressants were reduced, which was significant for tacrolimus (p = 0.002). At the end (mean 356 days after first BKV replication), 19 out of 32 patients had no detectable BKV replication, while 13 patients still had a median BKV replication of 2200 (500–38 630) copies/ml.

The only significant differences between the two groups regarding immunosuppression resulted from discontinuation of MMF after BKV replication was first detected (p < 0.001), and higher doses of prednisolone in MMFex at the time of first BKV replication (p = 0.001) and first follow-up (p = 0.034).

At the end of the observation period, significantly more patients in the group MMFex than in IMMUNred had no BKV replication (p = 0.022, OR = 0.112, 95% CI 0.013–0.968) (Figure 2), and this was also achieved more rapidly (207 vs 529.2 days, p = 0.048) (Figure 3).

Graft function

At the time of first BKV replication, creatinine levels were significantly higher in the group MMFex than in the control group (p < 0.012), whereas no statistical differences were detectable between IMMUNred and the control group, or between IMMUNred and MMFex. At the end of the observation period, no statistically significant differences could be detected, but creatinine levels tended to fall in MMFex, whereas values rose slightly in IMMUNred (Figure 4).

Only patients who still had a functioning graft at the end of the follow-up period were included in the statistical evaluation.

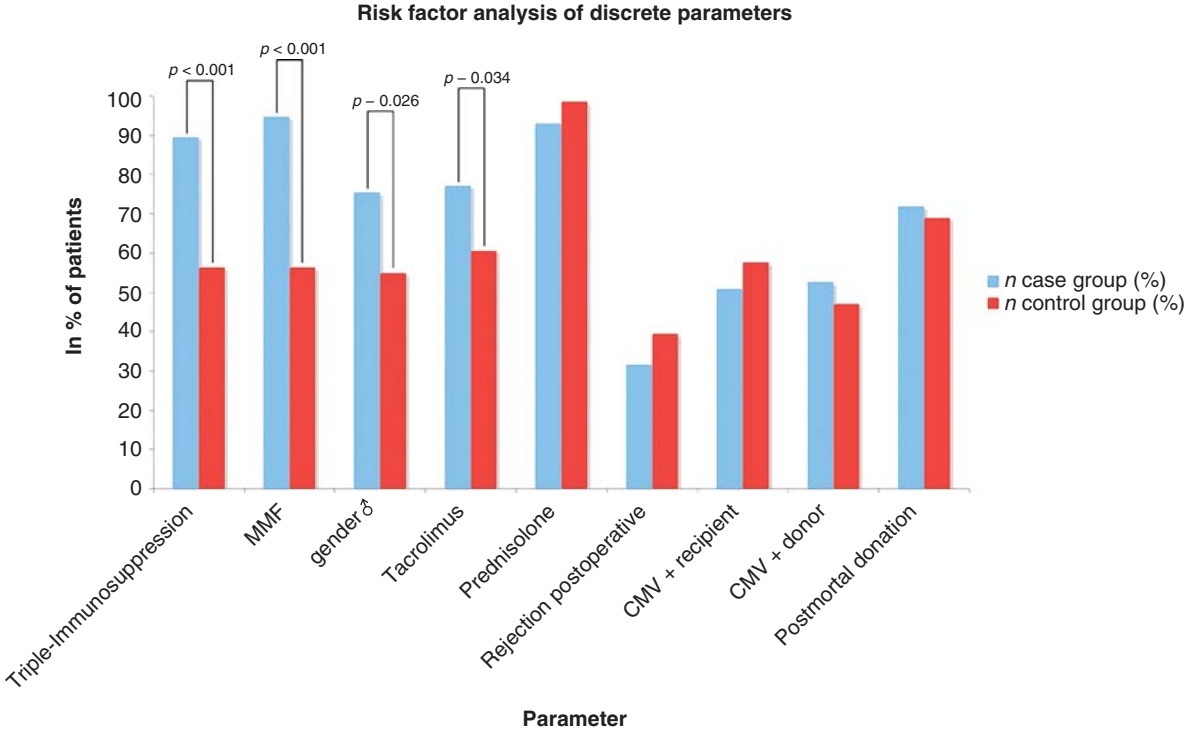

Figure 1. Risk factor analysis of discrete parameters. n = Number of patients; case group = number of patients with BK virus (BKV) replication; control group = number of patients without BKV replication; MMF = mycophenolate mofetil; CMV = cytomegalovirus.

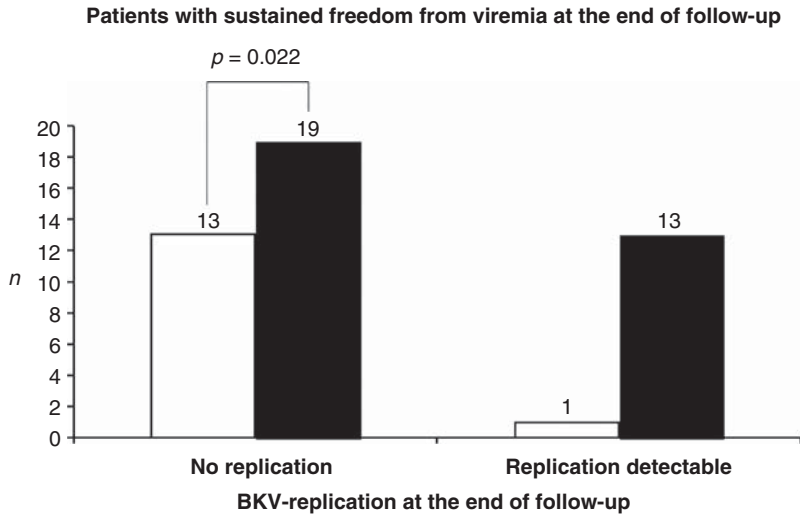

Figure 2. Patients with sustained freedom from viraemia and patients with BK virus (BKV) replication at the end of follow-up in the MMFex (□) and IMMUNred (■) groups. *n* = number of patients.

Graft loss

No patients lost their graft in the group MMFex (0/14, 0%), compared with eight patients in the group IMMUNred (8/32, 25%, $p = 0.04$).

Discussion

The incidence of BKV replication in the blood after renal transplantation was 6.7% in this analysis, while BKV replication was detected up to 18.6 months after transplantation (mean time 225 ± 218 days). This incidence is in the lower range compared to the results of other studies, which reported an incidence of 7.5–29% [3–6], while the latency to the start of BKV replication is in line with other observations (4 weeks to 32 months after transplantation) [3,4,15–17].

In this study triple immunosuppression as well as MMF and tacrolimus were strongly associated with BKV replication. This is in line with previous observations for the single drugs [3,17–19] and the combination [6,8,20,21] as a risk factor. Hirsch et al. [9] analysed 11 studies, in which tacrolimus was used in more than 50% of patients with BKV replication in nine

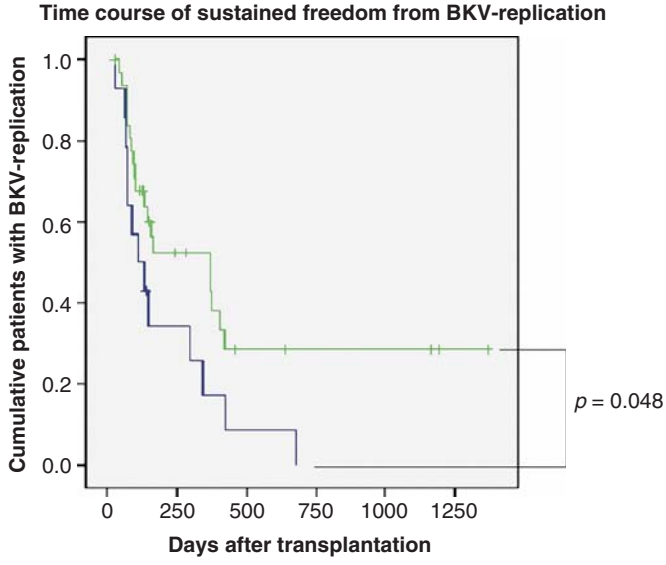

Figure 3. Time-course of sustained freedom from BK virus (BKV) replication, i.e. until BKV replication could no longer be detected. Dark blue line: MMFex group; pale green line: IMMUNred group.

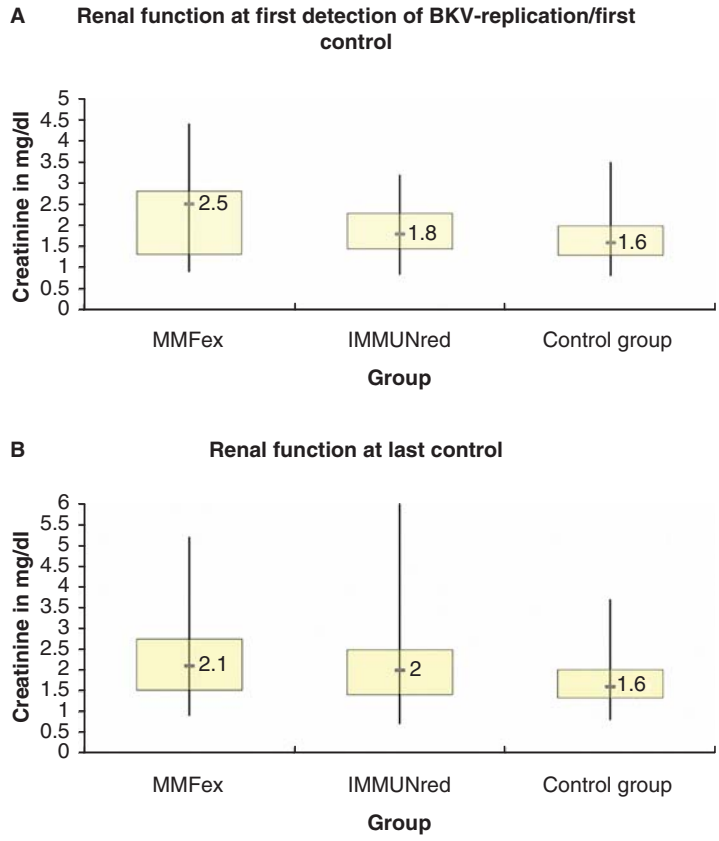

Figure 4. Renal function in the three groups: (a) at the first BKV replication detection/first control after transplantation (190 days in MMFex, 173 days in IMMUNred, 219 days in control group); (b) at the last control after transplantation (470 days in MMFex, 529 days in IMMUNred, 470 days in control group).

studies and MMF in seven studies. This has to be interpreted cautiously, since tacrolimus and MMF are standard immunosuppressants administered after renal transplantation and so are likely to be part of the immunosuppressive regimen when BKV replication occurs. However, both drugs seem to increase the risk of BKV replication, and this risk may be even higher if the drugs are administered in combination. Tacrolimus may increase the risk of BKV replication through an increased area under the curve (AUC) of mycophenolic acid when administered together with MMF owing to the increased enterohepatic recirculation of MMF [22]. Furthermore, the present study showed a mean tacrolimus concentration of 9.0 µg/l, which was significantly higher than in the control group. In earlier studies, serum levels of above 8–9 µg/l were reported to be associated with an increased risk of BKV replication [15,23]. In addition, male gender was associated with a 2.8-fold increased risk of BKV replication, which is in line with previous observations [15,16,18]. Furthermore, warm ischaemic time was significantly higher in patients with BKV replication, which has not been reported previously. However, experimental evidence suggests that a pathophysiological background may be responsible for this association [24,25]. Atencio et al. showed in an experimental model that adult mouse kidneys became susceptible to polyomavirus replication through ischaemia [24]. Fishman postulated that renal injury and a proinflammatory state, which are both increased by prolonged warm ischaemia, contribute to viral reactivation [25].

In the present study a reduced lymphocyte count was detected in patients with BKV replication, while the leucocyte count did not differ significantly. Lymphopenia could also play a role in the initiation of BKV replication. According to Comoli et al. [26,27], this could be related to changes in the number of BKV-specific $CD4^+$ and/or $CD8^+$ T cells. Lymphopenia could be due to elevated MMF serum concentrations. In the present study, lymphopenia could be explained by elevated tacrolimus concentrations, which lead to elevated MMF–AUC levels through the enterohepatic recirculation of MMF. The lymphocyte count could be another tool in assessing the level of immunosuppression and therefore the risk of opportunistic infections such as BKV.

It remains unclear whether discontinuing MMF would have different effects compared to dose reduction of immunosuppressants in patients with BKV replication. Alternatively, immunosuppressants such as leflunomide that may have antiviral activity [28] could be better alternatives.

Discontinuing MMF is mentioned as an option by current KDIGO guidelines [11]. Trofe et al. [29] summarized a large number of studies and their recommendations for modification, and concluded that the first line should be a reduction in the serum concentration/daily dosage of the administered drugs (for tacrolimus <6 μg/l with simultaneous reduction of MMF; for cyclosporine A 100–150 μg/l, MMF <1 g/day). In the present study, discontinuation of MMF was associated with a higher BKV replication clearance rate compared to a reduction in the dosages of the immunosuppressants. This is in line with results of more recent publications [14,30,31]. In these studies MMF was also successfully discontinued.

In addition, there were no graft losses, whereas in the control group eight patients developed end-stage renal disease.

A possible limitation of discontinuing an immunosuppressive drug could be allograft rejection. However, in this study no patient lost their graft when MMF was discontinued, while their renal function improved, whereas eight graft losses occurred in the dosage reduction group. It is not clear whether these patients lost their grafts owing to BKV nephropathy or to chronic rejection, since biopsies were not routinely performed. Bearing this caveat in mind, the results suggest that discontinuing MMF and reducing the dosage of the remaining immunosuppressants (tacrolimus serum concentration <7 μg/l, cyclosporine A <150 μg/l, prednisolone <7 mg/day) is a practical and safe way of modifying immunosuppression after BKV replication has been detected. A possible bias is that there were eight patients in the IMMUNred group with an initial viraemia greater than 10 000 copies/ml compared with four in the MMFex group; this might also have led to more patients experiencing graft loss. But since the number of patients included in the MMFex group was much smaller, the percentage of patients with a viraemia of more than 10 000 copies/ml was equal, so one would also expect an equal percentage of patients to lose their graft in both groups, which was not the case. Therefore, although it is unclear whether the graft losses occurred as a result of BKV or other causes, the discontinuation of MMF resulted in better graft survival.

Three patients who received leflunomide after detection of BKV replication were also evaluated. In these patients BKV replication was detected 342, 284 and 558 days after transplantation; in all patients BKV nephropathy was diagnosed (biopsy proven). Initial replication levels were 14 000 000, 1 200 000 and 6 000 000 copies/ml, respectively. In all patients overall immunosuppression was reduced (reduction/discontinuation of MMF, dosage reduction of calcineurin inhibitor/steroid) then leflumonide was added 95, 90 and 76 days after first BKV replication. Concerning the outcome, one patient lost his graft and returned to dialysis treatment 236 days after first BKV replication. The last BKV replication was 73 500 copies/ml. The second patient cleared the virus but also returned to haemodialysis treatment because of chronic graft failure, but this occurred after clearance of the virus. The third patient still had low BKV replication levels and a functioning graft at the end of follow-up. Summing up the experience from these cases, leflunomide did not lead to a very favourable outcome in patients with BKV replication, but one has to keep in mind that all patients had very high initial replication levels and leflunomide was not started when first BKV replication was detected. It may be speculated that had MMF been changed to leflunomide earlier this might have resulted in a better graft function and termination of viral replication [32].

There were several limitations to this study. The small number of patients included could lead to type 1 or type 2 statistical errors and low power. Furthermore, all results were analysed retrospectively. The IMMUNred group was quite heterogeneous and so comparison with MMFex may be limited. No significant differences between the two groups regarding immunosuppression could be detected, apart from discontinuation of MMF. In addition, the diagnosis of BKV nephropathy via biopsy was not performed routinely. Therefore, the authors cannot be certain whether clinical findings such as deterioration of renal function or graft losses were due to BKV replication or to other pathologies such as rejection.

In conclusion, this study analysed risk factors that could help to identify recipients who may be at risk for the development of BKV replication. In addition, reduction of immunosuppression with discontinuation of MMF is a promising strategy to cope with BKV replication.

Declaration of interest: There are no conflicts of interest.

References

[1] Hariharan S. BK virus nephritis after renal transplantation. Kidney Int 2006;69:655–62.

[2] Gardner SD, Field AM, Coleman DV, Hulme B. New human papilloma virus (B.K.) isolated from the urine after renal transplantation. Lancet 1971;i:1253–7.

[3] Hirsch HH, Knowles W, Dickenmann M, Passweg J, Klimkait T, Mihatsch MJ, et al. Prospective study of polyomavirus type BK replication and nephropathy in renal transplant recipients. N Engl J Med 2002;347:488–96.

[4] Bressolette-Bodin C, Coste-Burel M, Hourmant M, Sebille V, Andre-Garnier E, Imbert-Marcille BM. A prospective longitudinal study of BK virus infection in 104 renal renal transplant recipients. Am J Transplant 2005;5:1926–33.

[5] Vera-Sempere FJ, Rubio L, Moreno-Baylach MJ, Garcia A, Prieto M, Camanas A, et al. Polymerase chain reaction detection of BK virus and monitoring of BK nephropathy in renal transplant recipients at the University Hospital Santa Fe. Transplant Proc 2005;37:3770–3.

[6] Brennan DC, Agha I, Bohl DL, Schnitzler MA, Hardinger KL, Lockwood M, et al. Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. Am J Transplant 2005;5: 582–94.

[7] Nickeleit V, Mihatsch MJ. Polyomavirus nephropathy in native kidneys and renal allografts: an update on an escalating threat. Transpl Int 2006;19:960–73.

[8] Ramos E, Drachenberg CB, Portocarrero M, Wali R, Klassen DK, Fink JC, et al. BK virus nephropathy diagnosis and treatment: experience at the University of Maryland Renal Transplant Program. Clin Transpl 2002;143–53.

[9] Hirsch HH, Brennan DC, Drachenberg CB, Ginevri F, Gordon J, Limaye AP, et al. Polyomavirus-associated nephropathy in renal transplantation: interdisciplinary analyses and recommendations. Transplantation 2005;79:1277–86.

[10] Manitpisitkul W, Wilson NS, Haririan A. Immunosuppressive agents as risk factors for BK virus nephropathy: an overview and update. Expert Opin Drug Saf 2010;9: 959–69.

[11] Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009;9:S1–155.

[12] Almeras C, Vetromile F, Garrique V, Szwarc I, Foulogne V, Mourad G. Monthly screening for BK viremia is an effective strategy to prevent BK virus nephropathy in renal transplant recipients. Transpl Infect Dis 2011;13:101–8.

[13] Huang G, Chen LZ, Qiu J, Wang CX, Fei JG, Deng SX, et al. Prospective study of polyomavirus BK replication and nephropathy in renal transplant recipients in China: a single-center analysis of incidence, reduction in immunosuppression and clinical course. Clin Transplant 2010;24: 599–609.

[14] Almeras C, Foulongne V, Garrigue V, Szwarc I, Vetromile F, Segondy M, et al. Does reduction in immunosuppression in viremic patients prevent BK virus nephropathy in de novo renal transplant recipients? A prospective study. Transplantation 2008;85:1099–104.

[15] Ramos E, Drachenberg CB, Papadimitriou JC, Hamze O, Fink JC, Klassen DK, et al. Clinical course of polyoma virus nephropathy in 67 renal transplant patients. J Am Soc Nephrol 2002;13:2145–51.

[16] Trofe J, Gaber LW, Stratta RJ, Shokouh-Amiri MH, Vera SR, Alloway RR, et al. Polyomavirus in kidney and kidney–pancreas transplant recipients. Transpl Infect Dis 2003;5:21–8.

[17] Kim HC, Hwang EA, Han SY, Park SB, Park KK. Polyomavirus nephropathy after renal transplantation: a single centre experience. Nephrology (Carlton) 2005;10:198–203.

[18] Randhawa P, Brennan DC. BK virus infection in transplant recipients: an overview and update. Am J Transplant 2006;6: 2000–5.

[19] Barri YM, Ahmad I, Ketel BL, Barone GW, Walker PD, Bonsib SM, et al. Polyoma viral infection in renal transplantation: the role of immunosuppressive therapy. Clin Transplant 2001;15:240–6.

[20] Crew RJ, Markowitz G, Radhakrishnan J. Therapeutic options in BK virus-associated interstitial nephritis. Kidney Int 2006;70:399–402.

[21] Maiza H, Fontaniere B, Dijoud F, Pouteil-Noble C. Graft dysfunction and polyomavirus infection in renal allograft recipients. Transplant Proc 2002;34:809.

[22] Undre NA. Pharmacokinetics of Tacrolimus-based combination therapies. Nephrol Dial Transplant 2003;18:i12–15.

[23] Mengel M, Marwedel M, Radermacher J, Eden G, Schwarz A, Haller H, et al. Incidence of polyomavirus-nephropathy in renal allografts: influence of modern immunosuppressive drugs. Nephrol Dial Transplant 2003;18: 1190–6.

[24] Atencio IA, Shadan FF, Zhou XJ, Vaziri ND, Villareal LP. Adult mouse kidneys become permissive to acute polyomavirus infection and reactivate persistent infections in response to cellular damage and regeneration. J Virol 1993;67:1424.

[25] Fishman JA. BK virus nephropathy–polyomavirus adding insult to injury. N Engl J Med 2002;247:527–30.

[26] Comoli P, Basso S, Azzi A, Moretta A, De Santis R, Del Galdo F, et al. Polyomavirus BK-specific immunity after kidney transplantation. Transplantation 2004;78:1229–32.

[27] Comoli P, Binggeli S, Ginevri F, Hirsch HH. Polyoma-associated nephropathy: update on BK-virus-specific immunity. Transpl Infect Dis 2006;8:86–94.

[28] Josephson MA, Williams JW, Chandraker A, Randhawa PS. Polyomavirus associated nephropathy: update on antiviral strategies. Transpl Infect Dis 2006;8:95–101.

[29] Trofe J, Hirsch HH, Ramos E. Polyomavirus-associated nephropathy: update of clinical management in kidney transplant patients. Transpl Infect Dis 2006;8:76–85.

[30] Hardinger KL, Koch MJ, Bohl DJ, Storch GA, Brennan DC. BK-virus and the impact of pre-emptive immunosuppression reduction: 5-year results. Am J Transplant 2010;10:407–15.

[31] Weiss AS, Gralla J, Chan L, Klem P, Wiseman AC. Aggressive immunosuppression minimization reduces graft loss following diagnosis of BK virus-associated nephropathy: a comparison of two reduction strategies. Clin J Am Soc Nephrol 2008;3:1812–19.

[32] Wu JK, Harris MT. Use of leflunomide in the treatment of polyomavirus BK-associated nephropathy. Ann Pharmacother 2008;42:1679–85.