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# Conversion to mTOR-inhibitors with adjunction of IV immunoglobulins in kidney-transplant recipients with BKV infection: a retrospective study

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Carla Vela. Conversion to mTOR-inhibitors with adjunction of IV immunoglobulins in kidney-transplant recipients with BKV infection: a retrospective study. Human health and pathology. 2021. dumas-03352461

**HAL Id: dumas-03352461**

**<https://dumas.ccsd.cnrs.fr/dumas-03352461>**

Submitted on 23 Sep 2021

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Année : 2021

**TRAITEMENT DE L'INFECTION À BK VIRUS EN  
TRANSPLANTATION RÉNALE PAR INHIBITEUR DE MTOR ET  
IMMUNOGLOBULINES POLYVALENTES :  
ÉTUDE RÉTROSPECTIVE**

THÈSE  
POUR LE DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE  
SPÉCIALITÉ : NÉPHROLOGIE

Par Mme Carla VELA

*[Données à caractère personnel]*

THÈSE SOUTENUE PUBLIQUEMENT À LA FACULTÉ DE MÉDECINE DE GRENOBLE

Le 13/09/2021

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## **Remerciements**

### *Aux membres du jury*

Au Professeur Rostaing, pour votre bienveillance et votre encadrement. Merci pour votre accueil dans cette unité.

Au Dr Germi, pour votre aide précieuse pour le recueil des données, et votre expertise virologique qui enrichira ce travail.

Au Dr Noble, pour avoir accepté de co-créer cette thèse, et pour ces moments passés à t'entendre chantonner dans le bureau des assistants pendant nos séances travail (ça valait le coup).

Au Dr Malvezzi, pour ton franc parler, mais surtout pour ton écoute et ta sympathie. Promis, je ne mettrai plus d'amaretto dans mon tiramisu...

Au Dr Le Maréchal, pour m'avoir fait aimer l'infectiologie grâce à toutes ces CV digressives, et les pauses thé entre deux debriefing d'avis... Je regarde toujours si la porte est ouverte quand je passe dans le couloir du 3<sup>ème</sup>, au cas où !

### *A toute l'équipe de Néphrologie*

Aux premiers assistants, Dr Cerba meilleur superviseur de biopsies rénales, et Dr Terrec, qui m'aura appris à taper du pied quand je suis pas content, et qui m'aura aidée dans les moments chafouins.

Au Dr Naciri Bennani, le roi du cathé, grâce à qui ce début d'internat est passé « comme du beurre ».

Au Dr Tetaz, pour ta supervision sans faille lors de mes premiers pas au CHU, tu auras illuminé mes lundi midi passés à l'AGDUC.

Au Dr Chevallier, qui m'aura beaucoup appris de son humanité envers les patients. Et qui remarque tous mes passages chez le coiffeur.

Au Dr Jouve, pour avoir gardé Brandade et m'avoir volé mon co-interne tous les jeudi midi quand j'oubliais mes affaires pour aller courir.

Au Dr Padilla, et aux week end d'astreintes « géniaux ». Au Dr Janbon pour son modèle d'investissement auprès des patients.



Aux Infirmiers, AS et secrétaires de Néphro, à Mounia pour les goûters de 4h du matin, Tom, Lucas, Etienne, Quentin, Sonia, Sylvie, Tiphaine, Tatiana pour votre aide et votre bonne humeur...

A la team dialyse pour m'avoir laissée investir le territoire du 14<sup>ème</sup> pendant 5 mois géniaux.

Aux Dr Giovannini et Emprou pour les colloques de néphrophat'.

*A tous mes co-internes, collègues et amis,*

A Jules, co-interne parmi les co-internes, mais surtout ami, qui ne fait même pas exprès d'être une personne exceptionnelle.

A Omar et Ariane, compagnons du 3<sup>o</sup>L, chaque année qui passe est une « année d'expérience » !

A Catoch, la plus tubulopathologiste des néphrologues, gaufriériste la plus douée que je connaisse.

A Anne So pour son phlegme, ses conseils et ses cahiers de cours qui m'ont sauvée quelques fois... A Antoine et Lionel, voisins du 14<sup>ème</sup>.

A Reda & Alexandra, les Nîmois expatriés que j'ai réussi à embusquer jusqu'ici !

A Louise, Lara, Valentine ; et Marie pour son passage dans le pays de la Néphrologie et pour y avoir importé les midi à l'Absolu...

Aux copains de Thonon, Jonathan, Marie, Antoine, Adèle, Yannick, Robin, les Juliette, Mélanie, Elise et tout le Gallia.

Aux Dr Epron, Bakoto, Gallen et Megri et à l'équipe de Néphrologie des HDL, pour avoir accompagné mes premiers pas en tant qu'interne. Merci Catherine pour tes conseils, et pour les soirées chez Avicenne !

Au service d'infectiologie et à tous les médecins, infirmiers, aides-soignants, secrétaires géniaux qui le composent. A Isa, Myriam, Anne Laure et Fanny. Au Dr Pavese et au Pr Epaulard pour m'avoir accordé leur confiance. A mes co-internes d'infectiologie pour avoir partagé ce semestre si spécial, Natacha, Tiphaine, Tiphanie, Yanis et Rémi.

A Justin et Olive pour avoir formé un trio de choc, et avoir permis des débats très drôles à modérer...

A la réanimation de Chambéry, aux grands, Manon, Alex (moins grand) et Maxence qui m'ont appris à avoir le lactate facile (astuce de réanimateur). A Baptiste et Léa, pour avoir partagé la découverte de cette spécialité.

A Clémence, pour m'avoir fait rechuter dans le Coca... Aux David, pour leur compétence et leur bienveillance.

Au 5°C d'hémato, aux Docteurs Thiebaut, Carré et Bubblewood et à toute l'équipe, pour votre bonne ambiance et votre écoute.

A Victoria, pour ses menaces perpétuelles, Mathilde pour son enthousiasme (t'es la meilleure !), Dr Lulu pour être tout le temps là quand il faut, Alexandra pour ta gentillesse et Amandine, mon binôme du placard à interne, cheffe avant l'heure et très (très) bon public...

Aux GreNîmois, Stella, Arnaud, Thibaut (par alliance) et Thibaud, qui ont fait la transition entre ici et là-bas.

A tous les copains Nîmois pour ce bel externat,

Simon, Jeff, Justine, Clément, Maël, Charles, Julien, Neel, Antoine, Thu, et tous les habitants/passagers de la Rue Dorée.

A Iris et Agathe, soutien infaillible de l'externat, (presque) toujours prêtes pour partir en week-end, tant que c'est pas moi qui conduis...

A Julie et Charlotte, la belle surprise de mon arrivée à Grenoble, toujours là pour me sortir la tête de l'hôpital.

A mes copines de PACES et au Theresianum, sans qui tout ça n'aurait jamais eu lieu.

A Sophia, la meilleure pour partager un bon 29 février à la bougie du sapeur !

A Philippine & Marion et à nos treize ans d'amitié, partis pour durer encore un bout de temps.

A Julie et à nos révisions du bac à l'Ubu le mercredi après-midi, on se retrouve à Paris !

A Laurence, mon p'tit poulet et mon homologue de parcours, on sera pas allées à Berkeley mais pour le reste on a réussi ! Et à Numerus, qui m'accompagne encore aujourd'hui ! (il a bien grandi)

### *A ma famille*

A mes parents, Carlito et Marianita, pour m'avoir accompagnée tout au long de ces aventures (et c'est pas fini !), pour les staff au téléphone (oui, j'ai cherché le SAPL papa...) et les empanadas dans la valise le dimanche soir. Pour m'avoir emmenée à la plage quand y en avait marre des montagnes.

A Pilou, pour avoir garni ma garde-robe gratos toutes ces dernières années, et pour tous ces moments partagés.

A Geoffroy, à mes côtés depuis 6 belles années, qui continue à me rassurer tous les jours de ciel gris et à me sortir tous les jours de ciel bleu...

A Christine, PF, Elvina et Claire pour les encouragements sur la dernière ligne droite.

A Brandade, qui aura littéralement accompagné toute la rédaction de ce travail affalée à côté du clavier.

A tous ceux qui ne seront pas dans ces lignes mais qui m'auront accompagnée au cours des dix dernières années, pardon... Et Merci.



**Abbreviations:**

ABMR : Antibody Mediated Rejection

ATG : antithymocyte globulins

BKV : BK virus

CNI : calcineurin inhibitors

DCGS : Death-censored graft survival

eGFR : estimated glomerular filtration rate

IVIg : Intravenous Immunoglobulins

KT : Kidney Transplant

MMF : Mycophenolate Mofetil

mTORi : Mammalian Target Of Rapamycin

NHBD : non heart beating donor

PvAN : polyomavirus associated nephropathy

qPCR : quantitative polymerase-chain reaction

SOC : Standard Of Care

TCMR : T-Cell Mediated Rejection

## **Conversion to mTOR-inhibitors with adjunction of IV immunoglobulins in kidney-transplant recipients with BKV infection: a retrospective study**

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## Traitement de l'infection à BK Virus en transplantation rénale par inhibiteur de mTOR et Immunoglobulines polyvalentes : étude rétrospective

### Résumé

**Introduction :** La néphropathie associée au BK virus (PvAN, Polyomavirus Associated Nephropathy) est associée à un risque augmenté de dysfonction et de perte de greffon et justifie un traitement actif. La conversion aux inhibiteurs de mTOR (imTOR) et la réduction de l'immunosuppression pourraient prévenir le risque de PvAN. Les immunoglobulines polyclonales humaines (IgIV) augmentent le titre des anticorps anti-BKV chez les greffés rénaux. Dans cette étude rétrospective monocentrique nous avons évalué l'efficacité sur la clairance virale du BKV d'un traitement combiné par imTOR et IgIV en comparaison au traitement de référence par baisse de l'immunosuppression.

**Méthodes :** Quarante patients transplantés rénaux ayant présenté une première virémie BKV ont été inclus entre mars 2013 et octobre 2020 et séparés en un groupe imTOR/IgIV (conversion de l'immunosuppression pour l'évérolimus et 1200 mg/kg d'IgIV sur 6 mois) et un groupe contrôle où l'immunosuppression était réduite. Le critère de jugement principal était la négativation de la virémie à un an. La fonction rénale, l'incidence des rejets, l'évolution vers la PvAN et la tolérance à l'évérolimus ont également été évalués.

**Résultats :** Le taux de négativation de la virémie à un an était plus important dans le groupe contrôle que dans le groupe imTORi/IgIV (100 % vs 45,5 %,  $p=0,004$ ). La survie du greffon censurée sur le décès ne différait pas entre le groupe imTORi/IgIV et le groupe contrôle. L'incidence des rejets cellulaires et humoraux et la fonction rénale à 12 mois étaient similaires entre les deux groupes. En analyse multivariée, les facteurs de risque de persistance de la virémie à 12 mois étaient l'appartenance au groupe de traitement

imTOR/IgIV et la présence d'une virémie soutenue au cours du suivi (OR = 0,04 [0,01–0,39], p=0,015 et 0,07 [0,01–0,65], p= 0,03, respectivement).

**Conclusion :** Dans notre cohorte, le traitement de référence par réduction de l'immunosuppression standard a montré un avantage sur la négativation de la virémie à un an en comparaison à un traitement par conversion aux imTOR combiné à l'administration d'IgIV. Des études prospectives randomisées sont nécessaires afin d'évaluer l'intérêt des imTOR et des Ig IV dans le traitement des infections à BK Virus.

**Nombre de mots :** 353

**Mots-clés :** infection à BK virus, Immunoglobulines polyvalentes, imTOR, transplantation rénale



## **Conversion to mTOR-inhibitors with adjunction of IV immunoglobulins in kidney-transplant recipients with BKV infection: a retrospective study**

### **Abstract**

**Introduction:** BK virus-associated nephropathy (PvAN) is linked to a high risk of graft failure and, thus, justifies active therapy. Studies suggest that conversion to mammalian target of rapamycin inhibitors (mTORi) and lowering immunosuppression could prevent the risk of PvAN. Human polyclonal immunoglobulins (IVIg) increase anti-BKV antibody titers in kidney-transplant (KT) recipients. Our monocentric retrospective study assessed the efficacy of mTORi/IVIg therapy versus reduced immunosuppression on BKV DNAemia clearance at 1-year post-KT.

**Methods:** Forty KT patients were included between March 2013 and October 2020. They formed an intervention group: mTORi/IVIg (everolimus conversion and 1200 mg/kg of IVIg over 6 months) after the first incidence of DNAemia; and a control group where immunosuppression was reduced. The primary outcome was BKV DNAemia clearance at one year. Renal function, rejection rate, evolution to PvAN, and complications were assessed.

**Results:** BKV DNAemia clearance at 1-year post-treatment was greater in the control group compared to the mTORi/IVIg group (100% vs. 45.5%,  $p=0.004$ ). Death-censored graft survival did not differ between the mTORi/IVIg and control groups after 20.6 [19.4 – 21.8] and 59.2 [43.9 – 68.9] months, respectively ( $p=0.18$ ), after medical interventions. Rate of T-cell and antibody-mediated rejections and kidney-graft function at 12-months were similar between the two groups. Multivariate analyses showed that reducing immunosuppression compared to mTORi/IVIg conversion and an absence of sustained viremia were significantly associated with BKV DNAemia clearance (OR = 0.04 [0.01 – 0.39],  $p=0.015$  and 0.07 [0.01 – 0.65],  $p= 0.03$ , respectively).

**Conclusions:** Our study demonstrates a benefit to standard-of-care treatment for BKV infections (i.e., reduced immunosuppression) over a treatment based on mTORi conversion plus IVIg perfusion. Larger randomized studies need to evaluate the responses of mTORi and/or IVIg to treat active BKV infections.

**Word count :** 276

**Keywords :** BK virus infection, mTOR inhibitors, Intravenous immunoglobulins, renal transplantation

## 1. Introduction

Kidney transplantation (KT) is the optimal therapeutic option for end-stage renal disease in terms of patient survival, quality of life, and health-care savings. The most frequent complications associated with immunosuppressive drugs, including calcineurin inhibitors (CNI), are cancers and infections that appear to be correlated with the intensity of the immunosuppression.<sup>1</sup>

One of the most common viral infections post-KT is BK virus (BKV) infection. This polyomavirus was first identified in 1971, isolated from the urine of a renal-allograft recipient with ureteric obstruction, but its pathogenicity was initially underestimated.<sup>2,3</sup>

Primary BKV infection occurs during childhood, with a worldwide seroprevalence of about 75% among adults. The virus then persists mainly in the reno-urinary tract.<sup>4</sup>

Post-KT, the virus may reactivate and multiply within the reno-urinary tract, leading to the destruction of tubular epithelial cells and, subsequently, to a virus-associated nephropathy responsible for chronic graft dysfunction and an increased risk of graft loss.<sup>5</sup> In previous studies, BKV DNAemia was estimated to occur in 11–13% of KT recipients, with 8% having BK/polyomavirus-associated nephropathy (PvAN).<sup>6,7</sup>

Identified risk factors include donor determinants, such as a deceased donor, a female donor, ABO incompatibility, and systemic factors at post-KT (such as acute tubular necrosis and acute rejection, use of corticosteroids, and powerful immunosuppression, especially tacrolimus).<sup>8,9</sup> A systematic review by Johnston *et al.* and the 2019 Guidelines of the American Society of Transplantation recommend a reduction in immunosuppression as the first-line treatment for BK DNAemia and PvAN.<sup>8,10</sup> The incidence of graft failure has been reported to be similar in acute cellular rejection and PvAN, which justifies active care of BKV infections. However, lowering immunosuppression increases the risk of rejection.<sup>11,12</sup>

Some experimental and clinical studies suggest that mammalian target of rapamycin inhibitors (mTORi) have a specific antiviral effect on BKV tubular epithelial-cell replication, and that conversion from calcineurin inhibitors to mTORi, plus lowering immunosuppression, may prevent the risk of PvAN.<sup>13,14</sup>

Another approach to BKV therapy is human IV polyclonal immunoglobulin (IVIg) preparations, which contain BKV-neutralizing antibodies.<sup>15</sup> IVIg administration is associated with an increase in BKV antibody titers in KT recipients, especially for the genotype I BKV (which is the most common).<sup>16</sup> However, the efficacy of IVIg as a potential treatment for PvAN is controversial.<sup>17-22</sup> To date, no studies have assessed the efficacy of mTORi conversion associated with IVIg to treat BKV infection in KT recipients.

In this retrospective study, we assessed the clearance of BKV DNAemia in KT patients treated with IVIg combined with mTORi conversion as compared to the standard of care (i.e., reducing immunosuppression).

## **2. Materials and methods**

### **2.1. Study population**

In this retrospective single-center study, we screened all adult KT recipients with positive blood BKV DNAemia at Grenoble University Hospital between March 3<sup>rd</sup>, 2013 and October 7<sup>th</sup>, 2020. The patients had to meet the following inclusion criteria: conversion to mTORi after the first BKV DNAemia with adjunction of polyclonal IVIg in the mTORi/IVIg group ; the controls underwent reduced immunosuppression after first case of BKV DNAemia.

Patients receiving mTORi at the first incidence of BKV DNAemia were excluded. All medical data were collected from our database [CNIL (French National committee for data protection) approval number 1987785v0].

## 2.2. BKV quantification

Positive BKV DNAemia was defined by a positive quantitative polymerase-chain reaction (qPCR)  $\geq 500$  copies/mL (= 2.69 log copies/mL) in the blood. Nucleic acids were extracted from blood using MagNaPure LC® (Roche Diagnostics) automatic extraction technology and from urine using EasyMag® (Biomérieux) automatic extraction technology. The BK viral load was measured by real-time qPCR using a BKV Rgene® kit (Biomérieux) on a LightCycler® 480 Instrument II (Roche Diagnostics). Sustained DNAemia was defined by a PCR of  $\geq 4$  log copies/mL (10,000 copies/mL) on two successive tests.<sup>23</sup> BKV DNAemia clearance was defined as a blood qPCR of  $< 500$  copies/mL or an undetectable viral load. BKV viruria was defined by a qPCR of  $\geq 500$  copies/mL in the urine.

PvAN was defined by a histologically detected tubulointerstitial inflammation associated with basophilic intra-nuclear inclusions in tubular epithelial cells and/or positivity of immunostaining with SimianVirus 40 (Anti-SV40 T-antigen - clone Pab416 - Abcam - 1:50 – Manual technique).

Presumptive PvAN was defined as plasma BKV DNAemia  $\geq 10\,000$  copies/ mL (4 log 10 copies/mL).<sup>24</sup>

## 2.3. Endpoints

The primary endpoint was BKV DNAemia clearance at one year after the therapeutic intervention. A composite endpoint included BKV DNAemia clearance or a decrease of at least 1 log copies/mL of BKV viremia at one year after the therapeutic change.

We also assessed estimated glomerular filtration rate (eGFR) at one year, graft loss, death, evolution to PvAN, humoral or cellular rejection, and treatment tolerability.

Antibody-mediated rejection and cellular rejection were biopsy-proven according to the most recent updated Banff classification at the time of the biopsy. Biopsies were systematically

performed at 3 months post-KT. eGFR was calculated using the CKD-EPI method and was expressed in mL/min/1.73m<sup>2</sup>. Treatment intolerability was considered when treatment was discontinued due to its side effects.

#### 2.4. Immunosuppression

Immunosuppression at post-KT consisted of a triple therapy: mycophenolate mofetil (MMF, 1g/day), tacrolimus (with trough levels targeted between 6 and 8 ng/mL after 1-month post-KT), and prednisolone (given at 500 mg pre-operatively, then progressively tapered to 10 mg/day, and then discontinued at month-3 in the absence of rejection or a donor-specific antibody but was maintained for IgA nephropathy patients).

The date of medical intervention was defined by the day that treatment was modified, *i.e.*, conversion to mTORi / IVIg or reduced immunosuppression.

In the mTORi/IVIg group, mTORi (everolimus) was introduced to obtain a trough level between 5 and 7 ng/mL, MMF was discontinued, and tacrolimus dose was reduced to reach trough levels of between 3 and 5 ng/mL. IVIg infusion consisted of human polyclonal immunoglobulins (Clairyg, LFB-BIOMEDICAMENTS, France): this was given at 200 mg/kg every month for 6 months or 400 mg/kg every 2 months for 6 months.

In the control group, reduced immunosuppression included reduction or discontinuation of corticosteroids and/or MMF and/or CNL.

Data on tacrolimus trough levels were collected at one year before medical intervention and at six months after to assess the impact of over or lower immunosuppression on BKV clearance.

#### 2.5. Statistical analyses

Symmetrically and heterogeneous quantitative variables are shown as means  $\pm$  standard deviations, and median [ranges] respectively. Qualitative variables are expressed as

percentages. Student's t-test or the Mann-Whitney U test was used to compare continuous variables. The chi-square test or Fisher's exact test was used to compare qualitative variables. Variables with a significance of  $p < 0.05$  in univariate analyses were included in the multivariate analyses. We used a multivariate regression model to predict BKV DNAemia clearance. In the multivariate analyses we included all significant parameters associated with BKV DNAemia clearance in our model. A  $p$ -value of  $< 0.05$  was considered to be statistically significant. Analyses were performed using R software.

### 3. Results

#### 3.1. Cohort characteristics

##### 3.1.1 *Clinical characteristics*

Between March 26, 2013 and October 7, 2020, at Grenoble University Hospital, 305 patients had positive BKV viruria, of which 67 patients had a positive BKV DNAemia of  $> 500$  copies/mL (21.96%). Fifty-three patients did not receive mTORi treatment at the time of the first incidence of DNAemia. Among these, 22 patients were converted to mTORi with simultaneous infusion of IVIg (mTORi/IVIg group) and 18 underwent reduced immunosuppression (control group, i.e., standard of care).

Twelve patients did not meet the inclusion criteria (see Flow chart in **Figure 1**). Baseline characteristics of the included population are shown in **Table 1**. Clinical characteristics, such as age at time of viremia, gender, body-mass index (BMI), initial nephropathy, diabetes mellitus pre KT and vascular impairment, were similar between the two groups. The mTORi/IVIg group was more likely to have received a graft from a living donor (52.4% vs. 5.6%,  $p = 0.006$ ), be ABO-incompatible at transplantation (22.7% vs. 0%,  $p = 0.031$ ), and to be receiving rituximab

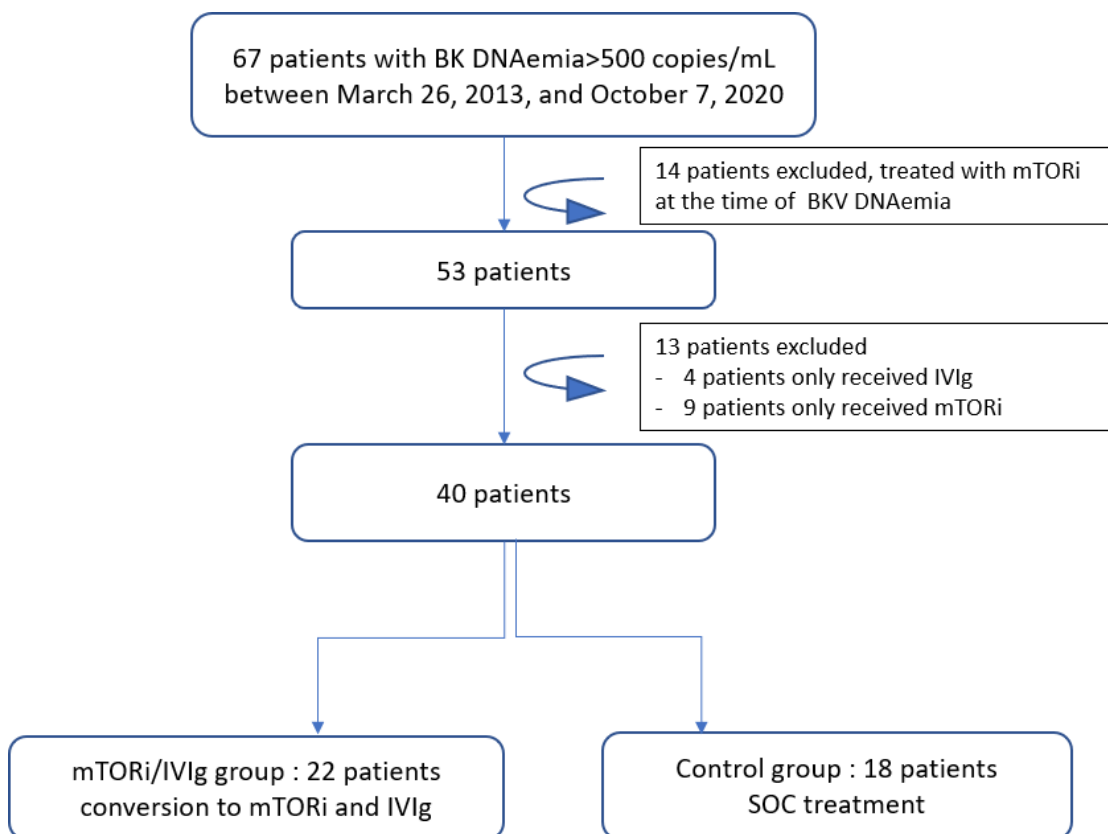
therapy at the time of transplantation (36.8% vs. 0%,  $p=0.004$ ) compared to the control group, respectively.

Median follow-up time of the study population from medical intervention until the last follow-up was 31.2 [19.6 – 74.9] months: with a shorter time for the mTORi/IVIg group compared to the control group (respectively, 24.5 [19 – 29] vs. 76.1 [62.9 – 86.9] months,  $p<0.001$ ).

The mTORi/IVIg group received a median IVIg dose of 1.3 [1.1 – 1.9] g/kg.

**Figure 1: Flowchart of patients.**

mTORi: mammalian target of rapamycin inhibitor; IVIg: intravenous immunoglobulins; SOC: standard of care treatment.





**Table 1** : Baseline characteristics of the population.

BMI: body-mass index; NHBD: non heart-beating donor; ATG: antithymocyte globulins; MMF: mycophenolate mofetil

	<b>mTORi/IVIg group N= 22</b>	<b>Control group N = 18</b>	<b>Total N=40</b>	<b>p-value</b>
<b>Age (years)</b>	57.8 (17.5)	60.1 (11.2)	58.8 (14.9)	0.935
<b>Male (%)</b>	81.8	94.4	87.5	0.230
<b>BMI (kg/m<sup>2</sup>)</b>	25.4 (3.8)	25.1 (4.4)	25.2 (4.1)	0.554
<b>Diabetes (%)</b>	22.7	11.1	17.5	0.336
<b>High blood pressure (%)</b>	90.9	83.3	87.5	0.471
<b>Nephropathy (%)</b>				0.525
- <b>Diabetic</b>	13.6	11.1	12.5	
- <b>Nephroangiosclerosis</b>	13.6	16.7	15	
- <b>Glomerulopathy</b>	27.3	33.4	30	
- <b>Other</b>	40	45.4	42.5	
<b>Vascular impairment</b>				
- <b>Arteriopathy</b>	4.5	5.9	5.1	0.851
- <b>Stroke</b>	0	0	0	0.423
<b>Gender of donor: female (%)</b>	57.1	66.7	61.5	0.542
<b>Type of donor (%)</b>				0.006
- <b>NHBD</b>	9.5	11.1	10.3	
- <b>Encephalic death</b>	38.1	83.3	59	
- <b>Living donor</b>	52.4	5.6	30.8	
<b>Age of donor (years)</b>	56.8 (12.4)	62.7 (12.4)	59.5 (15.8)	0.317
<b>ABO-incompatible (%)</b>	22.7	0	12.5	<b>0.031</b>
<b>HLA-incompatible (%)</b>	13.6	0	7.5	0.103
<b>Transplantation rank</b>				0.751
<b>1</b>	81.8%	77.8%		
<b>2</b>	18.2%	22.2%		
<b>ATG (%)</b>	81	100		0.501
<b>Mismatch I (%)</b>				0.132
<b>[0-2]</b>	40	33.4		
<b>[3-4]</b>	60	66.6		
<b>Mismatch II (%)</b>				0.104
<b>[0-2]</b>	45	77.8		
<b>[3-4]</b>	55	22.2		
<b>Rituximab (%)</b>	36.8	0		<b>0.004</b>
<b>Immunosuppression at medical intervention</b>				
- <b>MMF (%)</b>	95.2	100	97.4	0.348
- <b>MMF mean dose mg/day</b>	956.4 (267.9)	1058 (390.6)	1001 (326.4)	0.186
<b>Corticoids (%)</b>	95	88.9	92.1	0.485
- <b>Corticoids mean dose mg/day</b>	7.5 (8.4)	5.6 (4)	6.7 (6.9)	0.593
- <b>Tacrolimus (%)</b>	100%	100%	100%	
- <b>Tacrolimus median dose mg/day</b>	7.9 [6.2,9.7]	7.5 [5.8,10.2]		0.607
<b>Lymphocytes G/L</b>	0.7 [0.4-0.9]	0.6 [0.5-0.9]		0.877

### 3.1.2 BKV at the time of medical intervention

BKV DNAemias at the time of medical intervention were significantly lower in the mTORi/IVIg group compared to the control group: *i.e.*, respectively,  $3.5 \pm 1.3$  log copies/mL versus  $4.6 \pm 0.8$  log copies/mL,  $p=0.006$ .

Similar frequencies of renal-allograft biopsies were taken at the time of viremia from both groups (86.4% in the mTORi/IVIg group and 72.2% in the control group,  $p=0.26$ ). There were no significant differences between the two groups for biopsy-proven PvAN: seven patients, (33.3%) in the mTORi/IVIg group versus two patients (11.1%) in the control group ( $p=0.1$ ). This was similar for both groups if presumptive PvAN with BKV DNAemia of  $\geq 4$  log copies/mL was considered: 41% versus 60% in the mTORi/IVIg and control groups, respectively ( $p=0.2$ ). Sustained BKV viremia was present in 13 patients (61.9%) from the mTORi/IVIg group versus 7 patients (38.9%) from the control group ( $p=0.15$ ).

### 3.2 Primary endpoint and BKV viremia outcomes

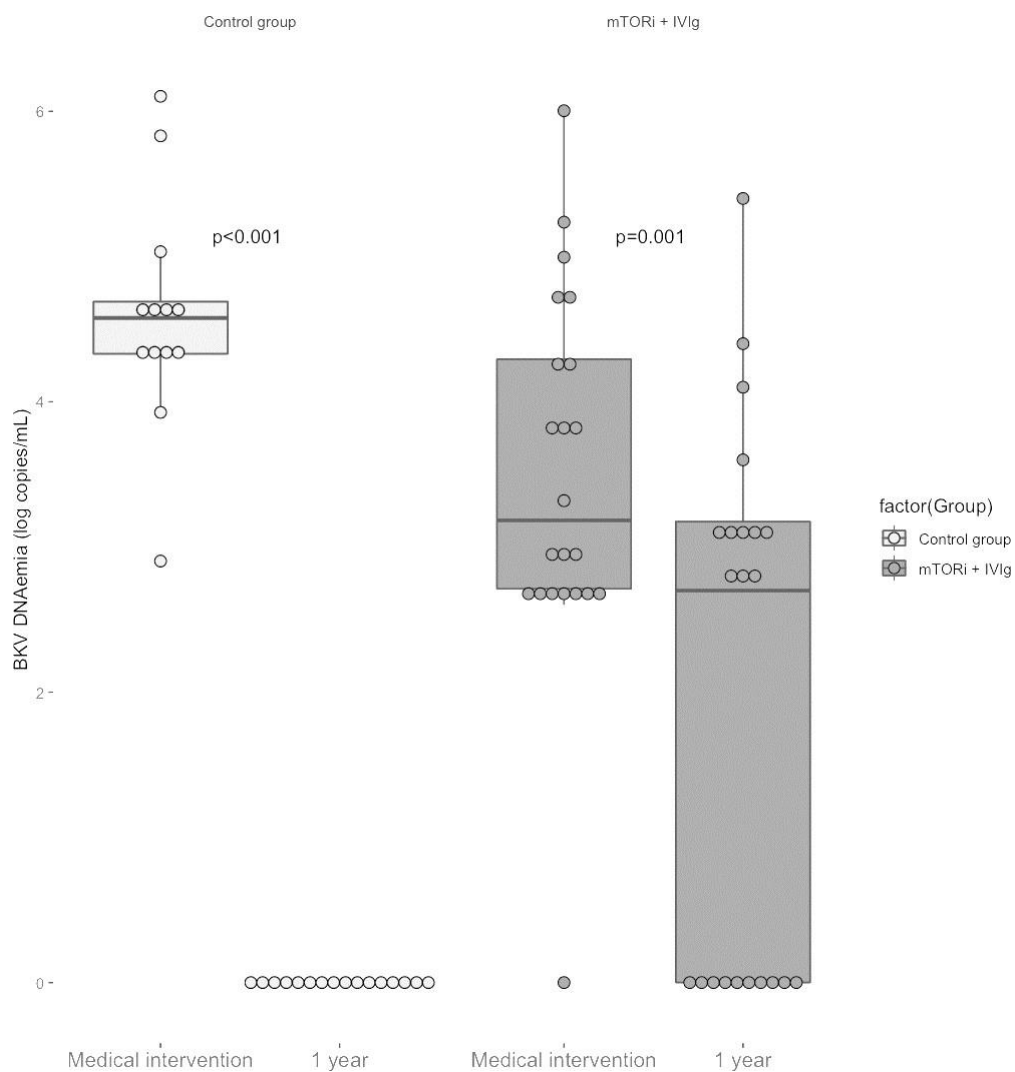
The median times between KT and BKV DNAemia when medical intervention was conducted were similar: *i.e.*, 3.3 [1.4 – 6.0] months for the mTORi/IVIg group, and 3.8 [3.4 – 5.5] months for the control group ( $p=0.3$ ).

Regarding the primary endpoint, the prevalence of BKV DNAemia clearance was significantly greater in the control group compared to the mTORi/IVIg group (88.9% vs. 45.5%;  $p=0.004$ ).

We also assessed a composite criterion: a decrease in BKV DNAemia of at least 1 log copies/mL or clearance of BKV DNAemia at one year. Similarly, although non-significant, the prevalence of this composite endpoint was higher in the control group compared to the mTORi/IVIg group, respectively, at 100% vs. 63.6% ( $p=0.06$ ).

In patients with positive BKV DNAemia at 1-year, viral load was  $3.4 \pm 0.7$  log copies/mL in the mTORi/IVIg group whereas no patients had a positive BKV DNAemia in the control group (Figure 2).

**Figure 2. BKV DNAemia viral load (log copies/mL) at the time of medical intervention and at 1-year post-treatment in both groups. BKV: BK virus; mTORi: mammalian target of rapamycin inhibitor; IVIg: intravenous immunoglobulins.**



During follow-up, two patients (5%) developed biopsy-proven PvAN. Both were in the mTORi/IVIg group.

In the subgroup analysis that only included patients with a BKV DNAemia of  $\geq 4$  log copies/mL, the prevalence of BKV viremia clearance was higher in the control group compared to the mTORi/IVIg group (100% vs. 14.3%,  $p < 0.001$ ).

### 3.3. Kidney outcomes

#### 3.3.1 *Graft survival*

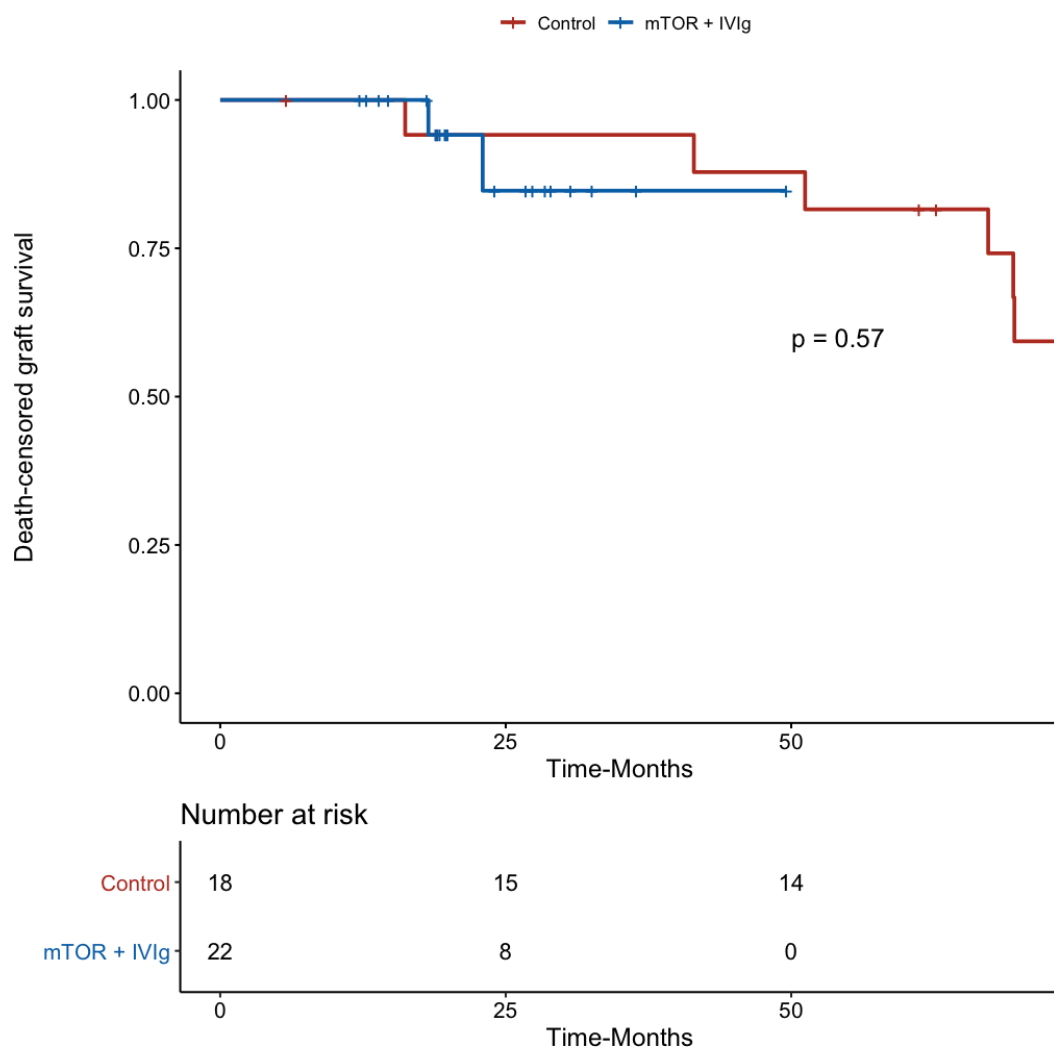
The prevalence of death-censored graft survival (DCGS) did not differ between the mTORi/IVIg and control groups after a median time of 46.3 [21.8 – 67.8] months from medical intervention: 20.6 [19.4 – 21.8] months and 59.2 [43.9 – 68.9] months, respectively ( $p = 0.182$ ).

**Figure 3** shows Kaplan – Meyer survival curves of DCGS in both groups.

No patient lost their graft during the first-year post-medical intervention.

Causes of graft loss are presented in **Table 2**.

**Figure 3. Outcomes of Death-censored graft survival (DCGS) according to BKV DNAemia treatment.** Kaplan-Meier analysis curve, showing death-censored graft survival rates regarding in patients that received mTORi/IVIg for BKV DNAemia compared to the control group.



**Table 2 :** Etiologies of graft loss

Control group	mTORi/IVIg group
1 Chronic T-cell-mediated rejection 3 Chronic antibody-mediated rejection 1 Disease recurrence 1 Chronic graft dysfunction	3 Polyomavirus BK-associated nephropathy

### 3.3.2 Rejection rate

The rate of T-cell-mediated rejection was similar between the mTORi/IVIg and control groups: 16.7% versus 18.8%, respectively ( $p=0.87$ ). The rate of antibody-mediated rejections was similar between the mTORi/IVIg and control groups: 16.7% versus 25%, respectively,  $p=0.54$ .

**Table 3** reports the patients treated for rejection who developed a positive BKV DNAemia after treatment.

**Table 3 :** Days between treated rejection and first positive BKV DNAemia

	Days between treated rejection and BKV DNAemia	Type of rejection	Group
patient 1	178	TCMR	mTORi/IVIg
patient 2	24	TCMR and ABMR	mTORi/IVIg
patient 3	373	ABMR	mTORi/IVIg
patient 4	139	ABMR	mTORi/IVIg
patient 5	404	ABMR	control

### 3.3.3 Kidney function

At the time of medical intervention, mean eGFR was  $56 \pm 19$  mL/min/1.73m<sup>2</sup>. There was no statistical difference in eGFR between the groups:  $58.4 \pm 21$  mL/min/1.73m<sup>2</sup> in the mTORi/IVIg group and  $52.8 \pm 17$  mL/min/1.73m<sup>2</sup> in the control group ( $p=0.53$ ). Similarly, median proteinuria level at the time of medical intervention was 0.2 [0.1-0.3] g/L. Proteinuria also did not statistically differ between the two groups: 0.3 [0.2 – 0.4] g/L versus 0.2 [0 – 0.3] g/L in the mTORi/IVIg group and control groups, respectively ( $p=0.12$ ).

Kidney-graft function at 12-months post-medical intervention did not significantly differ between the mTORi/IVIg and control groups, respectively:  $55.5 \pm 20$  mL/min/1.73m<sup>2</sup> and  $52.1 \pm 24$  mL/min/1.73m<sup>2</sup> ( $p=0.41$ ).

Proteinuria at 12 months post-medical intervention was significantly higher in the mTORi/IVIg group compared to the control group: 0.3 [0.2 – 1] g/L versus 0.1 [0 – 0.2] g/L, respectively,  $p=0.014$ .

### 3.4. Immunosuppression dose and tolerability

We then assessed the potential influence of dose of immunosuppression on BKV outcomes. Patients in the mTORi/IVIg group received the same mean ATG-induction dose as the control group:  $5 \pm 2.6$  mg/kg, versus  $3.8 \pm 1$  mg/kg ( $p=0.5$ ).

During the first year before medical intervention, median tacrolimus trough level was 7.9 [6.2,9.7] ng/mL in the mTORi/IVIg group and 7.5 [5.8,10.2] ng/mL in the control group ( $p=0.6$ ). During the 6 months after medical intervention, median tacrolimus trough level was statistically lower in the mTORi/IVIg group: 4.2 [3.4-5.5] ng/mL versus 6 [4.7-7.5] ng/mL in the control group ( $p<0.001$ ).

**Table 4** details the immunosuppression reduction protocol in the control group.

**Table 4 :** Type of immunosuppression reduction in the control group

<b>Immunosuppression modifications in the control group</b>	<b><i>n</i></b>
Lowering CNI	5
Lowering MMF	1
Lowering MMF and CNI	4
Lowering MMF and CNI and stop corticoids	1
Stop corticoids	4
Stop corticoids and lowering CNI	2
Stop MMF and lowering CNI	1
<b>Total</b>	<b>18</b>

Regarding mTORi tolerance, 81.8% of patients in the mTORi/IVIg group did not discontinue everolimus at the end of follow-up.

Opportunistic-infection rates during the follow-up did not significantly differ between the mTORi/IVIg and control groups: respectively, 27.3% versus 38.9% of infections (including infection-induced hospitalization and CMV infections),  $p=0.43$ ; with a similar time of occurrence: respectively, 13.1 [11.3 – 14.8] months versus 7.8 [6.8 – 13.6] months ( $p=0.46$ ).

Occurrence of cancer did not significantly differ between the mTORi/IVIg and control groups: respectively, 9.1% versus 27.8% of cancers ( $p=0.12$ ), with non significant different times of occurrence at, respectively, 4.8 [0.6 – 9.0] months versus 47 [31.0 – 65.3] months; ( $p=0.12$ ).

### 3.5 Factors associated with BKV DNAemia clearance

We also assessed factors associated significantly with our primary endpoint: *i.e.*, BKV DNAemia clearance at 1-year after medical intervention (**Table 5**).

In univariate analysis, being a female donor, non-sustained DNAemia, and reduced immunosuppression versus mTORi/IVIg conversion were significantly associated with BKV DNAemia clearance (**Table 5**). Time of occurrence between transplantation and BKV DNAemia did not significantly differ between the BKV DNAemia clearance groups: 3.2 [2.3 – 4.7] months versus 2.9 [1.7 – 3.1] months for persistent BKV DNAemia patients ( $p=0.14$ ), nor did lymphocyte level at time of medical intervention.

In the multivariate model, only two factors remained associated with BKV DNAemia clearance at 1-year: reducing immunosuppression (vs. mTORi/IVIg conversion) and the absence of sustained viremia (as defined in the Methods section): OR = 0.04 [0.01 – 0.39],  $p=0.01$  and 0.07 [0.01 – 0.65],  $p= 0.03$ , respectively.



**Table 5.** Univariate and multivariate analyses of factors associated with BKV DNAemia clearance at 1-year

	<b>Univariate analysis</b>		<b>Multivariate analysis</b>	
	Odd-ratio [2.5 – 97.5%]	<i>p</i> -value	Odd-ratio [2.5 – 97.5%]	<i>p</i> -value
<b>Donor gender: male</b>	0.17 [0.03 – 0.69]	0.01	0.14 [0.01 – 1.38]	0.11
<b>High lymphocyte number at medical intervention</b>	7.58 [0.98 – 97.2]	0.07	35 [1.9 – 4127]	0.053
<b>Sustained viremia</b>	0.08 [0.01 – 0.37]	0.004	<b>0.07 [0.01 – 0.65]</b>	<b>0.03</b>
<b>mTORi/IVIg conversion versus reduced immunosuppression</b>	0.10 [0.01 – 0.48]	0.008	<b>0.04 [0.01 -0.39]</b>	<b>0.01</b>

#### 4. Discussion

We retrospectively compared two therapeutic strategies for BKV infection. The prevalence of BKV DNAemia clearance at 1 year was greater in KT recipients that had reduced immunosuppression compared to those that were converted to mTORi/IVIg. Moreover, in patients still viremic at 1 year, BKV viral load was significantly higher in the mTORi/IVIg group.

Time between KT and positive DNAemia did not significantly differ between patients that had 1-year viral clearance compared to those that were still viremic, nor did lymphocyte level at time of medical intervention.

Most published studies have compared the effect of mTORi on BKV DNAemia prevention but not on BKV DNAemia treatment. To our knowledge, this is the first study to compare the use of mTORi plus IVIg with the standard-of-care treatment.

Reduced immunosuppression is the first recommended step to manage BKV infection.<sup>24</sup> Reducing immunosuppression has shown efficacy in large prospective studies, although no randomized controlled trials are currently ongoing. One long-term study investigated outcomes at 6 years post-transplantation following a reduced immunosuppression protocol to treat sustained BKV DNAemia. Graft survival, clinical rejection, and eGFR were similar to non-viremic KT patients.<sup>25</sup>

Successful clearance of BKV-positive DNAemia and the prevention of PvAN after KT relies on the efficiency of the immune system and, more precisely, specific T-cell immunity.<sup>26</sup> A review published in 2017 by Ambalathingal *et al.* reports that BKV latency and reactivation are likely dependent on a stable antiviral memory T-cell response and humoral passive immunity.<sup>27</sup>

There is *in vitro* evidence for the antiviral activity of mTORi. Comparison of the effects of mTORi and CNI on BKV replication in primary human renal-tubular epithelial cells<sup>13</sup> showed that sirolimus impaired BKV replication, with rapid and effective inhibition during early viral gene expression, but not during later viral gene expression. This is consistent with current data that report a lower incidence of BKV infection in patients already treated with mTORi and may explain why mTORi efficacy on active BKV infections has not yet been proven. mTORi, like rapamycin, does not inhibit BKV-specific T-cell activation,<sup>28</sup> nor does it impair cytokine secretion and cytotoxic capacity of BKV-specific T cells.<sup>29</sup> Moreover, mTOR-inhibition promotes memory-cell generation in mice,<sup>30</sup> and may improve the response of virally induced memory T cells.<sup>31</sup>

The use of mTORi was associated with a reduced incidence of BKV DNAemia in the TRANSFORM study compared to standard-exposure to CNIs.<sup>32</sup> Similarly, the OPTN American registry analysis showed a significantly lower incidence of BKV infection in transplant recipients treated with mTORi compared to other immunosuppressive treatments.<sup>33</sup> However, a meta-analysis of randomized controlled trials did not highlight a reduction in BKV infections in patients receiving mTORi therapy.<sup>34</sup>

A small study compared KT recipients of whom seven were treated with mTORi for an active BKV infection, eight were undergoing reduced immunosuppression, and fifteen patients were receiving cidofovir and IVIg. Improvement in BKV clearance in plasma and urine was shown in the mTORi group,<sup>35</sup> but the reduced immunosuppression and cidofovir groups received

several lines of treatment, making it difficult to interpret those results. Moreover, a prospective randomized study with 40 patients compared conversion to an everolimus strategy versus a 50% reduction in MMF to treat BKV infection after KT. There was no statistically significant difference in BKV DNAemia clearance at 3 months,<sup>36</sup> which agrees with our results.

Passive humoral immunity appears to be more effective during early phases of viral replication. This may explain why we could not show a clear benefit of IVIg to treat active established BKV infections. In 2010, it was shown that human IVIg contains BKV neutralizing antibodies that can cause *in vitro* inhibition of viral DNA. The effect was lower when treatment was delayed after anti-viral inoculation.<sup>15</sup> More recently, a team from Strasbourg Hospital reported that IVIg may be a valuable preventive strategy for BKV replication. They confirmed that IVIg administration increased neutralizing antibody titers in KT recipients.<sup>16</sup> They also found that the incidence of BKV DNAemia in a high-risk group (defined by a low rate of neutralizing antibodies) was similar to that in a low-risk group (with an initial high rate of neutralizing antibodies) after supplementing the high-risk group with IVIg.<sup>23</sup>

A series of case reports with poor levels of proof reported the efficacy of IVIg as a treatment for active BKV infection. Sener *et al.* treated eight patients with biopsy-proven PvAN by reducing immunosuppression and giving IVIg. In half of their patients, BKV DNAemia was negative at 15 months follow-up.<sup>17</sup> Histological resolution of PvAN and a reduction in BKV DNAemia was described after IVIg therapy was given to pediatric KT recipients with persistent BKV DNAemia and after immunosuppression was reduced and/or cidofovir therapy.<sup>18,37</sup> In 2020, Matsumura *et al.* treated five cases of PvAN with IVIg: three cases had decreased blood BK DNAemia, and large SV40 T antigens became reduced on all graft biopsies.<sup>21</sup>

Some studies with larger cohorts have been published, although they have often used combined immunosuppressive strategies. Vu *et al.* reported in 2015 on clearing viremia by 90% in 30

patients treated with IVIg after unsuccessfully lowering immunosuppression and leflunomide therapy.<sup>19</sup> A recent retrospective study assessed the benefit of IVIg therapy. 86 patients with proven BK virus nephropathy were separated into an intervention group receiving IVIG therapy and a control group treated with leflunomide and ciprofloxacin.

Forty-seven of the 52 (90%) IVIg-treated patients had lowered BKV DNA loads of <500 copies/mL.<sup>22</sup> A retrospective, single-center cohort study observed more BKV clearance and a faster BKV DNAemia decrease in viral load in a group that received IVIg as well as cyclosporine, leflunomide, ciprofloxacin, and intravenous cidofovir.<sup>38</sup>

In our study, the presence of a control group that received the recommended standard-of-care, with no other treatment modifications, may explain this difference. We may argue that reducing immunosuppression alone could have played the same role as IVIg in these patients.

This study has some limitations because of its small cohort size and its retrospective design. Our two groups were formed from a historical cohort of patients treated between 2013 and 2020, which included time-related changes to the standard of care. The mTORi/IVIg group included more ABO-incompatible KT's that had not undergone the same initial immunosuppression regimen and were more at risk for BKV infection, as suggest by Schachtner *et al.*<sup>39</sup> This may have weakened our results: thus, a prospective, larger study is necessary to confirm our results.

Due to the retrospective design of our study, immunosuppression protocols were not formally codified. Indeed, IVIg doses were heterogeneous depending on the practitioner, despite a common initial protocol, as well as a delay in medical intervention after the first positive BKV DNAemia. In the same way, reduced immunosuppression in the control group was not standardized but was left to the discretion of the physician. However, these variabilities in

strategies of care for BKV infections reflect the current common practice and, thus, real-life situations.

#### **4. Conclusion**

Our study did not show a benefit for mTORi conversion combined with IVIg to treat BKV infection in KT recipients when compared to patients receiving the actual standard of care, *i.e.*, reduced immunosuppression. Its retrospective design and limited sample size may, however, underestimate the efficacy of the mTORi/IVIg strategy.

**THÈSE SOUTENUE PAR :** Carla VELA

**TITRE :**

TRAITEMENT DE L'INFECTION À BK VIRUS EN TRANSPLANTATION RÉNALE  
PAR INHIBITEUR DE MTOR ET IMMUNOGLOBULINES POLYVALENTES : ÉTUDE  
RÉTROSPECTIVE.

**CONCLUSION :**

Notre étude n'a pas montré de bénéfice de la conversion aux inhibiteurs de mTOR en association avec les IgIV dans le traitement de l'infection à BK virus chez les patients greffés rénaux par rapport au standard de soin actuel, c'est-à-dire la réduction de l'immunosuppression. Son design rétrospectif et la taille limitée de l'échantillon peuvent sous-estimer l'efficacité de cette stratégie.

VU ET PERMIS D'IMPRIMER

Grenoble, le : 23/08/2021

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# Le serment d'Hippocrate

Texte revu par l'Ordre des médecins en 2012

“ **Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.**

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque. ”

