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**CLEARENCE OF BK VIRUS NEPHROPATHY BY COMBINATION  
ANTIVIRAL THERAPY WITH INTRAVENOUS IMMUNOGLOBULIN**

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## SUPPLEMENTARY DIGITAL CONTENT

**SDC Table 1.** Demographic features of patients with BKVAN at diagnosis, stratified by use of IVIG therapy. Mean±SD.

Factor	Conventional	IVIG	P
Number	28	22	
Recipient age (years)	44.6±10.3	49.7±13.2	NS (0.13)
Recipient male (n, %)	25 (89.3%)	15 (68.2%)	NS (0.07)
Body weight (kg)	72.2±19.3	80.7±13.6	NS (0.08)
Living donors (n, %)	11 (39.3%)	5 (22.7%)	NS (0.21)
Retransplant (n, %)	8 (28.6%)	1 (4.5%)	0.03
Pre-transplant DSA	5 (17.9%)	2 (10%)	NS (0.38)
HLA mismatch (of 6)	3.5±1.8	4.0±1.6	NS (0.32)
Delayed graft function (%)	3 (10.7%)	1 (4.5%)	NS (0.42)
Prior cellular rejection (%)	6 (21.4%)	5 (22.7%)	NS (0.91)
Prior antibody rejection (%)	1 (3.6%)	1 (4.5%)	NS (0.86)
Prior pulse corticosteroids (%)	10 (35.7%)	9 (42.8%)	NS (0.71)
Prior antithymocyte therapy (%)	5 (17.9%)	3 (13.6%)	NS (0.68)
Tacrolimus dose (mg/day)	5.3±3.5	5.9±3.2	NS (0.57)
Tacrolimus level (ng/ml)	9.1±3.4	8.0±1.9	NS (0.55)
Mycophenolate dose (g/day)	1.8±0.5	1.7±0.4	NS (0.43)
Prednisolone dose (mg/day)	14.3±6.2	14.2±5.2	NS (0.72)

**SDC Table 2.** Other outcomes of treatment stratified by use of IVIG therapy.

Mean±SD.

<b>Factor</b>	<b>Conventional</b>	<b>IVIG</b>	<b>P</b>
Number	28	22	
<b>Renal function</b>			
Serum creatinine (umol/l)			
Prior to BKVAN	131±33	122±34	NS (0.46)
At diagnosis of BKVAN	184±54	164±52	NS (0.25)
3 months end-treatment	235±108	199±102	NS (0.14)
Last serum creatinine value	385±245	262±193	NS (0.06)
<b>Viral load (log<sub>e</sub> transformed)</b>			
At diagnosis of BKVAN	10.97±4.64	11.27±2.93	NS (0.81)
Mid-treatment	8.82±3.86	9.24±4.14	NS (0.79)
3 months end-treatment	7.66±4.68	6.93±4.45	NS (0.69)
Last viral load value	6.30±6.09	2.45±4.58	0.037

**SDC Table 3.** Univariate Cox regressions of viral clearance from blood, where a lower hazard ratio (HR) indicates impaired resolution of viremia and treatment failure. Key: BFC is biopsy for cause, DSA is donor specific antibody, 95%CI is 95 percent confidence interval, and Ln is the natural logarithm (base e) to transform viral load data.

Risk factor:	HR	95%CI	P value
<b>Demographic and transplant factors</b>			
Recipient age (years)	1.023	0.985-1.062	0.242
Body weight (kg)	1.027	1.002-1.052	0.032
Cadaveric donor	0.906	0.393-2.088	0.818
Male recipient sex	0.800	0.354-1.808	0.591
Recipient diabetes	1.487	0.620-3.568	0.374
Kidney pancreas recipient	1.307	0.489-3.49	0.594
HLA mismatch	0.944	0.758-1.176	0.606
Cytomegalovirus risk	0.906	0.614-1.335	0.616
Antithymocyte induction	1.066	0.614-1.849	0.821
Delayed graft function	0.287	0.039-2.126	0.222
Prior T cell rejection	1.035	0.433-2.474	0.938
Pre-transplant DSA	0.806	0.240-2.709	0.727
Retransplant	0.189	0.026-1.401	0.103
Prior methyprednisolone	0.934	0.412-2.118	0.870
Prior antithymocyte	0.688	0.204-2.314	0.545
<b>Diagnostic BKVAN histopathology</b>			
All biopsy for cause	0.885	0.394-1.990	0.767
BFC: indication creatinine	1.171	0.534-2.57	0.694
BFC: indication viremia	0.679	0.251-1.833	0.444
Protocol biopsy discovery	1.130	0.503-2.541	0.767
Time post-transplant (mths)	0.951	0.906-0.999	0.044
Serum creatinine (Ln umol/l)	0.895	0.243-3.293	0.867
Viremia (Ln copies/ml)	0.880	0.788-0.983	0.024
Urinary decoy cells	0.084	0.012-0.598	0.013

Banff i score	0.854	0.586-1.243	0.409
Banff ct score	0.645	0.366-1.139	0.131
Banff ci score	0.885	0.540-1.451	0.629
SV40 extent(score)	0.424	0.220-0.817	0.010

### **Treatment modalities after diagnosis of BKVAN**

IVIG therapy use	3.683	1.562-8.681	0.003
IVIG dose (gm/kg)	3.244	0.245-42.972	0.372
IVIG duration (months)	1.102	0.516-2.350	0.802
Tacrolimus to cyclosporine	4.274	1.671-10.93	0.002
Mycophenolate to leflunomide	1.127	0.386-3.293	0.827
Prednisolone reduction	1.627	0.750-3.531	0.218
Sirolimus therapy (any use)	0.254	0.076-0.852	0.026
Cidovovir therapy	1.432	0.428-4.789	0.560
Fluoroquinolone therapy	0.823	0.405-2.051	0.823
Pulse methylprednisolone	0.831	0.376-1.839	0.648

(given for inflammation on biopsy at diagnosis)

### **Abridged risk factor outcomes**

Later acute dysfunction	0.399	0.156-0.733	0.006
IV pulse methylprednisolone	0.672	0.309-1.465	0.318
(used inflammation on biopsy undertaken because of transplant dysfunction following reduced immunosuppression)			
Residual SV40 score at 3 mo	0.496	0.291-0.845	0.010

**SDC Table 4.** The effects of IVIG therapy and conversion of tacrolimus to cyclosporine, on the clearance of viremia using multivariate Cox regression. Interaction term for IVIG and cyclosporine was used to adjust for colinearity.

<b>Risk factor:</b>	<b>HR</b>	<b>95%CI</b>	<b>P value</b>
IVIG therapy use	6.82	1.032-45.113	0.046
Tacrolimus to cyclosporine	4.264	1.043-17.436	0.044
Time post-transplant (mths)	0.961	0.910-1.014	0.146
SV40 extent(score)	0.464	0.199-1.084	0.076
Interaction term	0.142	0.015-1.343	0.089

**SDC Table 5.** Post hoc analysis of treatment groups with IVIG patients sub-classified by primary IVIG as initial treatment or late salvage treatment after conventional therapy failed. Mean $\pm$ SD. Key for primary IVIG versus salvage IVIG: a P<0.05, b P<0.01, c P<0.001. Key for conventional versus primary IVIG: \* P<0.05, \*\* P<0.01, \*\*\* P<0.001.

Factor	Conventional	IVIG	IVIG salvage
Number	28	15	7
Recipient age (years)	44.6 $\pm$ 10.3	50.0 $\pm$ 13.0	49.3 $\pm$ 14.6
Recipient male (n, %)	25 (89.3%)	10 (66.7%)	5 (71.4%)
Living donors (n, %)	11 (39.3%)	3 (20.0%)	2 (28.6%)
Retransplant (n, %)	8 (28.6%)	1 (6.6%)	0 (0%)
HLA mismatch (of 6)	3.5 $\pm$ 1.8	4.1 $\pm$ 1.7	4.0 $\pm$ 1.5
Delayed function (%)	3 (10.7%)	1 (6.7%)	0 (0%)
Past TCMR (%)	6 (21.4%)	4 (26.7%)	1 (14.3%)
Prior AMR (%)	1 (3.6%)	1 (6.7%)	0 (0%)
Past IV steroids (%)	10 (35.7%)	6 (40.0%)	3 (42.9%)
Prior ATG (%)	5 (17.9%)	3 (20.0%)	0 (0%)

#### **Renal pathology and viral load at BKVAN diagnosis**

Banff i score	1.4 $\pm$ 0.9	1.4 $\pm$ 1.0	1.7 $\pm$ 1.6
Banff ci score	1.1 $\pm$ 0.9	0.8 $\pm$ 0.7	0.7 $\pm$ 0.5
Banff ct score	1.3 $\pm$ 0.8	0.9 $\pm$ 0.6	1.1 $\pm$ 0.7
SV40T extent	1.5 $\pm$ 0.7	1.2 $\pm$ 0.6	1.6 $\pm$ 0.5

#### **Renal function and viral load at diagnosis**

S. creatinine (umol/l)	184 $\pm$ 54	169 $\pm$ 56	154 $\pm$ 46
Viral load ( $\log_e$ )	10.97 $\pm$ 4.64	9.95 $\pm$ 3.52	12.72 $\pm$ 2.81

#### **Renal transplant histology at 3 months at later**

Banff i score	1.4 $\pm$ 0.9	0.7 $\pm$ 0.8*	1.4 $\pm$ 1.0
Banff ci fibrosis	1.5 $\pm$ 0.9	1.1 $\pm$ 1.0	1.1 $\pm$ 1.1

Banff ct atrophy	$1.4 \pm 0.9$	$1.2 \pm 0.9$	$1.1 \pm 1.1$
SV40T histology	$1.2 \pm 0.9$	$0.3 \pm 0.5^{**}$	$1.0 \pm 0.8^a$

Note: The 3 month biopsy was undertaken in the salvage IVIG group used conventional treatment (patients had not yet received IVIG) and where failed treatment was the indication for use.

**SDC Table 6.** Abridged univariate Cox regression of factors affecting the clearance of BK virus from repeated biopsy samples, by univariate Cox regression. A lower hazard ratio (HR) indicates impaired viral clearance for tissue and BKVAN persisting on histopathology. Key: 95%CI is 95 percent confidence interval, and Ln is the natural logarithm (base e) to transform viral load data.

Risk factor:	HR	95%CI	P value
<b>General demographic factors</b>			
Recipient age (years)	1.019	0.988-1.052	0.232
Male recipient sex	0.935	0.423-2.066	0.868
HLA mismatch	1.056	0.861-1.295	0.603
Delayed graft function	1.132	0.344-3.729	0.838
Prior T cell rejection	1.123	0.504-2.502	0.777
Prior methyprednisolone	1.216	0.589-2.509	0.597
Prior antithymocyte	0.934	0.358-2.438	0.890
<b>At diagnostic BKVAN</b>			
Time post-transplant (mths)	0.962	0.924-1.001	0.055
Serum creatinine (Ln umol/l)	0.907	0.273-3.007	0.873
Viremia (Ln copies/ml)	0.902	0.814-0.999	0.049
Banff i score	0.833	0.595-1.167	0.289
Banff ct score	0.475	0.277-0.816	0.007
Banff ci score	0.616	0.382-0.993	0.047
SV40 extent(score)	0.213	0.112-0.405	<0.001
<b>Treatment modalities and outcomes after diagnosis of BKVAN</b>			
IVIG therapy use	2.236	1.091-4.584	0.028
Tacrolimus to cyclosporine	2.252	1.043-4.863	0.039
Mycophenolate to leflunomide	2.466	0.869-7.084	0.094
Prednisolone reduction	1.758	0.875-3.531	0.113
Sirolimus therapy (any use)	0.269	0.092-0.788	0.017
Cidovovir therapy	1.910	0.665-5.483	0.229

Fluoroquinolone therapy      1.279      0.604-2.702      0.520  
Pulse methylprednisolone      0.788      0.384-1.620      0.517

(given for inflammation on biopsy at diagnosis)

Later acute dysfunction      0.571      0.279-1.169      0.125  
IV pulse methylprednisolone      0.808      0.394-1.658      0.561

(used inflammation on biopsy undertaken because of transplant dysfunction following reduced immunosuppression)

**SDC Table 7.** The effects of IVIG therapy and conversion of tacrolimus to cyclosporine, on the clearance of virus from repeated biopsy tissue, using multivariate Cox regression after backwards elimination.

<b>Risk factor:</b>	<b>HR</b>	<b>95%CI</b>	<b>P value</b>
IVIG therapy use	1.439	0.614-3.372	0.403
Tacrolimus to cyclosporine	1.663	0.681-4.062	0.265
Banff ct score	0.515	0.295-0.900	0.020

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