Screening and Treatment Strategies for BK Virus in Kidney Transplant Recipients

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Discovery of Human Polyomaviruses

<table>
<thead>
<tr>
<th>Human polyomavirus</th>
<th>Date of discovery</th>
<th>Major cell type infected</th>
<th>Associated diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>BKV</td>
<td>1971 (Gardner et al.)</td>
<td>Kidney epithelium, urothelium</td>
<td>Hemorrhagic cystitis (HC), polyomavirus nephropathy (PVN)</td>
</tr>
<tr>
<td>JCV</td>
<td>1971 (Padgett et al.)</td>
<td>Kidney epithelium, lymphocytes, oligodendrocytes</td>
<td>Progressive multifocal leukoencephalopathy (PML)</td>
</tr>
<tr>
<td>KI</td>
<td>2007 (Allander et al.)</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>WU</td>
<td>2007 (Gaynor et al.)</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>MCV</td>
<td>2008 (Feng et al.)</td>
<td>Merkel cells</td>
<td>Merkel cell carcinoma</td>
</tr>
</tbody>
</table>

*SV40: simian virus introduced to the population through contaminated polio and adenovirus vaccines*
## Risk Factors

### Table 1. Risk factors for the development of BKVN after renal transplantation

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Patients</th>
<th>BKVN (n [%])</th>
<th>Risk Factors</th>
<th>P</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997 to 2000</td>
<td>444</td>
<td>40 (4)</td>
<td>HLA mismatches</td>
<td>0.001</td>
<td>Awadhala et al. (29)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Previous acute rejection</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Use of antilymphocyte therapy</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>1997 to 2002</td>
<td>100</td>
<td>3 (3)</td>
<td>Recipient’s humoral deficiency (BKV IgG)</td>
<td>&lt;0.05</td>
<td>Ginevri et al. (28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MMF use at baseline</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>2000 to 2004</td>
<td>1027</td>
<td>74 (7)</td>
<td>Recipient age</td>
<td>&lt;0.001</td>
<td>Khamash et al. (64)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recipient age &gt;55</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Donor female</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>1999 to 2001</td>
<td>286</td>
<td>9 (3.1)</td>
<td>Recipient race (white)</td>
<td>0.05</td>
<td>Rocha et al. (70)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recipient gender (male)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increase tacrolimus level</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>1984 to 2002</td>
<td>173</td>
<td>6 (3.5)</td>
<td>Recipient seronegativity</td>
<td>0.01</td>
<td>Smith et al. (27)</td>
</tr>
<tr>
<td>1996 to 2003</td>
<td>1001</td>
<td>41 (4)</td>
<td>No risk factors</td>
<td></td>
<td>Vasudev et al. (67)</td>
</tr>
</tbody>
</table>

*aRace and gender (recipient); age and race (donor); cold ischemia time, panel-reactive antibodies, previous transplant, cadaver versus living donor, and kidney versus kidney-pancreas (transplant); and delayed graft function, use of IL-2 receptor blocker, and maintenance immunosuppression cyclosporine versus tacrolimus (posttransplantation) were not identified as risk factors for the occurrence of BKVN.*

**Pathogenesis**

- Diminished immune response
- Uroepithelial injury
  - Ischemia
  - Ureteral stent
  - Rejection
  - Donor BKV*

Lysis of tubular cells releases BKV into tubules with bare basement membranes. Virus particles can leak into the interstitium; the virus gains access to capillaries: viremia results.

*Figure 1. Proposed pathogenesis of BKV reactivation and disease in kidney transplant recipients*
13.1: BK POLYOMA VIRUS
13.1.1: We suggest screening all KTRs for BKV with quantitative plasma NAT (2C) at least:
- monthly for the first 3–6 months after transplantation (2D);
- then every 3 months until the end of the first post-transplant year (2D);
- whenever there is an unexplained rise in serum creatinine (2D); and
- after treatment for acute rejection. (2D)

13.1.2: We suggest reducing immunosuppressive medications when BKV plasma NAT is persistently greater than 10,000 copies/mL \( (10^7 \text{ copies/L}) \). (2D)

BKV, BK polyoma virus; KTRs, kidney transplant recipients; NAT, nucleic acid testing.
Treatment of BKV

Immune Suppression

Inadequate
- Rejection
- Allograft dysfunction
- Tubulointerstitial nephritis
- Fibrosis

Excessive
- BKV Nephropathy
Treatment of BK Viremia

Reduction of immunosuppression!
Treatment of BK Viremia

- Prospective study of 200 new renal transplant recipients
- 23 developed BK viremia
- Anti-metabolite was stopped
- If viremia failed to clear after 4 weeks CNI dose was reduced (CSA trough of 100-200 ng/ml; TAC trough of 3-5 ng/ml)

Treatment of BK Viremia

- 22/23 (95%) cleared viremia by 1 year post-transplant
- Mean time to clearance was 54 days
- 1 patient developed acute rejection related to immunosuppression reduction
- No patients developed BK nephropathy

Treatment of BK Viremia

- No BK nephropathy identified on cause biopsies
- No new BK viremia after month-12
  - Only checked on patients undergoing a cause biopsy

BK Nephropathy Treatment

- First-step: Immunosuppression Reduction
- Second-step: Active therapy
  - Anti-Viral Agents
    - Leflunomide
    - Cidofovir
    - Fluoroquinolones
  - IVIG
Leflunomide

- Metabolized to A77 1726
- Inhibits dihydroorotic acid dehydrogenase (necessary for de novo pyrimidine synthesis) and tyrosine kinases involved in T and B cell signaling cascades

MOA against BK unclear
- May inhibit viral assembly
Leflunomide

- 26 patients with biopsy proven BKVAN (mean time to diagnosis 15.4 months post-transplant)
- MMF stopped
- TAC trough target 4-6 ng/ml
- Prednisone 5-10 mg/day
- Leflunomide started with a loading dose of 100 mg/day for 5 days
- Leflunomide maintenance dose: 40 mg/day (target trough 50-100 µg/ml)
- *Cidofovir could be added at the discretion of the treating physician

In Vitro Data

Leflunomide

FIGURE 3. BK virus loads in blood and urine.

FIGURE 4. Serum creatinines in patients treated with leflunomide plus cidofovir or leflunomide alone.

Leflunomide

- Repeat biopsies in 16 patients ≥4 weeks after initial biopsy
- 4 had no evidence of SV40 staining
- 8 had significantly reduced SV40 staining
- 2 had persistent or worse staining (neither pt had A77 1726 blood level >35 at time of repeat bx)
- Follow-up of 6-40 months graft loss 4/26 (15%)
Cidofovir

- Nucleotide analogue of cytosine active against a wide array of DNA viruses

- Use limited by renal toxicity (accumulates in RTC causing apoptosis and ARF)

- Given at 10-20% of that needed for the treatment of CMV (0.25-1 mg/kg)
Cidofovir

- Prospective, non-randomized trial, biopsy proven BKVAN
- Cidofovir dosed at 1 mg/kg for a maximum duration of 10 weeks
- Immunosuppression reduction also employed
- No significant difference in BK viremia between groups
- 5/41 experienced acute rejection
  - 4/26 (15.4%) cidofovir; 1/15 (6.7%) no cidofovir

Fluoroquinolones

- Inhibit bacterial DNA replication by targeting the enzymes gyrase and topoisomerase IV
- Inhibit helicase activity of SV40 T-antigen \textit{in vitro}^{1}
- Two conflicting studies:
  - 1) 10 day course of gatifloxacin in 10 patients with active BKV replication^{2}
    - 70% had reduction in viremia by \textgreater 80% or disappearance of detectable urinary decoy cells
  - 2) No improvement in viral clearance in 4 patients after a 10 day course of ciprofloxacin^{3}

Fluoroquinolones

### Table 1. Demographic data and transplant characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I (n = 160)</th>
<th>Group II (n = 25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years; mean ± SD)</td>
<td>50.6 ± 14.8</td>
<td>53.4 ± 14.9</td>
<td>ns</td>
</tr>
<tr>
<td>Male gender</td>
<td>102 (63.8%)</td>
<td>12 (48%)</td>
<td>ns</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>9 (5.7%)</td>
<td>2 (8%)</td>
<td>ns</td>
</tr>
<tr>
<td>African American</td>
<td>39 (21.6%)</td>
<td>5 (20%)</td>
<td>ns</td>
</tr>
<tr>
<td>Caucasian</td>
<td>96 (62.4%)</td>
<td>15 (60%)</td>
<td>ns</td>
</tr>
<tr>
<td>Hispanic</td>
<td>15 (9.3%)</td>
<td>2 (8%)</td>
<td>ns</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.0%)</td>
<td>1 (4%)</td>
<td>ns</td>
</tr>
<tr>
<td>Transplant donor type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living donor</td>
<td>73 (45.6%)</td>
<td>13 (52%)</td>
<td>ns</td>
</tr>
<tr>
<td>Deceased donor</td>
<td>87 (54.4%)</td>
<td>12 (48%)</td>
<td>ns</td>
</tr>
<tr>
<td>Expanded criteria donor</td>
<td>42 (48.3%)</td>
<td>3 (25%)</td>
<td>ns</td>
</tr>
<tr>
<td>History of previous transplant</td>
<td>25 (15.6%)</td>
<td>1 (4%)</td>
<td>ns</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>53 (33.1%)</td>
<td>5 (20%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

### Table 3. BKV-related outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group I (n = 160)</th>
<th>Group II (n = 25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BK viremia at 1 year (±1 month)</td>
<td>36 (22.5%)</td>
<td>1 (4%)</td>
<td>0.03</td>
</tr>
<tr>
<td>BK viremia at any time point</td>
<td>40 (25%)</td>
<td>1 (4%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Continued viremia after therapeutic intervention(s)</td>
<td>20 (50%) (n = 40)</td>
<td>0 (0%) (n = 1)</td>
<td>ns</td>
</tr>
<tr>
<td>BKVN</td>
<td>14 (35%) (n = 40)</td>
<td>1 (100%) (n = 1)</td>
<td>ns</td>
</tr>
<tr>
<td>Serum creatinine at 12 months (mg/dl; mean ± SD)</td>
<td>1.8 ± 0.9 (n = 138)</td>
<td>1.6 ± 0.6 (n = 20)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Allograft loss secondary to BKV</td>
<td>4 (10%) (n = 40)</td>
<td>0 (0%) (n = 1)</td>
<td>ns</td>
</tr>
</tbody>
</table>

**Fluoroquinolones**

**Recipient Age, years (SD)**
- **Group 1 (n=106):** 53.1 (12.4)
- **Group 2 (n=130):** 50.4 (13.8)
- **P-value:** 0.33

**Recipient gender, male, n (%):**
- **Group 1 (n=106):** 64 (60.4)
- **Group 2 (n=130):** 81 (62.3)
- **P-value:** 0.76

**Recipient race, n (%):**
- **Caucasian:** 38 (35.8) vs 39 (30.0), **P-value:** 0.16
- **African American:** 11 (10.4) vs 25 (19.2)
- **Others:** 57 (53.8) vs 66 (50.8)

**ESRD, n (%):**
- **Diabetes:** 33 (31.1) vs 34 (26.2), **P-value:** 0.14
- **Hypertension:** 20 (18.9) vs 27 (20.8)
- **GN:** 18 (17.0) vs 39 (30.0)
- **PCKD:** 10 (9.4) vs 10 (7.7)
- **Other:** 25 (23.6) vs 15 (11.5)

**Donor Type, n (%):**
- **Deceased:** 64 (60.4) vs 77 (59.2), **P-value:** 0.86
- **Living:** 42 (39.6) vs 53 (40.8)

**Ureteral stent at time of transplant, n (%):**
- **Group 1 (n=106):** 10 (9.4)
- **Group 2 (n=130):** 13 (10), **P-value:** 0.89

**HLA mismatches, mean (SD):**
- **Group 1 (n=106):** 4.2 (1.7)
- **Group 2 (n=130):** 3.9 (1.9), **P-value:** 0.21

**PRA, mean (SD):**
- **Group 1 (n=106):** 10.5 (26)
- **Group 2 (n=130):** 17.4 (30.7), **P-value:** 0.07

**Wojciechowski et al. Ciprofloxacin prophylaxis in kidney transplant recipients reduces BK virus infection at 3 months but not at 1 year. Transplantation 2012 (In Press).**
Figure 1: Kaplan-Meier plot of proportion of patients with BK viremia and viruria during the first 12-months post-transplantation.

Wojciechowski et al. Ciprofloxacin prophylaxis in kidney transplant recipients reduces BK virus infection at 3 months but not at 1 year. Transplantation 2012 (In Press).
Treatment: IVIG

- Contains polyomavirus-reactive antibodies
- Retrospective study of 8/216 renal transplant recipients who developed biopsy proven BKVAN and BK viremia
- All underwent reduction of immunosuppression by 50%
- IVIG given at 2g/kg divided over 2-5 days

Treatment: IVIG

- 5/8 patients cleared viremia
- One graft loss


<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cidofovir</th>
<th>Leflunomide</th>
<th>Fluoroquinolones</th>
<th>IVIg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of reports</td>
<td>27</td>
<td>18</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>No. of patients per report</td>
<td>1–26</td>
<td>1–30</td>
<td>4–10</td>
<td>1–11</td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>184&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>189&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>14</td>
<td>29&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Percentage of eventually cleared viraemia</td>
<td>82/168 (49%)</td>
<td>72/148 (49%)</td>
<td>0/10 (0%)</td>
<td>15/29 (52%)</td>
</tr>
<tr>
<td>Percentage of graft loss</td>
<td>42/184 (23%)</td>
<td>32/189 (17%)</td>
<td>0/14 (0%)</td>
<td>2/29 (7%)</td>
</tr>
<tr>
<td>References</td>
<td>12, 17–42</td>
<td>12, 16, 27, 32, 37, 40, 43–54</td>
<td>55, 56</td>
<td>32, 41, 48, 57, 58</td>
</tr>
</tbody>
</table>

All patients also had concomitant immunosuppression dose reduction.
Future Directions

- Sirolimus + Leflunomide
- In vitro reduced large T antigen expression and BK DNA replication

Screening/Treatment Summary

- Months 1-6, 9, and 12
  - PCR +
  - Stable Creatinine
    - Decrease immunosuppression and monitor PCR biweekly until undetectable
    - PCR +
    - Persistent Viremia
  - and Allograft dysfunction
    - Biopsy
      - No BKV Nephropathy
        - PCR +
        - BKV nephropathy +/- tubulitis
          - Consider IVIG
          - Cidofovir
          - Leflunamide
          - Quinolones
Thank You!
Questions???