Current recommendations for diagnosis and management of polyoma BK virus nephropathy in renal transplant recipients

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Introduction

Polyoma BK virus (BKV) is a ubiquitous DNA virus from the papova virus family [1]. Approximately 60–90% of the adult population worldwide is seropositive for BKV. Primary infection is usually asymptomatic, but the virus establishes latency within the genitourinary tract [1–3]. Reactivation may occur in conditions associated with impaired immunity and is common in renal transplant recipients (10–68%) [1]. Only 1–10% of patients progress from reactivated infection to histologically manifest polyoma BKV nephropathy (BKVN) [1,2,4]. Up to 80% of the patients with BKVN were reported to lose their graft, but early reduction of immunosuppression has been associated with improved prognosis [2,4,5]. We will discuss the available diagnostic tools to identify BKVN and the current practices of adjusting the immunosuppressive regimen. In addition, we review the available evidence supporting the use of cidofovir and leflunomide in established BKVN. Finally, the approach to acute rejection complicating BKVN, including the use of immunoglobulins, will be highlighted.

Diagnostic evaluation

Clinically silent viruria always precedes BKVN, thus allowing the identification of patients at risk for BKVN and creating a window of opportunity for pre-emptive measures [2,4,6,7]. An inexpensive screening tool is the examination of a Papanicolaou-stained urine sediment for the presence of decoy cells. These are epithelial cells with enlarged nuclei and large basophilic ground-glass intranuclear viral inclusions [4,6,7]. Quantification of viruria with a polymerase chain reaction (PCR) for BKV DNA is more sensitive than urine cytology, but gives little additional information above repeated urine cytology to justify the extra effort and expenses [7]. The presence of circulating virus is associated with active nephropathy, because virions enter the circulation through peritubular capillaries following tubular damage. Detection of BKV DNA in plasma with quantitative PCR has therefore been proposed as a surrogate marker for the diagnosis of BKVN [8]. Progression of BKVN is typically associated with increasing levels of viraemia [2]. Hirsch et al. [2,6] have suggested that a plasma viral titre >10000 copies/ml is 'presumptive' BKVN, even in the absence of histological evidence of BKVN. A definite diagnosis of BKVN requires the demonstration of viral cytopathic changes in tubular epithelium on a renal biopsy [1,4,7]. Stages A–C have been defined, with increasing severity and duration of the involvement and corresponding adverse effects on graft survival [1]. Standardized staging is a valuable tool to render future intervention and outcome studies more comparable.

Treatment of BKVN

Reduction of immunosuppression

The recent surge in the incidence of BKVN is commensurate with the widespread use of highly potent immunosuppressive regimens. Specific drugs or drug combinations have been associated with BKVN, in particular tacrolimus and the combined use of tacrolimus and mycophenolate mofetil (MMF) [9,10]. In a prospective study, however, no difference was found in the incidence of viruria and viraemia in patients treated with tacrolimus vs ciclosporin or MMF vs azathioprine [2]. In a series of 13 BKVN patients on various triple immunosuppressant combinations, no specific agent could be identified as the culprit [3]. These observations support the contention that the overall immunosuppressive load, rather than individual immunosuppressive agents, accounts for the
inability of the host to mount a successful antiviral immune response.

The cornerstone of treatment of BKVN is a decrease in maintenance immunosuppression. Various interventions have been pursued, most commonly withdrawal of MMF or tacrolimus [2,5,10,11], replacement of tacrolimus by ciclosporin [6,11–13] and overall reduction of the immunosuppressive load [3,5,10,13]. In a retrospective analysis of 67 patients, graft survival was similar after reduction vs discontinuation of tacrolimus or MMF [5]. No specific threshold values for drug levels or doses have been identified.

Switch to leflunomide

Leflunomide is an anti-inflammatory drug approved for the treatment of rheumatoid arthritis. Leflunomide has considerable immunosuppressive potency in human renal and liver transplant recipients [14]. Its active form has substantial antiviral activity against cytomegalovirus (CMV), herpes and BKV in vitro and in experimental animals [15]. The rationale for the use of leflunomide in BKVN rests on these combined immunosuppressive and antiviral actions. In two large case series, the same research group reported 26 and 17 patients, respectively, who developed BKVN on triple therapy with tacrolimus, MMF and steroids [15,16]. In all patients, MMF was withdrawn and leflunomide was administered at a loading dose of 100 mg daily for 3–5 days followed by a maintenance dose of 20–60 mg daily, aiming at through levels of 50–100 μg/ml. Clearance or a progressive reduction in viral load and a stabilization or improvement of graft function was achieved in 84 and 88% of patients, respectively. The patients who deteriorated had leflunomide plasma levels <40 μg/ml. Further studies are warranted to compare the effect of reduction of immunosuppression alone vs reduction of immunosuppression with association of leflunomide.

Antiviral agents: cidofovir

Various antiviral drugs have failed to affect the activity of BKV, including acyclovir, ganciclovir, foscarnet, vidarabine and ribavirin [1]. Cidofovir is a phosphonate purine analogue of cytosine that potently inhibits viral DNA polymerases, and has a broadspectrum activity against herpesviruses, papillomaviruses and poxviruses [17]. Cidofovir is approved for the treatment of CMV retinitis in patients with AIDS. Polyomaviruses, however, do not encode a DNA polymerase. Therefore, any potential antiviral activity against polyomaviruses must be achieved by alternative mechanisms that are not fully understood. Cidofovir is active against non-human polyomaviruses in vitro [17] and human polyoma JC virus in vitro [18]. Cidofovir is primarily eliminated by the kidneys, but accumulates in tubular cells. At a dose of 5 mg/kg substantial nephrotoxicity occurs, but this can be mitigated by the concomitant administration of probenecid to reduce renal clearance. Since high tissue levels are achieved in the kidney and urinary tract, lower cidofovir doses suffice for the treatment of BKVN [12,19–23]. Addition of probenecid appears non-sequitur for this purpose.

Successful treatment of BKVN by cidofovir has been reported in several cases and case series (Table 1). Dosage, duration and timing of administration and selection of patients were variable. Outcome was almost uniformly favourable, although the impact of cidofovir could often not be separated from the effect of reduced immunosuppression. No nephrotoxicity was reported [12,19–23]. Further studies are needed to determine the exact position of cidofovir, as a first line treatment or after the failure of reduced immunosuppression.

BKVN and acute rejection

The simultaneous occurrence of acute rejection and BKVN is a frequent clinical problem. The treatment of acute rejection with pulse steroids has been associated with an increased risk of BKVN [6]. In addition, reduction of immunosuppression to treat BKVN evidently carries a high risk (25–45%) of acute rejection [13,24]. Patients with acute rejection episodes prior to BKVN are at risk for acute rejection after reduction of immunosuppression to treat BKVN [24]. A brief increase in immunosuppression followed by a subsequent decrease has been recommended in these cases [1,4]. The rationale for this approach is that anti-rejection treatment is expected to stabilize allograft function within 5–10 days, whereas clearance of BKVN takes several weeks [1]. In a study by Howell et al. [10] however, two of three patients with BKVN and concomitant rejection treated with pulse steroids followed by decreased maintenance immunosuppression experienced progressive loss of renal function.

Intravenous immunoglobulins

The use of immunoglobulins may be a valuable treatment option in patients with BKVN and coexisting rejection. Immunoglobulins (500 mg/kg BW daily for seven consecutive days) were equally effective and much better tolerated than OKT3 in patients with steroid-resistant rejection [25]. In addition, transfer of protective immunity can be expected, since the majority of adults have antibodies against BKV. The activity of immunoglobulins against BKV has been confirmed in vitro [26]. A few anecdotal observations of successful use in patients with BKVN and rejection have been reported [2,22,24]. More recently, eight patients with BKVN, but without concomitant rejection were treated with intravenous immunoglobulins (2 g/kg BW divided over 2–5 days) following reduction of maintenance immunosuppression, resulting in clearance of viraemia in four patients [27]. Prospective trials
are warranted to define the optimal dose and potential role of immunoglobulins as first line treatment in BKVN and/or concomitant rejection.

Pre-emptive treatment of BKV replication

In patients with persistent viraemia and negative biopsy findings, pre-emptive reduction of immunosuppression should be considered. In a prospective study, reduction of immunosuppression by withdrawal of the antimetabolite resulted in resolution of viraemia before the development of BKVN, without a significant risk for acute rejection [2].

Recommendations

Screening for decy cells should be performed in all renal transplant recipients every 3 months during the first 2 years after transplantation and annually for the following 3 years, as well as in those patients who develop allograft dysfunction [4,7]. A positive screening result should be followed by a quantitative PCR for BKV DNA in plasma. If this test is positive, a renal biopsy is indicated [4]. Alternatively, it has been recommended to perform a renal biopsy if there is persistence of decy cells over a period of 3 months [7]. Clearance of BKV after a therapeutic intervention occurred with a t1/2 of 6 h–17 days [28], suggesting that monitoring viral load every 2–4 weeks is sufficient.

Confirmed BKVN should lead to prompt reduction of immunosuppression. Only opinion-based recommendations can be forwarded. Hirsch et al. [4] suggested that during the first year post-transplantation and in patients at risk for rejection, switching (tacrolimus to ciclosporin, MMF to azathioprine) or dose reduction is the preferred strategy. In other patients, reducing triple to dual therapy (discontinuation of tacrolimus or MMF or switching to tacrolimus/prednisone) can be attempted. Switching MMF to leflunomide is an attractive alternative strategy, pending confirmation by other research groups. However, widespread off-label use of leflunomide may be limited by reimbursement policies. Low-dose cidofovir (0.25–1 mg/kg depending on renal function, given at 2-week intervals, at least four times) can be recommended in cases refractory to dual therapy (discontinuation of tacrolimus or MMF or switching to tacrolimus/prednisone) can be attempted. Whether cidofovir merits a place in the first-line treatment of BKVN should be the subject of a prospective trial.

In patients with BKV viraemia and negative biopsy findings, pre-emptive reduction of immunosuppression appears sensible. In patients with concurrent acute rejection, anti-rejection treatment followed by reduction of immunosuppression 2 weeks later should be considered. In refractory cases, the use of immunoglobulins can be attempted.

Table 1. Studies using cidofovir in BKVN

<table>
<thead>
<tr>
<th>Reference n</th>
<th>Modification of Immunosuppression</th>
<th>Cidofovir</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>[20] n = 1</td>
<td>↓CORTb, AZAb → MMFd, ↓TACd, stop MMF</td>
<td>0.25 mg/kg, then 0.42 mg/kg every 2 weeks, 3 doses</td>
<td>1) Stable renal function, 2) Clearance viraemia, 3) Control biopsy: NAf</td>
</tr>
<tr>
<td>[22] n = 4</td>
<td>↓TAC/MMF/CORT or ↓TAC/MMF/CORT or TAC/stopp MMF/add rapamycine, then ↓TAC, stop rapamycine</td>
<td>0.25–1 mg/kg every 2–10 weeks, 1–4 doses</td>
<td>1) Stable renal function, 2) Clearance viraemia, 3) Control biopsy: NA</td>
</tr>
<tr>
<td>[21] n = 2</td>
<td>↓TAC/MMF</td>
<td>0.25 mg/kg every 2 weeks, 11–16 doses</td>
<td>1) Stable renal function, 2) Clearance viraemia, 3) Clearance BKV in biopsy</td>
</tr>
<tr>
<td>[23] n = 1</td>
<td>↓TAC/SIRh/CORT, then ↓TAC/CORT, SIR → MMF</td>
<td>0.25 mg/kg every 2 weeks, 8 doses</td>
<td>1) Improved renal function, 2) Clearance viraemia, 3) Clearance BKV in biopsy</td>
</tr>
<tr>
<td>[18] n = 2</td>
<td>↓TAC/SIR/CORT, then →CYC/mmF/MMF/CORT or ↓TAC/MMF/CORT</td>
<td>0.3 mg/kg every 2 weeks, 7 doses</td>
<td>1) Stable renal function (n = 1), graft loss (n = 1)</td>
</tr>
<tr>
<td>[29] n = 2</td>
<td>SIR/MMF/CORT or SIR/MMF/CORT or SIR/CORT</td>
<td>0.25–0.33 mg/kg monthly or every 2 weeks, 2–6 doses</td>
<td>1) Improved renal function (n = 1), graft loss (n = 1)</td>
</tr>
<tr>
<td>[12] n = 21</td>
<td>↓ Or = or stop MMF, ↓TAC or TAC → CYC or stop TAC</td>
<td>0.5–1 mg/kg weekly, 4–10 doses</td>
<td>1) Stable renal function, 2) Decline viraemia, 3) Control biopsy: NA</td>
</tr>
</tbody>
</table>

*Patient number; b/corticosteroids; a/azathioprine; d/mycophenolate mofetil; e/tacrolimus; fnot available; g/intravenous immunoglobulins; h/sirolimus; i/cyclosporin; j/of which 8 received cidofovir.
Despite the importance of BKVN in clinical practice, the optimal schedule and targets of reduction of immunosuppression as well as the position of cidofovir, leflunomide and immunoglobulins are unresolved issues. Research efforts under the aegis of scientific societies will hopefully lead to the availability of more solid guidelines in the near future.

Conflict of interest statement. None declared.

References

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