Original article

Low-dose cidofovir for the treatment of polyomavirus-associated nephropathy: two case reports and review of the literature

Frédéric Lamoth1,2*, Manuel Pascual2, Véronique Erard1, Jean-Pierre Venetz2, Ghaleb Nseir2 and Pascal Meylan1,3

1Infectious Diseases Service, Department of Medicine, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland
2Transplantation Centre, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland
3Institute of Microbiology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland

*Corresponding author: E-mail: Frederic.Lamoth@chuv.ch

Background: Polyomavirus-associated nephropathy (PVAN) is a serious complication and cause of graft loss in kidney transplant recipients. In the absence of specific antiviral drugs, early detection of the disease and reduction of immunosuppressive regimen is the cornerstone of therapy. Cidofovir, a nucleoside analogue, has been found to inhibit BK virus (BKV) replication in vitro and has been proposed as treatment of refractory PVAN at low doses; however, its efficacy has never been demonstrated in randomized controlled trials.

Methods: Cidofovir therapy (0.5 mg/kg at a 2-week interval for eight consecutive doses) was initiated in two patients with biopsy-proven PVAN and persistent BKV viraemia (≥10,000 copies/ml despite sustained reduction of the immunosuppressive regimen). In addition to these two case reports, we performed a critical review of the literature on the use of cidofovir in PVAN.

Results: No significant decrease of BKV viral load in blood was observed during cidofovir therapy and in follow-up of the two patients treated with cidofovir. Our literature review identified 21 publications reporting the use of cidofovir for the treatment of PVAN. All were case reports or small series. The efficacy of cidofovir therapy could not be assessed in 17 of these publications because of lack of data or concomitant reduction of immunosuppressive regimen. The four remaining publications were case reports.

Conclusions: In vitro and clinical data to support the efficacy of cidofovir in the treatment of PVAN are currently lacking. More promising compounds should be identified for further clinical studies.

Introduction

Since its initial description in 1995 [1], polyomavirus-associated nephropathy (PVAN) has become a problem of increasing importance in kidney transplantation, with an incidence ranging from 2 to 8% [2–6]. Despite active screening strategies and early intervention, this complication leads to graft loss in 10–50% of cases [4–6]. Because of the lack of specific antiviral treatment directed against BK virus (BKV), reduction of immunosuppression remains the cornerstone of therapy [4]. However, some drugs, such as leflunomide, quinolones, cidofovir or other nucleoside analogues have demonstrated efficacy on BKV replication in vitro [7–13].

Cidofovir is a nucleoside analogue approved for the treatment of AIDS-related cytomegalovirus retinitis. This drug is effective against herpesviruses by its inhibition of the viral DNA polymerase. In vitro studies have demonstrated a broad spectrum antiviral activity of cidofovir including pox-, papilloma- and polyomaviruses [14]. The mechanism of action of cidofovir against polyomaviruses is unclear because these viruses use a cellular DNA polymerase for their replication. It is believed that the drug might inhibit the activity of the T antigen that is necessary for the initiation of viral DNA replication. Its antiviral effect might also result from the inhibition of cellular DNA polymerases that are implicated in viral DNA synthesis [7,11]. Notable pharmacological properties of cidofovir are its poor oral bioavailability necessitating an intravenous administration, its potential renal toxicity and its prolonged intracellular half-life allowing a
large interdose interval (1–3 weeks) for the treatment of cytomegalovirus infection [15–17]. The drug is cleared by the kidney and is usually prescribed with the adjunction of probenecid, which inhibits its renal tubular excretion. Because of its nephrotoxicity and its renal mode of elimination, it has been proposed that cidofovir should be administered at low doses (0.25–1 mg/kg, approximately 10-fold lower than doses recommended for the treatment of cytomegalovirus retinitis) without probenecid for the treatment of PVAN, as the disease is limited to the kidney [9,18].

Here, we report the outcome of two consecutive kidney transplant recipients with PVAN treated with cidofovir, and discuss the efficacy and indication of cidofovir therapy for PVAN through a critical review of the literature.

Methods

Patients
Approximately 30 kidney transplantations are performed annually at the University Hospital of Lausanne (Lausanne, Switzerland). Specific BKV DNA detection in blood by quantitative real-time PCR, according to methods previously described [3], is routinely performed at 3 and 6 months after transplantation and in cases of increased creatinine level (>50% baseline). Patients with BKV DNA viraemia ≥10,000 copies/ml are treated by reduction of the immunosuppressive regimen (that is, reduction of 50% or interruption of mycophenolate mofetil and target plasma level of tacrolimus at 4–6 µg/l or cyclosporine at 80–100 µg/l).

Cidofovir therapy was initiated in two patients with persistent viraemia ≥10,000 copies/ml despite sustained reduction of the immunosuppressive regimen and after confirmation of PVAN by histological examination and immunohistochemistry. Cidofovir was administered intravenously without probenecid every 2 weeks for 4 months (eight consecutive infusions) at the dose of 0.25 mg/kg (first infusion) and then 0.5 mg/kg (second to eighth infusion). Response to therapy was assessed by quantification of BKV DNA in blood every 2 weeks during cidofovir therapy and monthly thereafter. Serum creatinine, proteinuria and complete blood cell count were determined simultaneously.

Search strategy and selection criteria
We looked for existing data in the literature about the use of cidofovir in the treatment of PVAN. A search of the PubMed database was performed using the keyword ‘cidofovir’ in combination with ‘BK virus’, ‘BK nephropathy’, ‘polyomavirus’ or ‘polyomavirus nephropathy’. The search was restricted to the English language literature and publications before 1 May 2008. All studies reporting the use of cidofovir in solid-organ transplant recipients for the treatment of PVAN were considered. Data about cidofovir doses, dose interval and total number of doses were collected, as well as BKV viral load in blood and serum creatinine values before, during and after cidofovir therapy. Stage of PVAN was assessed according to the classification described previously as histological stage A, B or C [4,19], when a histological description of kidney biopsy was available. The occurrence of adverse events possibly related to cidofovir and the incidence of graft loss in follow-up were also recorded. On the basis of the data provided by these studies, we attempted to assess the efficacy and safety of cidofovir in the treatment of PVAN with respect to different outcomes, including renal function at the end of cidofovir therapy, long-term graft survival, histological cure (absence of BKV detection by immunohistochemistry in graft biopsy), clearance of BKV in blood, recurrence of the disease (new detectable BKV viraemia) and reported adverse events. We made a distinction between publications evaluating the efficacy of cidofovir in the absence of confounding factors (that is, after prior stabilization of immunosuppression, defined as ≥1 month between the last change in immunosuppressive regimen and start of cidofovir, and in the absence of concomitant use of other antiviral drugs with potential anti-BKV effects, such as leflunomide) and those in whom concomitant interventions (changes in immunosuppressive regimen <1 month before the start of cidofovir therapy or concomitant use of antiviral drugs) might have confounded the response to cidofovir.

Results

Patients

Patient 1

A 58-year-old woman with end-stage renal disease secondary to hypertensive nephroangiosclerosis underwent kidney transplantation (deceased donor). The panel reactive antibody (PRA) level was 0% and the number of human leukocyte antigen (HLA) mismatches was six. She received induction therapy with basiliximab (20 mg at days 0 and 4) and maintenance immunosuppressive therapy consisted of tacrolimus (target plasma level 6–10 µg/l), mycophenolate mofetil (initially 2 g/day, tapered to 1 g/day at 3 months after transplantation) and steroids (high-dose methylprednisolone for the first 3 days after transplantation, followed by tapered prednisone to a dose of 5 mg/day at 3 months after transplantation). There was immediate graft function, with serum creatinine falling to 129 µmol/l by day 3 after transplantation. No early rejection episode was observed.

The patient developed PVAN (stage A) 8 months after kidney transplantation. Serum creatinine value and BKV viraemia at the time of diagnosis were 161 µmol/l and 389,372 copies/ml, respectively. Mycophenolate
mofetil and tacrolimus were discontinued and sirolimus was initiated for a target plasma level 5–8 µg/l, whereas prednisone doses remained unchanged (5 mg once daily). Viraemia remained very high (>400,000 copies/ml) and creatinine values remained at approximately 160 µmol/l despite reduction of immunosuppression. A new graft biopsy was performed 22 months after transplantation and showed that PVAN had progressed to stage C with positive immunohistochemistry for BKV. Cidofovir therapy was initiated at that time because of persistent high-level viraemia in the hope of preserving graft function. BKV viraemia and serum creatinine values were 217,256 copies/ml and 154 µmol/l, respectively, at the start of therapy. No significant decrease of BKV viral load in blood was observed during cidofovir therapy and over a 7-month follow-up after the last dose of cidofovir. The immunosuppressive regimen was not modified during this period. Creatinine levels increased to 190 µmol/l during cidofovir therapy and remained stable thereafter (Figure 1A). The patient did not complain of any particular symptoms during and after cidofovir therapy and no haematological toxicity was observed. No new biopsy was performed thereafter.

**Patient 2**

A 63-year-old man underwent a second kidney transplantation (deceased donor) for a chronic allograft nephropathy 12 years after having received a first allograft for end-stage renal disease secondary to a membranoproliferative glomerulonephritis. The PRA level was 80% and the number of HLA mismatches was four. Induction therapy consisted in thymoglobulin 1.5 mg/kg/day for 4 days and maintenance immunosuppressive regimen was the same as described in Patient 1. There was no delayed graft function (serum creatinine 185 µmol/l at day 3 after transplantation) and no early episode of rejection.
The patient was diagnosed with PVAN (stage B) 14 months later. Serum creatinine value and BKV viraemia at the time of diagnosis were 196 µmol/l and 12,146,825 copies/ml, respectively. Mycophenolate mofetil and tacrolimus were discontinued, prednisone doses remained unchanged (5 mg once daily) and cyclosporine was introduced for a target plasma level of 100–120 µg/l. Immunosuppression was not further reduced because of the high risk of graft rejection (high PRA level) existing in this patient. Cidofovir therapy was initiated 33 months after transplantation because BKV viraemia persisted at about 10,000 copies/ml and serum creatinine was 249 µmol/l. Kidney biopsy was not repeated at that time. No significant change was observed with regard to BKV viral load in blood and creatinine level during cidofovir therapy and for 4 months of follow-up after the end of cidofovir therapy (Figure 1B). Immunosuppressive regimen remained unchanged during follow-up. No signs of toxicity were observed and no graft biopsy was performed thereafter.

Review of the literature
Our review of the literature identified 21 publications that reported the use of cidofovir therapy in PVAN (Tables 1 & 2). Suppression of BKV in blood could be attributed unambiguously to cidofovir in five cases (three publications), of which four were kidney transplant recipients (Table 1) [20–22]. Those four patients had PVAN with histological stage B (three cases) or C (one case) and received cidofovir doses of 0.25–0.3 mg/kg every 2 weeks (4–16 doses). All four responded to therapy with a rapid clearance (1–3 months) of the virus in blood and histological resolution of PVAN. One patient with advanced disease (stage C) from the beginning of cidofovir therapy lost the graft.

We identified 17 other publications for which the clinical efficacy of cidofovir could not be clearly assessed because of confounding factors (concomitant reduction of immunosuppression) and/or lack of information with regard to the outcomes of the disease. Data provided by these studies are summarized in Table 2.

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**Figure 1. Continued**

### B

<table>
<thead>
<tr>
<th>Tacrolimus, µg/l</th>
<th>5–8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine, µg/l</td>
<td>100–150</td>
</tr>
<tr>
<td>MMF, g/day</td>
<td>1–1.5</td>
</tr>
<tr>
<td>Prednisone, mg/day</td>
<td>10–20</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
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<td></td>
<td>5</td>
</tr>
</tbody>
</table>

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**Figure 1.**

**A**

- **BKV pos PVAN, B**
- **BKV pos PVAN, B**
- **Cidofovir therapy**
  - (0.5 mg/kg every 2 weeks)

**Months after transplantation**

- **BKV viraemia, log₁₀ copies/ml**
- **Serum creatinine, µmol/l**

---

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- **Serum creatinine, µmol/l**

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- **BKV pos PVAN, B**
- **Cidofovir therapy**
  - (0.5 mg/kg every 2 weeks)

**Months after transplantation**

- **BKV viraemia, log₁₀ copies/ml**
- **Serum creatinine, µmol/l**
Table 1. Literature review: cidofovir therapy after stabilization of immunosuppression (≥1 month after last change in immunosuppressive regimen) and no other concomitant interventions

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>Baseline characteristics</th>
<th>Intervention</th>
<th>End points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PVAN stage at start of cidofovir*</td>
<td>Cidofovir dosage, mg/kg</td>
<td>Dose interval, weeks</td>
</tr>
<tr>
<td>Kadambi [20]</td>
<td>2 (adults)</td>
<td>KT B</td>
<td>4.1×10⁴ and 5.1×10³</td>
<td>0.25</td>
</tr>
<tr>
<td>Lim [21]</td>
<td>2 (adults)</td>
<td>KT B, C</td>
<td>NA</td>
<td>0.3</td>
</tr>
<tr>
<td>Limaye [22]</td>
<td>1 (adult)</td>
<td>aHSCT B</td>
<td>1.1×10⁴</td>
<td>0.1</td>
</tr>
<tr>
<td>Schwarz [44]</td>
<td>1 (adult)</td>
<td>LT B</td>
<td>1.2×10⁴</td>
<td>3.5</td>
</tr>
</tbody>
</table>

*Histological staging according to the classification recommended by experts [4,19]. †Number of patients/total number of assessable cases. ‡End-stage renal failure. aHSCT, autologous haematopoietic stem cell transplantation; BKV, BK virus; KT, kidney transplantation; LT, lung transplantation; NA, data not available; PVAN, polyomavirus-associated nephropathy.
Table 2. Literature review: cidofovir therapy concomitant to the reduction of immunosuppression (<1 month after last change in immunosuppressive regimen).

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline characteristics</th>
<th>Intervention</th>
<th>End points</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVAN</td>
<td>BKV viraemia</td>
<td>Kidney</td>
<td>Recurrence</td>
</tr>
<tr>
<td>Bjorang 1 (adult) KT NA 1  \times 10^3</td>
<td>0.42</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Ginevri 1 (child) KT NA 5  \times 10^6</td>
<td>0.6</td>
<td>NA</td>
<td>2</td>
</tr>
<tr>
<td>Keller 1 (adult) KT B 1  \times 10^4</td>
<td>0.25</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Vats 4 (children KT NA 0.7 \times 10^6–3.7 \times 10^6</td>
<td>0.25–3</td>
<td>2–8</td>
<td>1–4</td>
</tr>
<tr>
<td>Herman 1 (child) KT B 2.8 \times 10^3</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Lipshutz 2 (adults) KT NA 1.7 \times 10^4 and 0.25–0.33</td>
<td>2–4</td>
<td>2–7</td>
<td>2–3</td>
</tr>
<tr>
<td>Tong 5 (adults) KT NA 1  \times 10^2–1  \times 10^7</td>
<td>0.25</td>
<td>2</td>
<td>4–16</td>
</tr>
<tr>
<td>Kuypers 8 (adults) KT B 2.2 \times 10^5</td>
<td>0.5–1</td>
<td>1</td>
<td>4–10</td>
</tr>
<tr>
<td>Lipshutz 4 (adults) SPK NA NA 0.25</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Araya 3 (children) KT NA 7  \times 10^5–2.4  \times 10^6</td>
<td>0.25–1</td>
<td>2</td>
<td>7–15</td>
</tr>
<tr>
<td>Gupta 6 (adults) SPK NA 1  \times 10^2–1.3  \times 10^6</td>
<td>0.2–0.5</td>
<td>2–3</td>
<td>1–12</td>
</tr>
<tr>
<td>Hymes 7 (children) KT NA 3.8 \times 10^6</td>
<td>0.3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Josephson 9 (adults) KT NA 1  \times 10^6</td>
<td>0.25§</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>Lopez 14 (adults) KT (12), SPK (2) NA NA 0.5</td>
<td>2</td>
<td>5–11</td>
<td>Uveitis (5/12)</td>
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<tr>
<td>Benavides 9 (adults) KT (6), SPK (3) B, C 6.3 \times 10^4–1.1 \times 10^7</td>
<td>0.25–0.5</td>
<td>2</td>
<td>1–22</td>
</tr>
<tr>
<td>Ott 3 (adults) KT B NA 0.25</td>
<td>2</td>
<td>4</td>
<td>None</td>
</tr>
<tr>
<td>Puliyanda 2 (children) KT A, B 2.5  \times 10^5 and 0.25–0.5</td>
<td>1</td>
<td>4</td>
<td>None</td>
</tr>
</tbody>
</table>

*Histological staging according to the classification recommended by experts [4,19]. †Number of patients/total number of assessable cases. ‡Viraemia was initially detected in only two patients. §Concomitant use of leflunomide. KT, kidney transplantation; NA, not available; PVAN, polyomavirus-associated nephropathy; SPK, simultaneous pancreas–kidney transplantation.
Discussion

We described two cases of PVAN in whom low-dose cidofovir (0.5 mg/kg every 2 weeks) was not effective in suppressing BKV replication. Renal function remained stable after 4 and 7 months of follow-up, respectively, and no toxic effects of cidofovir were observed. Although one can argue that the immunosuppression might have been further reduced, these patients were considered to have refractory PVAN at >6 months after the last change of immunosuppressive regimen when cidofovir therapy was initiated.

Cidofovir in PVAN: clinical data

In contrast with our observations, cidofovir has been associated with clearance of viraemia in previous case reports and small series [18,20–32]. However, confounding factors, such as concomitant modification of immunosuppression, were present in most studies and conclusions could not be drawn from these. In our analysis, we considered that a reduction of immunosuppression occurring in the preceding month might have confounded the response to cidofovir therapy. Previous data, however, suggest that the recovery of BKV-specific T-cells after reducing immunosuppression might be even longer (6–12 weeks) [33,34]. Only one study (Kuypers et al. [29]) addressed the effectiveness of cidofovir therapy in PVAN as a primary endpoint with a control group. Among 21 patients with biopsy-proven PVAN managed by reduction of immunosuppressive regimen, eight received concomitant low-dose cidofovir (0.5–1 mg/kg weekly). Most of these patients had histological stage B nephropathy and high-level viraemia. The incidence of graft loss was significantly lower in the group of patients treated with cidofovir when compared with the group of patients treated by reduction of immunosuppressive regimen only (0/8 versus 9/13, respectively; \( P=0.005 \)), whereas baseline characteristics and the degree of immunosuppressive dose reduction were similar in both groups. There was no significant difference in the decline of blood viral load at any point during follow-up between patients receiving or not receiving cidofovir.

Considering the clearance or a significant decrease of BKV viraemia as the main outcome to define success of therapy, the efficacy of cidofovir in PVAN may be questioned by some recent publications. In a study evaluating the course of PVAN in a large cohort of patients receiving sirolimus-based regimens, the disease was found to be particularly severe with >50% of patients experiencing graft loss. The decline of plasma viral load after cidofovir therapy was not statistically significant and all patients had persistent viraemia after therapy [35]. Similar disappointing results were recently reported in three adult patients and in seven children [36,37].

A common feature of these studies was that patients had advanced-stage disease (histological stages B2–B3 or C) with high-level viraemia when cidofovir therapy was initiated. These characteristics were also observed in the two present cases. This raises the hypothesis that the benefit of cidofovir might be restricted to early-stage diseases before irreversible tissue damage occurs. Unfortunately, the small number of cases reported, the lack of accurate data and the heterogeneity of these studies with respect to the staging of the disease at start of cidofovir, the duration of therapy and the criteria used to evaluate the response to therapy does not allow conclusions to be drawn.

Many experts have emphasized the need to perform randomized controlled trials to assess the clinical efficacy of cidofovir and other antiviral drugs in the treatment of PVAN [4,9,13,29]. However, the rationale of this approach should be carefully re-evaluated before undertaking such studies.

Cidofovir in PVAN: in vitro data

The activity of cidofovir against BKV in human embryonic lung fibroblasts has been shown to be modest [8,11]. In a recent analysis in renal proximal tubule epithelial cells, the 90% effective concentration (\( EC_{90} \); the concentration required to reduce the BKV load by an average of 90%) was 40 \( \mu \)g/ml [38]. As discussed by the authors, this value is approximately 10–50× greater than the median peak serum concentrations measured in patients receiving cidofovir at a dose of 0.5 and 1 mg/kg (0.8 and 3.1 \( \mu \)g/ml, respectively) [29,39]. Pharmacokinetic studies of cidofovir have shown that 90% of the intravenous dose was recovered unchanged in the 24 h urine volume [39]. Considering its nephrotoxicity, cidofovir has been proposed at low doses for the treatment of PVAN, as the disease is considered to be limited to the kidney where this drug is actively secreted [9]. All authors reporting the use of cidofovir in PVAN have used doses ranging from 0.25 to 1 mg/kg (corresponding to approximately 1/10 of those recommended for the treatment of cytomegalovirus retinitis) with large interdose intervals (1–2 weeks) and without the adjunction of probenecid that inhibits the intratubular excretion of the drug and would thus impede its accumulation in the affected organ; however, data regarding the concentrations of cidofovir recovered in urine after these dosing regimens are lacking. In a study evaluating the tissue distribution of radiolabelled cidofovir in mice, high concentrations were achieved in the kidney 1 h after intraperitoneal administration of the drug. However, the rapid elimination of cidofovir resulted in very low levels in kidney (15–20-fold inferior to the maximum concentration) within 24 h [40]. In vitro data suggest that such dosing regimens are definitely inappropriate.

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and should be ineffective in reducing BKV viraemia as the concentrations of cidofovir in serum are markedly inferior to the EC\textsubscript{90} of BKV and almost totally cleared by the kidney within 24 h.

Promising compounds for the treatment of PVAN Hexadecyloxypropyl (HDP)-cidofovir and octadecyloxyethyl (ODE)-cidofovir, two alkoxyalkyl esters of cidofovir, have shown significantly lower effective concentrations (1,000-fold lower than that of cidofovir) and higher selectivity indices and could represent an interesting option for the treatment of PVAN in further studies [11]. Their enhanced activity is not specific for BKV and results, in part, from their increased cellular penetration [41]. Other advantages of the ester derivatives of cidofovir are their excellent oral bioavailability in animal models and reduced affinity for the renal cortex when compared with cidofovir [40]. Ciesla et al. [40] have demonstrated that the peak concentrations in the kidney of HDP-, ODE- and oleyloxypropyl-cidofovir are about 150-fold lower than that obtained with the equimolar dose of cidofovir. However, cidofovir levels rapidly decline in the first 24 h, whereas its ester derivatives are able to maintain concentrations which are approximately 5\times superior to their ECs. This finding suggests that these drugs may be associated with a prolonged efficacy against BKV in the absence of a toxic peak level. In \textit{vitro} studies investigating the anti-BKV activity of other nucleoside analogues such as HDP-(S)-HPMPA (the adenine analogue of cidofovir) have also given promising results [12].

Conclusions
Although cidofovir has demonstrated a modest \textit{in vitro} anti-BKV activity, reports about its clinical use in PVAN are anecdotal and do not provide sufficient evidence to support its efficacy because of many confounding factors (such as concomitant reduction of immunosuppression, absence of a control group, inaccuracy of data and lack of standardized parameters to assess efficacy). Moreover, \textit{in vitro} analyses and results derived from animal models suggest that the dosing regimens of these previous reports are inappropriate. In addition, the nephrotoxicity of cidofovir is a limitation for its use at higher doses in kidney transplant recipients. Similarly, leflunomide and quinolones have demonstrated some anti-BKV activity \textit{in vitro}, but clinical data to support their efficacy are lacking [37,42,43]. More potent and selective agents against BKV, such as ester derivatives of cidofovir (HDP- and ODE-cidofovir) or other nucleoside analogues (HDP-(S)-HPMPA) are currently under investigation and represent an interesting option for the antiviral therapy of PVAN. Randomized controlled trials are needed to assess the efficacy of cidofovir, as well as that of other promising compounds, for the treatment of PVAN. Such drugs, and their dosing regimens, should be carefully selected according to their \textit{in vitro} activity and pharmacokinetic profile.

Acknowledgements
We would like to thank Marc Voeffray and Gregory Podilsky from the pharmacy of the Centre Hospitalier Universitaire Vaudois (Lausanne, Switzerland) and the nurses of the Transplantation Centre of the Centre Hospitalier Universitaire Vaudois for the outstanding assistance in the management of the patients.

Disclosure statement
The authors declare no competing interests.

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