An update on herpes virus infections in graft recipients

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**Introduction**

Acute rejection rates after renal transplantation are steadily decreasing due to more effective immunosuppressive therapies. However, more powerful prevention of immunological damage to the kidney by increasing immunosuppression is a two-edged sword, as infectious complications tend to rise in such a setting. Viral infections significantly contribute to morbidity and mortality after renal transplantation [1], and the spectrum of some viral diseases may have changed in recent years. Rapid diagnosis, appropriate antiviral treatment and management of concurrent medications are warranted to prevent patients from potentially severe disease manifestations. This brief review will focus on current considerations concerning infections with human herpes viruses (HHV) and their treatment in renal transplant recipients.

**Cytomegalovirus (HHV-5)**

Cytomegalovirus (CMV) infection is the most prevalent viral infection in renal transplant recipients [2]. Depending on the individual serostatus, patients may develop either primary infection, superinfection or reactivation of CMV infection. Seropositive transplant recipients with detectable CMV-IgG-antibodies develop a symptomatic CMV infection in ~10% of cases, whereas seronegative recipients transplanted from a seropositive donor (D+/R−) have a risk of up to 50% of developing CMV disease [1,2]. In order to minimize the occurrence of ‘tissue-invasive’ CMV disease (hepatitis, enteritis, pneumonitis), virus replication should be monitored weekly by immunostaining of the pp65 antigen in peripheral blood leucocytes or by quantitative real-time–PCR techniques during the first 3–4 months after transplantation. D+/R− recipients and patients with anti-lymphocyte induction or rejection therapy are recommended to receive antiviral prophylaxis. Most transplantation centres otherwise initiate preemptive antiviral treatment at the time when detection of virus replication becomes significant, but before symptoms of CMV disease occur. However, it is not clear whether this preemptive approach is indeed superior when compared with a deferred therapy, i.e., started at the time when overt CMV disease manifestations are present. There is also the unresolved question, at which threshold should preemptive therapy be initiated to prevent CMV disease? For example, are one to two pp65-positive cells per 50 000 leucocytes sufficient to justify antiviral treatment, or could reduction of immunosuppression alone be effective in suppressing CMV replication?

The recognition of CMV infection and disease seems to have changed in recent years. This may either be due to more sophisticated and more frequent testing, or to changing patterns of disease manifestations, possibly because of more effective immunosuppression. For example, CMV enteritis showing a variable clinical picture including diarrhoea, dysphagia, epigastric pain as well as upper and lower gastrointestinal bleeding is increasingly observed in transplant recipients, but
may not necessarily be associated with detectable systemic pp65-antigenaemia or systemic CMV DNA-amplification [3]. Consequently, if CMV enteritis is suspected, any possible attempt should be made to prove or exclude this diagnosis by immunostaining of intestinal biopsies using antibodies directed against early CMV antigen (e.g. clone CCH2) [4].

Antiviral treatment is currently based on i.v. or oral ganciclovir, but may shift to the pro-drug valganciclovir in the very near future due to its excellent oral bioavailability [5]. Ganciclovir is a guanosine analogue inhibiting CMV DNA polymerase and requiring triphosphorylation to be activated. Mutations in the UL97 phosphotransferase, representing the first enzyme responsible for intraviral ganciclovir phosphorylation, can cause resistance of CMV to ganciclovir treatment, especially in D+/R- recipients [6]. Relative or absolute underdosing of ganciclovir therapy can lead to a dominance of resistant CMV populations by selection mechanisms; therefore, ensuring sufficiently high initial ganciclovir blood levels by i.v. therapy or by valganciclovir may be advantageous over oral ganciclovir (bioavailability < 10%). Valganciclovir has recently demonstrated similar efficacy as i.v. ganciclovir in the treatment of CMV chorioretinitis in HIV-positive individuals enabling management of affected patients in an out-patient setting [7]. Dosage recommendations for renal transplant recipients are given in Table 1. Although foscarnet or cidofovir are therapeutic options for patients with a proven ganciclovir resistance, both are of limited value in renal transplant patients because of their nephrotoxicity. Moreover, resistance to these compounds may occur as well [8].

The role of concurrent immunosuppression in the changing recognition of CMV disease manifestations must also be considered. The therapeutic consequence must be lowering immunosuppressive therapy until successful antiviral treatment of CMV infection is established and documented by disappearance of symptoms and/or significant drops in CMV replication. In accordance with many transplantation centres, we temporarily decrease or discontinue mycophenolate mofetil (MMF) in patients with symptoms and/or significant drops in CMV replication, respectively, depending on the magnitude of the virus burden and the individual risk of the patient. Calcineurin inhibitors are maintained at plasma trough levels in the lower therapeutic range and steroid doses are unchanged. In the case of life-threatening complications such as interstitial pneumonitis, immunosuppression must be reduced even more rigorously including cessation of calcineurin inhibitors, whereas a steroid dose of 15–20mg prednisolone equivalent per day should probably be maintained.

In parallel to lowering immunosuppressive medication, ganciclovir therapy is initiated, and treatment should be maintained at least for 2–4 weeks after the patient is tested negative for virus replication. The question when to reinstall full immunosuppression after temporary reduction is unresolved. The increased rate of acute rejections in association with CMV infection may well be associated with under-immunosuppression in the vulnerable phase during recovery. In the future, biomonitoring of CMV-specific CD4-positive T-cells by FACS analysis may become an option to overcome this difficulty, as the emergence of many positive cells may indicate the development or restoration of a specific defence against CMV disease [9].

**Herpes simplex (HHV-1 and -2)**

In the majority of patients seropositive for herpes simplex virus (HSV)-1 or -2, virus replication occurs after transplantation, but only a minority of patients develop symptoms (~20%) [1]. Local ulcers at various mucocutaneous sites represent the most frequent manifestation, but dissemination to deeper tissues (bladder, esophagus, colon, etc.) is occasionally observed. Hepatitis and meningoencephalitis are rare but potentially life-threatening complications, mostly caused by HSV-1. We recently observed a HSV-2 related peritonitis in a tacrolimus/sirolimus-treated renal transplant recipient. The diagnosis was made by an excessive number of HSV-2 virus DNA copies in the peritoneal fluid.

The diagnosis of HSV infection is best made by culture and/or PCR of vesicular fluid or mucosal swabs. The mainstay of treatment is the oral or i.v. administration of aciclovir. Oral treatment is somewhat problematic because of low bioavailability, and valaciclovir is superior in this regard. However, some caution is advised, as there are reports about the association of haemolytic–uraemic syndrome with valaciclovir prophylaxis in HIV-positive patients [10]. In general, treatment recommendations for mucocutaneous manifestations of HSV infections do not differ significantly between immunocompetent and immunocompromised patients (Table 2).

**Varicella zoster (HHV-3)**

Varicella zoster virus (VZV) infections, which mostly occur as reactivation of latent virus, are more problematic than HSV infections for two reasons:

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**Table 1. Valganciclovir treatment and dose-adjustments to renal function in renal transplant recipients**

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Starting dosing</th>
<th>Maintenance dosing</th>
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<tbody>
<tr>
<td>≥60</td>
<td>2× 900 mg</td>
<td>1× 900 mg</td>
</tr>
<tr>
<td>40–59</td>
<td>2× 450 mg</td>
<td>1× 450 mg</td>
</tr>
<tr>
<td>25–39</td>
<td>1× 450 mg</td>
<td>450 mg (on alternate days)</td>
</tr>
<tr>
<td>10–24</td>
<td>450 mg (on alternate days)</td>
<td>450 mg (twice weekly)</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>450 mg (following dialysis sessions)</td>
<td></td>
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</table>
Measures of EBV replication are of limited value, as immunohistochemical analysis of tumour tissue. The diagnosis of PTLD is made by ganciclovir for the first 3 months after transplantation. Seronegative patients should receive an antiviral prophylaxis using oral aciclovir or develop PTLD. Seronegativity and previous administration of antilymphocyte preparations are major risk factors for the development of PTLD in immunocompromised transplant recipients with suspected visceral VZV disease manifestations. Increased dosing of oral aciclovir is recommended for renal transplant patients with cutaneous zoster, thereby limiting lesion severity and potentially preventing dissemination (Table 2). MMF should be discontinued temporarily.

Children on the waiting list for transplantation should receive vaccination, since an effective antibody response is usually seen. Administration of VZV immunoglobulins to individual patients without a history of VZV disease or with documented seronegativity as a post-exposure prophylaxis is feasible and effective within 72h after exposure to prevent or attenuate the disease. Post-herpetic neuralgic pain may persist for months and represents a substantial problem, as neither steroids nor aciclovir influence its course—carbamazepine, gabapentin or antidepressants may have to be considered as supportive therapy.

### Epstein–Barr virus (HHV-4) and HHV-8

Epstein–Barr virus (EBV)-associated post-transplant lymphoproliferative disease (PTLD) is one of the major problems in renal transplant recipients, accounting for ~20% of post-transplant tumours with a higher risk in children (52% of all post-transplant tumours in children vs 15% in adults) [1,11]. Pre-transplant EBV seronegativity and previous administration of antilymphocyte preparations are major risk factors for the development of PTLD. Seronegative patients should receive an antiviral prophylaxis using oral aciclovir or ganciclovir for the first 3 months after transplantation according to the most recent ‘European Best Practice Guidelines’ [12]. The diagnosis of PTLD is made by immunohistochemical analysis of tumour tissue. Measures of EBV replication are of limited value, as replication frequently occurs after transplantation without association to disease or PTLD development. Quantitative amplification of EBV DNA in plasma may however be more sensitive to distinguish asymptomatic from disease-associated replication [13]. Concerning treatment, the available evidence was partly controversial, but guidelines were recently implemented to direct appropriate therapeutic approaches [12]. Reduction or cessation of immunosuppression is the mainstay in PTLD patient management. In the future, switching patients from calcineurin inhibitor-based therapy to mammalian target of rapamycin (mTOR)-inhibitors (rapamycin, SDZ-RAD) may become an option to improve and, at the same time, continue immunosuppressive treatment. There is experimental evidence that mTOR-inhibitors may generally prevent tumour growth by their anti-proliferative, anti-angiogenic and pro-apoptotic actions as well as specifically block cell-cycle progression of PTLD-like EBV-positive B-cells in vitro and in vivo [14,15]. However, clinical evidence in this context is currently not sufficient to justify a general recommendation.

Many centres administer i.v. ganciclovir to patients with EBV-associated PTLD; however, evidence for this therapeutic approach is not sufficiently based on prospective studies, and efficacy on the latent cycle of EBV infection as in PTLD is unproven [16,17]. Reports of successful treatment of CD20-positive PTLD with the monoclonal antibody rituximab are available, but non-responders will have to be treated with chemotherapy, preferably according to the CHOP protocol [12,18].

**HHV-8** is the causative agent for Kaposi’s sarcoma. Southern Europe and the Middle East are regions with a high prevalence of HHV-8 carriers. Consequently, Kaposi’s sarcoma is found much more frequently among immunocompromised patients in these populations than in transplant recipients from Northwestern Europe or North America [1]. As with EBV-associated PTLD, reduction or cessation of immunosuppressive medication is the mainstay of therapy and quite successful with achieving complete remissions of up to 60%, while chemotherapy and irradiation must be considered in non-responders.

### Table 2. Treatment recommendations for HHV-1–3 infections in renal transplant patients with a glomerular filtration rate > 50 ml/min

<table>
<thead>
<tr>
<th>Disease manifestation</th>
<th>Therapy</th>
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<tr>
<td>HSV-1 (mucocutaneous)</td>
<td>Aciclovir 1% topically/4 days, or aciclovir 5x 500mg p.o. 5/5 days (severe ulcers)</td>
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<tr>
<td>HSV-1 encephalitis or hepatitis</td>
<td>i.v. aciclovir 3x 10–15mg/kg for 14–21 days</td>
</tr>
<tr>
<td>HSV-2 (mucocutaneous)</td>
<td>Aciclovir 5x 400mg p.o. 10/10 days (5 days in recurrent cases, or prophylaxis with 2x 400mg)</td>
</tr>
<tr>
<td>VZV (cutaneous, ‘zoster’)</td>
<td>Aciclovir 5x 800mg p.o. 10/7 days, or 3x 10mg/kg i.v. for 7 days</td>
</tr>
<tr>
<td>Primary VZV infection (‘varicella’)</td>
<td>i.v. aciclovir 3x 10 mg/kg for 7 days</td>
</tr>
<tr>
<td>Disseminated VZV infection/encephalitis</td>
<td>i.v. aciclovir 3x 10–15 mg/kg for 14–21 days</td>
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</table>

*Valaciclovir can be administered alternatively.

In reduced renal function (glomerular filtration rate 10–50 ml/min), oral aciclovir therapy recommendations for HSV-1 and -2 infections remain unchanged, oral aciclovir for zoster treatment is reduced to 3 times 800mg, and i.v. aciclovir is reduced to once or twice daily applications. In all cases clinically resistant to oral aciclovir treatment, i.v. administration should be considered.

(i) infections tend to disseminate (encephalitis, pneumonia) in up to one-third of affected patients; and (ii) VZV infections require larger doses of aciclovir given the lower sensitivity of VZV to this compound [1]. Thus, high-dose i.v. aciclovir treatment should be administered to immunocompromised transplant recipients with suspected visceral VZV disease manifestations. Increased dosing of oral aciclovir is recommended for renal transplant patients with cutaneous zoster, thereby limiting lesion severity and potentially preventing dissemination (Table 2). MMF should be discontinued temporarily.
HHV-6 and HHV-7

The role of these two herpes viruses in renal transplant recipients is not currently clear [1]. HHV-6 causes exanthema subitum, HHV-7 possibly a similar disease including rash, leukopenia with lymphocytosis and splenomegaly. Detectable reactivation occurs in one-to-two-thirds of transplant patients, but is rarely linked directly to a clinical syndrome. It appears possible and should be considered that CMV disease-like symptoms with negative tests for CMV replication may be attributable to HHV-6 infection in some patients, but clear-cut study data are lacking in this context.

Conclusions

CMV infection and disease impose a major burden on the management of renal transplant patients in both medical as well as economical terms. However, current diagnostic and therapeutic tools are quite satisfactory to prevent patients from or handle life-threatening complications. VZV infections have a tendency to disseminate in immunosuppressed transplant patients and should thus be treated systemically even when initial lesions are limited to cutaneous sites. Serious complications of herpes simplex infections are rare, however, clinical evidence of visceral infections should be treated appropriately. EBV- and HHV-8-associated malignant diseases are major threats after transplantation and should be treated according to current guidelines. In general, appropriate adaptation of immunosuppressive therapy during viral infections plays a central role to facilitate recovery of affected renal transplant patients.

Conflict of interest statement. None declared.

References

4. Niedobitek G, Finn T, Herbst H et al. Detection of cytomegalovirus by in situ hybridisation and immunohisto-