Expert Opinion

Pharmacotherapy of post-transplant viral infections

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Background: Management of a number of significant viral pathogens in transplant recipients remains challenging. *Objectives*: To define an optimal antiviral approach to the management of cytomegalovirus (CMV), human herpes virus-6 (HHV-6), Epstein–Barr (EBV)-associated post-transplant lymphoproliferative disorder (PTLD), and polyoma virus-associated nephropathy in transplant recipients. *Methods*: Clinical trials and existing data regarding use of antiviral agents for these viruses were reviewed to develop evidence-based recommendations for their management. *Conclusions*: Weighing the current evidence regarding the use of valganciclovir as pre-emptive therapy or prophylaxis, the former approach offers a greater benefit for the overall prevention of CMV disease. Limited data show that prophylaxis with antiviral agents is associated with a reduction in the risk of EBV-associated PTLD. Treatment options for HHV-6 and polyoma virus-associated nephropathy are still limited.

Keywords: cidofovir, cytomegalovirus, Epstein–Barr virus, foscarnet, antiviral ganciclovir, human herpes virus-6, leflunomide, maribavir, polyoma virus nephropathy, post-transplant lymphoproliferative disorder, rituximab, transplants, valganciclovir

1. Introduction

Post-transplant viral infections are primarily due to members of the herpesvirus family. Currently available nucleoside antiviral agents have proven effective and their use for the prevention and treatment of herpes simplex virus and varicella zoster virus has been standardized. However, optimal management of infection and disease caused by cytomegalovirus (CMV), human herpes virus-6 (HHV-6), Epstein–Barr virus (EBV)-associated post-transplant lymphoproliferative disorder (PTLD) and polyoma virus-associated nephropathy in transplant recipients remains controversial. An expanding armamentarium of antiviral agents and emerging data from key clinical trials have contributed to our evolving knowledge base to optimize the management of viral infections in transplant recipients. The present review, focused mainly on solid organ transplant (SOT) recipients, is an evidence-based discussion and gives our proposed recommendations regarding the prevention and treatment of CMV, HHV-6, EBV-associated PTLD and polyoma virus-associated nephropathy.

2. Cytomegalovirus (CMV)

2.1 Overview

CMV is the most common viral pathogen and causes significant morbidity and mortality in transplant recipients. In the absence of any form of preventive therapy, CMV infection (evidence of detectable virus, viral proteins or nucleic acid) develops in 36 – 100% of organ transplant recipients, and symptomatic

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disease in 11 – 72% of patients, most often during the first 3 months after transplantation [1]. CMV disease may present as viral syndrome characterized by fever, leukopenia and thrombocytopenia or as tissue-invasive disease including pneumonitis, hepatitis and focal gastrointestinal disease [2]. Additionally, CMV-mediated upregulation of chemokine expression and modulation of cytokine signaling and other host responses is a significant contributor to allograft injury and rejection [3,4], opportunistic infections [5,6], or late-onset malignancies [7].

Two main strategies are implemented for prevention of CMV disease: pre-emptive therapy and prophylaxis. Pre-emptive therapy is defined as employment of an anti-CMV agent upon detection of viremia by pp65 antigen or polymerase chain reaction (PCR) assay [8]. Prophylaxis is defined as administration of a course of anti-CMV agents at the time of, or soon after, transplantation in all patients, regardless of the risk [9]. In addition to acyclovir, valaciclovir, ganciclovir and CMV intravenous immunoglobulin (CMV IVIG or IVIG), new antiviral agents, such as valganciclovir and maribavir, are available at present. The following sections summarize the current status in the prevention and treatment of CMV disease in transplant recipients.

2.2 Prevention

2.2.1 Acyclovir, ganciclovir and valacyclovir

Acyclovir prophylaxis was shown to be effective in decreasing the risk of CMV infection and disease in some studies in hematopoietic stem cell transplant (HSTC) and SOT recipients [10-12]. However, subsequent studies did not support its use for the prevention of CMV disease, probably given its poor *in vitro* activity against CMV at clinically achievable levels [13,14]. Valacyclovir is a valyl ester of acyclovir with improved oral bioavailability of 54.5% (**Table 1**) [15]. It is effective for the prevention of CMV disease in D+/R- and R+ renal transplant recipients, and significantly decreases biopsy-confirmed acute graft rejection [16]. Although valacyclovir can be a cost-effective alternative to ganciclovir in renal transplant recipients, it is less effective than ganciclovir. Additionally, little data regarding its use exist in other types of organ transplant recipients.

Ganciclovir is 50 – 100 times more active than acyclovir against the laboratory strains and clinical isolates of human CMV [17,18], and is a more effective antiviral agent than acyclovir for the prevention of CMV disease in transplant recipients [14,19]. In a randomized controlled trial, intravenous ganciclovir as prophylaxis significantly decreased the incidence of CMV disease from 43% (31/73) in heart transplant recipients receiving placebo to 15% (12/76) in those receiving intravenous ganciclovir [20]. Similarly, intravenous ganciclovir initiated upon detectable CMV antigenemia or CMV DNAnemia also decreased the incidence of CMV disease in SOT patients [21-23].

Oral ganciclovir, despite low bioavailability of only 6.3% at a dose of 1000 mg three times a day, was effective for the prevention of CMV disease (**Table 1**) [8,9,24,25]. In a randomized controlled trial, the incidence of CMV disease at 6 months after transplantation was significantly lower in 150 liver transplant recipients receiving oral ganciclovir as prophylaxis than in 154 recipients receiving placebo (4.8 vs 18.9%, p < 0.001) [9]. Similar observations were also noted in patients with D+/R- (14.8 vs 44.0%, p = 0.02) and D+/R+ (2.7 vs 18.2%, p = 0.002) [9]. Compared with the placebo patients, liver transplant recipients treated with oral ganciclovir as pre-emptive therapy had lower incidence of CMV disease (0 vs 15%, p < 0.01) in a randomized controlled trial [24]. Furthermore, no significant difference in the risk of CMV disease was observed between liver transplant patients receiving pre-emptive oral ganciclovir and those receiving pre-emptive intravenous ganciclovir in another randomized, controlled trial [8].

Although few episodes of CMV disease occur during receipt of prophylactic agents, late-onset CMV disease has emerged as an important clinical problem after cessation of prophylaxis [26]. In SOT patients receiving oral ganciclovir prophylaxis, the incidence of late-onset CMV disease ranged from 2.6 to 19% [9,27-31], and D+/R- serostatus was strongly associated with the development of late-onset CMV disease with the incidence of 18 – 26% [27-31]. Furthermore, late-onset CMV disease has been independently associated with poor post-transplant outcomes [32].

Even though emergence of ganciclovir-resistance CMV has been reported in patients under pre-emptive therapy with ganciclovir [33], ganciclovir-resistant CMV is primarily a concern in heavily immunosuppresed patients receiving this agent as prophylaxis, especially those with D+/R- serostatus and having prolonged exposure to ganciclovir [34]. Ganciclovir-resistant CMV developed in 0% of liver transplant recipients, 0.28 – 1.5% of heart, 0.54 – 1% of renal, 3.3 – 9% of lung, and 13% of renal-pancreas [34,35]. The incidence of ganciclovir-resistant CMV in patients with D+/R- ranged from 0 to 27%. Ganciclovir-resistance CMV disease was significantly associated with D+/R- serostatus and greater prior exposure to ganciclovir [35]. Nine (14%) of 225 CMV D+/R- SOT recipients receiving valganciclovir prophylaxis for a median of 92 days were suspected to have a drug-resistant virus [36]. Two of four patients with proven drug-resistant CMV and three of five with clinically suspected drug-resistant CMV had allograft loss and mortality.

Randomized trials for treatment of ganciclovir-resistance CMV disease in SOT recipients are not available. However, increasing ganciclovir dosage (up to 7.5 – 10 mg/kg intravenously twice a day) in combination with CMV IVIG and reduction of immunosuppressants is recommended for asymptomatic or not severely ill patients with suspected ganciclovir-resistance CMV [34]. Foscarnet may be considered in the setting of progression of clinical disease or no virologic response to high-dose ganciclovir [34]. Additionally, maribavir [37], leflunomide [38], switching to a sirolimus-based

Table 1. Acyclovir and ganciclovir pharmacokinetics based on human data.

Ref.	Drugs	Dose (frequency)	AUC (µg·h/ml)	C_{max} (µg/ml)	T_{max} (h)	$T_{1/2}$ (h)	Bioavailability (%)
[15,132]	Valacyclovir	1 g (once daily)	19.52	5.65	1.75	3.03	54.5
[25]	Oral ganciclovir	1 g (3 times at 6-h intervals)	20.7	1.5	14.3	NA	6.3
[25]	IV ganaciclovir	5 mg/kg (over 1 h)	48.2	12.2	1.0	5.2	NA
[25]	Valganciclovir	450 mg (once daily)	21.1	3.0	3.0	5.2	60
[25]	Valganciclovir	900 mg (once daily)	41.7	6.2	2.9	5.1	59

AUC: Area under the curve calculated over 24 h; C_{max}: Maximum observed concentration; IV: Intravenous; NA: Not available; $T_{1/2}$: Half-life associated with the terminal elimination rate constant; T_{max}: Time to the maximum observed concentration.

regimen [39], and artesunate [40] may be potential options for ganciclovir-resistant virus.

2.2.2 Valganciclovir

Because of its oral availability, convenient dosing schedule, and 10-fold higher bioavailability than oral ganciclovir (**Table 1**) [25], valganciclovir is now widely used for the prevention of CMV in SOT recipients. In SOT recipients with D+/R- serostatus, the efficacy of valganciclovir and oral ganciclovir for the prevention of CMV disease were compared in a randomized, prospective, double-blind, double-dummy trial [27]. By 12 months, the incidence of CMV disease was 17.2% in 245 patients receiving valganciclovir and 18.4% in 127 receiving oral ganciclovir (p = 0.767). Most cases of CMV disease (valganciclovir: 99.2%, ganciclovir 98.4%) occurred after the discontinuation of prophylaxis. Subgroup analysis showed that valganciclovir was significantly more effective in preventing CMV disease than ganciclovir in renal transplant recipients (RR 0.27, 95% CI 0.01 – 0.75) compared with liver, heart or renal-pancreas transplant recipients at 6 months [41]. A trend toward higher incidence of neutrophil count of less than 1000 cells/µl (12.7 vs 7.9%, p = 0.166) with valganciclovir than with ganciclovir was observed. CMV UL97 mutations emerged in 1.9% (2/103) of the patients treated with ganciclovir at the end of prophylaxis and 6.1% (2/33) of those with suspected CMV disease up to 1 year after transplantation, but not in valganciclovir arm [42]. There were no differences in acute rejection, graft loss, opportunistic infections, death due to CMV disease, and all-cause mortality between valganciclovir and ganciclovir groups. The prophylactic dosing of valganciclovir is 900 mg once daily in PV16000 trial but a dose of 450 mg once per day also had good efficacy in some studies [29,43,44].

Subsequent surveys of CMV-prevention strategies after liver and renal transplantation have shown that valganciclovir is the most commonly prescribed antiviral agent for the prevention of CMV [45,46]. Recently, a systematic review evaluated the efficacy of valganciclovir for the prevention of post-transplant cytomegalovirus disease and related outcomes, and showed that the use of valganciclovir as pre-emptive

therapy and prophylaxis was associated with an incidence of CMV disease of 2.6 and 9.9%, respectively, within the first post-transplant year [47]. In D+/R- patients, the overall incidence of CMV disease was 5.5% in the pre-emptive group and 20.1% in the prophylactic group. Most CMV disease (92%) with the use of antiviral prophylaxis presents as late-onset CMV disease, defined as CMV disease occurring after 90 days post-transplantation [26]. The incidence of late-onset CMV disease in all patients and in those with D+/R- was 0% in pre-emptive therapy and 8.9 and 17.7% in the prophylactic group, respectively [47]. Late-onset CMV disease has been shown to be an independently significant predictor of mortality during the first post-transplant year [28,48].

2.2.3 Maribavir

Maribavir is a benzamidazole derivative with potent anti-CMV activity that targets UL97 viral protein kinase with subsequent inhibition of viral encapsidation and nuclear egress of viral particles [49-51]. Theoretically, mutations in the CMV DNA polymerase (UL54) gene that confer resistance to ganciclovir, foscarnet and cidofovir should not affect the anti-CMV activity of maribavir. In addition, resistance mutations of ganciclovir and maribavir appear to involve separate loci of the UL97 kinase function domains [52]. Clinical isolates and laboratory stains containing UL97 or UL54 DNA polymerase mutations and resistant to ganciclovir, foscarnet and cidofivir, individually or in combination, were tested for susceptibility to maribavir; maribavir was active *in vitro* against all these resistant strains [37]. On the other hand, the laboratory-derived UL97 L397R mutant, highly resistant to marivavir, remained susceptible to ganciclovir, foscarnet and cidofivir. Since maribavir is a UL97 kinase inhibitor, combination of maribavir and ganciclovir is expected to result in loss of ganciclovir antiviral activity because of prevention of initial phosphorylation of ganciclovir by UL97 kinase, which is inhibited by maribavir. Maribavir has been shown to antagonize the anti-CMV effect of ganciclovir, increasing the 50% inhibitory concentration of ganciclovir against a susceptible strain by up to 13-fold, while antiviral activities of foscarnet and cidofivir were

unaffected by maribavir [53]. Of note, maribavir lacks activity against HSV, and therefore HSV prophylaxis with acyclovir should be employed.

Maribavir has good oral bioavailability and has demonstrated favorable tolerability in clinical trials [54,55]. In a Phase II trial, placebo or maribavir with doses of 100 mg twice daily, 400 mg once daily, or 400 mg twice daily were prescribed randomly to CMV-seropositive allogeneic stem-cell transplant recipients after engraftment, respectively, for a maximum of 12 weeks following transplantation [55]. The incidence of CMV infection was lower in each of the maribavir groups compared with placebo (p < 0.05). CMV disease occurred in three patients with placebo but in none of the patients with maribavir over a maximum follow-up period of 8 weeks after the completion of the 12-week drug therapy.

The three dosing regimens of maribavir were equally effective in reducing the incidence of CMV infection and delaying the time to onset of CMV infection. Taste disturbance, nausea and vomiting were the most common clinical adverse events in maribavir recipients, but no increased neutropenia or thrombocytopenia was observed. An ongoing Phase III study has been powered to determine whether maribavir leads to significant reduction of CMV disease and includes a longer follow-up period for evaluation of late CMV disease.

2.2.4 Role of CMV IVIG

The efficacy of CMV IVIG for preventing cytomegalovirus disease and associated outcomes was assessed in a recent review of 37 randomized and quasi-randomized controlled trials with 2185 SOT recipients [56]. The risk for CMV disease and CMV infection did not differ between CMV IVIG/IVIG and placebo/no treatment in all transplant recipients, CMV positive recipients and CMV-negative recipients of CMV-positive organs. There was also no difference in the risk of acute rejection, graft loss or opportunistic infections between the CMV IVIG/IVIG and placebo/no treatment group. However, the risk of death from CMV disease was significantly reduced in patients receiving CMV IVIG compared with patients receiving placebo or no treatment (relative risk 0.33, 95% confidence interval 0.14 – 0.80). Nevertheless, there was no difference in the risk for CMV disease, CMV infection, all-cause mortality, acute rejection, graft loss or opportunistic infections between antiviral medications (acyclovir or ganciclovir) with IVIG and antiviral medications alone. Furthermore, the risk of CMV disease had a significant reduction in all trials with antiviral medication alone compared with IVIG alone (RR 0.68, 95% CI 0.48 – 0.98). It was concluded that CMV IVIG was not indicated for the prophylaxis of CMV disease in SOT recipients.

However, in heart transplant recipients, the rate and severity of transplant coronary artery disease was decreased by combination of antiviral agents and CMV IVIG as prophylaxis [57,58]. The coronary artery mean intimal thickness and the prevalence of intimal thickening > 0.3 mm were significantly lower in 27 heart transplant recipients receiving ganciclovir plus CMV IVIG than in 27 recipients receiving ganciclovir only (p < 0.05) [57]. In addition, the volumes of coronary artery lumen and vessel decreased significantly at 1 year post-transplant compared with those at baseline in heart transplant recipients receiving prophylaxis with ganciclovir alone than recipients receiving ganciclvoir/valganciclovir and CMV IVIG (p < 0.05) [58].

Unlabeled use of CMV IVIG as adjunct therapy in the treatment of CMV disease in immunocompromised patients is implemented in some transplant centers, although its efficacy is uncertain. In a large study, factors associated with survival among 370 hematopoietic cell transplant recipients diagnosed with CMV pneumonia from 1986 to 2006 were retrospectively analyzed [59]. The overall and CMV-attributable mortality at 6 months was 72.4% (95% CI, 67.9 – 77.0%) and 47.6% (95% CI, 42.5 – 52.7%). Multiple factors associated with survival were identified. However, combination therapy of an antiviral drug (ganciclovir or forscarnet) and CMV IVIG/IVIG versus an antiviral drug alone did not modify overall or attributable mortality in multivariable models [59].

2.3 Treatment

Intravenous ganciclovir, foscarnet and cidofovir are the available options at present for the treatment for CMV disease in SOT recipients [60,61]. However, requirement of long-term parenteral access and hospitalization pose challenging logistic issues, and potential nephrotoxicity of the last two drugs is a significant treatment limiting adverse effect. Valganciclovir at dose of 900 mg once daily has been shown to be equivalent to intravenous ganciclovir at dose of 5 mg/kg/day with regards to plasma ganciclovir exposure [25]. A randomized, multicenter trial demonstrated that oral valganciclovir has comparable safety and long-term outcomes, as intravenous ganciclovir does for the treatment of CMV disease in SOT patients (the VICTOR study) [62-64]. In this trial, 321 SOT recipients were randomized to receive valganciclovir (900 mg twice daily orally) or ganciclovir (5 mg/kg twice daily intravenously) as induction therapy for 21 days followed by 900 mg daily valganciclovir until day 49. Over 70% of the patients were renal transplant recipients, less than 30% belonged to the D+/R- subgroup, and approximately 50% had tissue-invasive disease.

After a 1-year follow-up, the prevalence of CMV disease was 14.5% in patients receiving valganciclovir and 15.3% receiving ganciclovir at day 21, and decreased to 2.1 and 5.6% at day 49, respectively [64]. The overall clinical recurrence was 14.4% and the overall virologic recurrence was 28.6%. There was no difference between the two groups in resolution of CMV disease or viral clearance throughout the follow-up [64]. The baseline viral load was the only factor predictive of viral eradication [63]. Patients with persistent CMV viremia at day 21 were more likely to have recurrence but not resistant mutations [62,64]. However,

patients with viremia at 49 days were more likely to have resistant virus and should be evaluated for resistance [62]. Patients with CMV IgG negative at day 0 compared with those with CMV IgG positive had a slower initial viral clearance and higher rates of recurrence [62].

No major differences in the frequencies of adverse events between the two arms were observed [63]. Eleven patients in the valganciclovir group and nine in the ganciclovir group died during follow-up (p < 0.05); none died of CMV disease [64]. The VICTOR study clearly demonstrated that oral valganciclovir and intravenous ganciclovir in the treatment of CMV disease have comparable long-term outcomes in organ transplant recipients, although it is limited by mainly renal transplant recipients and exclusion of life-threateningly ill patients, patients with extremely high viral loads (> 10^6 copies/ml) and children.

Treatment with forscarnet and cidofovir are mainly used in the circumstances of suspected or documented ganciclovir-resistant CMV disease, and both agents have significant nephrotoxicity. Leflunomide, an inhibitor of protein kinase activity and pyrimidine synthesis, also has activity against both ganciclovir-sensitive and -resistant CMV [65]. Eighteen renal transplant recipients with CMV disease and 3 with relapse of CMV disease treated with leflunomide have been reported [66,67]. Nineteen patients clinically responded to leflunomide and had viral clearance from the blood. In addition to the availability of oral formulation, its cost is much lower than that of intravenous ganciclovir. However, the exact dose and duration of treatment for CMV infection remains unknown.

3. Human herpes virus-6 (HHV-6)

3.1 Overview
Epidemiologic studies have documented that seroprevalence of HHV-6 in adults approaches 90%. Evidence of prior HHV-6 infection has been documented in 87 – 91% of SOT recipients and 78 – 100% of hematopoietic stem cell transplant recipients. Thus, most HHV-6 infection and disease in transplant recipients is due to reactivation infection. Overall, 38 – 55% of renal, 22 – 54% of the liver and 36 – 57% of the heart or heart lung transplant recipients have been shown to develop HHV-6 infection [68]. HHV-6 infections develop in 35 – 42% of allogeneic stem cell transplant recipients. Higher rates (87 – 92%) in cord blood transplant recipients are considered to be due to paucity of primed HHV-6 specific memory T cells and low ability of cord blood cells to produce protective cytokines [69,70].

Fever of unknown origin, with or without a skin rash, bone marrow suppression and encephalitis are the most frequently observed clinical manifestations of HHV-6. Meningoencephalitis due to HHV-6 was documented in 0.79% (8/1018) of the HSCT recipients in one report and 0.96% (11/1148) in another [71,72]. Symptomatic disease usually occurs within 4 weeks of transplantation. More

recently, HHV-6 has been identified as an etiologic agent for post-transplant acute limbic encephalitis, a distinct syndrome characterized by seizures, dense anterograde amnesia and neuroimaging abnormalities showing low attenuation lesions, typically involving bilateral medial temporal lobes [73,74].

3.2 Prevention
Of currently available antiviral agents, acyclovir has consistently shown poor activity against HHV-6 *in vitro* [75]. Ganciclovir on the other hand has anti-HHV-6 activity with EC_{50} ranging from 0.56 to > 25 in various studies. HHV-6 UL69 is the functional homolog of human CMV UL97-encoded kinase that converts ganciclovir to its monophosphate metabolite in the infected cell [75]. *In vitro* studies have shown that the capacity of HHV-6 UL69 phosphorylates ganciclovir is 10-fold lower compared with that of human CMV UL97 [75]. Furthermore, the affinity of ganciclovir triphosphate for HHV-6 DNA polymerase is 6-fold less than that for CMV and 800-fold less compared with acyclovir triphosphate for HSV DNA polymerase [76].

Antiviral prophylaxis with ganciclovir has been shown to be protective against HHV-6 infection in some but not all studies. In HSCT recipients, HHV-6 infection was documented in 39% (11/28) of the patients who did not receive ganciclovir compared with 0/13 in those who did [77]. In renal transplant recipients receiving ganciclovir HHV-6, viremia appeared later after transplantation (42 vs 21 days) and was shorter in duration (29 vs 62 days); however, there was no difference in the incidence of viremia (71 vs 61%) [78]. Low-grade viremia was documented in ~ 14% of the organ transplant recipients receiving valganciclovir for 100 days post-transplant; however, no clinical manifestations could be attributed to it [79]. By contrast, repression of CMV was complete. Thus, antiviral prophylaxis is not consistently effective for prevention.

3.3 Treatment
Overall mortality in patients with HHV-6 meningoencephalitis has ranged from 45 to 58% [80,81]. Treatment with currently available agents has a beneficial effect. Both ganciclovir and foscarnet have been successfully used for the treatment of meningoencephalitis, although outcomes have not been uniformly good. Of 13 HSCT recipients with HHV-6 encephalitis, 46% (6: 4 treated with ganciclovir and 2 who received ganciclovir and foscarnet) died [82]. In a review of HHV-6 encephalitis in transplant recipients, cure was documented in 7/8 patients who received ganciclovir or foscarnet for at least 7 days compared with 0/4 in those who did not receive these drugs or received them for less than 7 days (p = 0.01) [83].

There is evidence that antiviral activity against HHV-6 is different in serum and cerebrospinal fluid (CSF). In 11 HSCT recipients, median log decrease in the serum from 2.0 to

0 copies/ml and in the CSF from 4.4 to 2.0 copies/ml was documented with antiviral therapy [81]. Furthermore, decrease in CSF levels lagged behind that in the serum; earliest negativity in the CSF was observed at week 3 of antiviral therapy. Overall 5/11 patients died, including 4/5 who received foscarnet and ganciclovir [81]. A lower efficacy of antiviral agents for central nervous system infections could be related to the fact that UL69 is highly expressed in T cells but not in astrocytes. Foscarnet and cidofovir but not ganciclovir exhibited anti-HHV-6 activity in glial cells [84].

Maribavir has been shown to be inactive against HHV-6 [75]. However, a recent study that evaluated the activity of maribavir against HHV-6 in a cell culture to slow the growth of lymphocytes documented that maribavir inhibits the replication of HHV-6 and the activity of UL69 protein kinase [85].

4. Epstein–Barr virus (EBV)-associated post-transplant lymphoproliferative disorder (PTLD)

4.1 Overview

The most devastating sequelae of EBV infection in transplant recipients is PTLD, which usually occurs within the first year after SOT (early PTLD) [86]. In the setting of immunosuppression, EBV can cause dysregulated and uncontrolled B-cell proliferation resulting in the development of PTLD [87]. High incidence of PTLD has been observed in EBV-seronegative recipients of EBV-seropositive allografts [88-90]. The incidence of PTLD in pre-transplant EBV-seronegative recipients was 24 times higher than in pre-transplant EBV-seropositive recipients, after excluding the effects of CMV seromismatch and the use of OKT-3 [89]. Primary infection with EBV acquired from EBV-seropositive donors plays a pivotal role in PTLD since 85% of donors are EBV-seropositive [90]. In addition to primary EBV infection, OKT-3 and polyclonal antilymphocyte antibodies, CMV seromismatch, younger age, and type of organ transplanted are also risk factors of early PTLD [88-95]. Type of organ transplanted, older recipient age, and duration of immunosuppression are considered the risk factors for late PTLD (> 12 months after transplantation) [86].

4.2 Prevention

At present, the best approach for preventing PTLD is to reduce risk factors in an SOT recipient, such as limiting exposure to T-cell depleting antibodies and judicious use of immunosuppression. Prophylaxis with ganciclovir alone (in EBV D+/R- patients) or ganciclovir followed by acyclovir (in EBV R+ or D-/R- patients) and early detection of primary EBV infection with PCR followed by ganciclovir use and lowering or discontinuing immunosuppressive regimen led to a reduction in the incidence of PTLD in pediatric liver transplant recipients [96]. Reduced incidence of PTLD

was also demonstrated in SOT recipients receiving ganciclovir or acyclovir as prophylaxis in two retrospective studies, one compared with the previously reported incidence in the same institute and one with concurrent control (3.9 vs 0.5%, p < 0.03) [97,98]. In a multicenter case-control study, the risk of PTLD during the first year was lowered by 38% for every 30 days of ganciclovir, while the effects of acyclovir were less impressive [99]. No significant difference in EBV viral load suppression was observed in high-risk EBV D+/R- SOT recipients receiving ganciclovir alone or ganciclovir and IVIG, and all three PTLD cases occurred in the IVIG arm [100]. Nevertheless, prophylaxis with CMV IVIG, but not ganciclovir or acyclovir, prevented early PTLD in a multi-center retrospective study, although rates of lymphoma development in the subsequent 5 years of follow-up were similar in all three groups [101].

4.3 Treatment

Reduction or discontinuation of immunosuppression remains the mainstay for the treatment of PTLD with spontaneous regression documented in 23 – 50% of cases [86]. Other treatment options include rituximab, chemotherapy, surgical resection/local irradiation for localized disease, or interferon-α [86]. Rituximab is a more attractive option in the circumstances of failure of reduction in immunosuppression because of its promising results and lower toxicity compared with chemotherapy [102]. In two retrospective studies, the overall response rate of PTLD was 44 – 65% in SOT recipients treated with rituximab alone as the second-line therapy [103,104]. Three Phase II prospective clinical trials evaluated the efficacy of rituximab as the secondary approach for PTLD, and the overall response rate was 44.2 – 64% with a complete response (CR) rate of 28 – 55% [105-107]. All PTLD subjects were CD20+ positive and had EBV positivity of 55 – 65% in these three studies. Another prospective multicenter Phase II trial added a second course of rituximab if a SOT recipient with PTLD did not achieve CR after the first course, yielding an intention-to-treat CR rate of 60.5% [108]. In addition, salvage therapy rituximab was effective for intensively pretreated patients with relapsed or refractory PTLD [109]. On the other hand, in cases with refractory and relapsed PTLD after treatment with single-agent rituximab, salvage chemotherapy with cyclophosphamide, doxorubicin, hydroxydaunorubicin, vincristine and prednisolone (CHOP) achieved a favorable overall response rate of 70% [110]. However, given the marked toxicity, it is suggested that chemotherapy be reserved for patients who fail rituximab, have EBV-negative tumors, or need a rapid response [102].

5. Polyoma virus-associated nephropathy

5.1 Overview

Polyoma virus nephropathy affects 1 – 10% of the renal transplant recipients and results in allograft loss in 10 – 80%

of cases [111-113]. A positive BK virus serostatus prior to transplantation is not protective of viremia or nephropathy due to polyoma virus [114,115]. Potent immunosuppression that includes tacrolimus and mycophenolate mofetil containing regimens is regarded as a risk factor for polyoma virus-associated nephropathy [115]. Use of antilymphocyte antibodies pose a risk for polyoma virus viremia and nephropathy if used as antirejection but not as induction therapy [115].

5.2 Treatment

Reduction of immunosuppression remains the mainstay of therapy for polyoma virus nephropathy. However, this is often not effective and may result in subsequent rejection in nearly 25% of cases. At present, there is no approved antiviral therapy for polyoma virus nephropathy [116], but IVIG, fluoroquinolones, cidofovir, and leflunomide have been used. After being treated with IVIG at a dose of 2 g/kg divided over 2 – 5 days, 88% of the eight renal transplant recipients still had functioning grafts, although renal function continued to be impaired [117]. In addition, fluoroquinolones have a modest antipolyoma virus effect [118], and 7 of the 10 renal transplant recipients treated with a 10-day course of oral gatifloxacin 500 mg once daily had a significant reduction in viremia or disappearance/reduction of decoy cells in the urine [119].

Cidofovir, a cytosine phosphate analog, exhibits antiviral activity against this virus. Although the EC_{50} of cidofovir (36.3 μg/ml) exceeds the peak plasma concentrations attainable with cidofovir dosages typically used for the treatment of CMV (5 mg/kg weekly followed by every 2 weeks), high concentrations achieved in the renal tissue and urine have prompted attempts at the use of cidofovir as therapy for polyoma virus nephropathy. However, conventional dosages used for CMV are poorly tolerated and are limited by significant nephrotoxicity and proximal renal tubular injury in transplant recipients [112]. Consequently lower dosages of cidofovir every 2 weeks have been used, ranging from 0.25 to 1.0 mg/kg. Dosages in this range appear to be well tolerated. A review of the literature comprising 10 cases of polyoma virus nephropathy documented clearance of viremia in 9/10 [120]. Data from one of few studies that included a control group showed that use of cidofovir dosages ranging from 0.5 to 1.0 mg/kg led to stabilization of renal function and graft loss in 0/8 cidofovir recipients compared with 9/13 patients who did not receive cidofovir [111]. Similarly, other reports also demonstrated its efficacy in stabilization or improvement of renal function and clearance of BK virus in plasma, urine or allografts [121-123]. In addition to nephrotoxicity, a significant adverse effect reported in 35% of the cidofovir recipients is anterior uveiitis [124].

Leflunomide, a pyrimidine synthesis inhibitor exhibits modest *in vitro* activity against polyoma virus. It also exhibits antiviral activity against CMV, although pyrimidine inhibition is not regarded as the basis of its activity against enveloped viruses such as CMV or nonenveloped virus such as polyoma virus [125]. There are only limited data with regards to the efficacy of leflunomide in polyoma virus-associated nephropathy. In a study where leflunomide replaced mycophenolate mofetil in 12 renal transplant recipients with polyoma virus-associated nephropathy, viremia resolved in 42% and allograft loss occurred in 17%; however, significant adverse effects required discontinuation of leflunomide in 17% [126]. Another 26 renal transplant recipients with polyoma virus-associated nephropathy were treated with either leflunomide alone (n = 17) or leflunomide plus a course of cidofovir (n = 9) [127]. Four patients with inconsistent blood level of active drug of leflunomide (A77 1726) over 40 μg/ml failed to clear the virus until the levels were attained or the addition of cidofovir. Only four recipients (15%) lost their renal grafts in the study. Apart from their modest activity at best against polyoma virus nephropathy, leflunomide and cidofovir exhibit low selectivity index which is considered likely owing to their similar effect on host-DNA synthesis [125].

6. Conclusions

Although acyclovir and valacyclovir possess an anti-CMV effect, ganciclovir has demonstrated greater efficacy for the prevention of CMV disease in transplant patients [14,19]. The use of valganciclovir to prevent CMV disease in renal and liver transplant recipients has gained significant popularity because of higher bioavailability than oral ganciclovir [45,46]. Furthermore, valganciclovir has a comparable long-term outcome to intravenous ganciclovir for the treatment of CMV disease in SOT recipients [62-64]. Maribavir, a new oral antiviral agent with a different anti-CMV mechanism, might offer another option for the prevention of CMV disease in the near future. Its Phase II trial proved its efficacy for prevention of CMV disease in allogeneic stem-cell transplant recipients, and no myelosuppression was observed [55].

Both valganciclovir and ganciclovir effectively prevent CMV disease in transplant recipients regardless of the preventive strategy used [8,9,20,27,128]. However, the protective effect of prophylaxis seems to be limited to the time when patients receive antiviral agents. CMV disease continues to occur after cessation of prophylaxis [26]. Moreover, late-onset CMV disease is strongly associated with increased mortality [28,48]. On the contrary, late-onset CMV disease has not been reported to our knowledge in patients with pre-emptive therapy [47].

CMV IVIG with or without antiviral therapy contributed little to the prevention of CMV disease [56]. Additionally, in hematopoietic cell transplant recipients with CMV pneumonia, addition of CMV IVIG to antiviral drugs offered no additional benefit for overall or attributable mortality [59]. Nevertheless, combination of antiviral agents and CMV IVIG decreased the rate of transplant coronary artery disease in heart transplant recipients [57,58].

Protection of HHV-6 infection by prophylaxis with ganciclovir has been demonstrated in some but not all studies [77-79]. While both ganciclovir and foscarnet have been reported as being effective against HHV-6 meningoencephalitis after transplantation, the superiority of either ganciclovir or foscarnet over the other has not been established.

Effective strategies to prevent EBV-associated PTLD are still limited. Although reduction of immunosuppression remains the primary approach to treat EBV-associated PTLD, studies employing rituximab are emerging owing to its low toxicity and promising results.

No approved agents are available for the treatment of polyoma virus nephropathy at present. The fundamental therapy is to reduce immunosupression. However, this management is often not effective and patients might suffer subsequent rejections.

7. Expert opinion

7.1 Prevention
Debates between pre-emptive therapy and prophylaxis for prevention of CMV disease exist in the current literature.

7.2 Pre-emptive therapy
Because only patients at high risk for CMV disease defined by the detectable antigenemia or DNAnemia receive anti-CMV agents, pre-emptive therapy avoids unnecessary drug exposure and subsequent adverse drug reactions in patients without detectable antigenemia or DNAnemia. In addition, this strategy is cost effective [129,130]. Furthermore, pre-emptive therapy effectively prevents not only CMV disease but also late-onset CMV disease [47].

7.3 Prophylaxis
Prophylaxis is strongly associated with the development of late-onset disease even though CMV disease can be effectively prevented during the time when antiviral prophylaxis is used [26]. Patients receiving prophylaxis, especially those with D+/R-, have a high incidence of late-onset CMV disease after discontinuation of antiviral agents [47,128]. Additionally, late-onset CMV disease was independently associated with overall and infection-associated mortality at 1 year [48].

7.4 Recommendation
Valganciclovir with its oral availability and excellent bioavailability provides a convenient administration route and a comparable systemic exposure (24-h area under curve) as intravenous ganciclovir does. There are limited data regarding the use of pre-emptive therapy in lung transplant recipients. Pondering the pros and cons of the two preventive strategies, pre-emptive therapy with valganciclovir in all other organ transplant recipients offers a greater benefit to the patient without the cost of graft loss and life. Of

note, the success of pre-emptive therapy hinges upon the early detection of CMV infection and timely initiation of antiviral agent. Thus, the establishment of an infrastructure consisting of a dedicated clinical coordinator and follow-up of the protocol using an algorithmic approach is critical to ensure the success of this strategy [131].

7.5 Role of maribavir
Maribavir, a novel antiviral agent, is characterized by the unique anti-CMV mechanism, no cross-resistance with currently available anti-CMV agents, good bioavailability, and favorable tolerability. In addition, the results of the Phase II trial are promising [55]. The incidence of CMV infection compared with placebo decreased significantly, and no CMV disease developed in patients on maribavir prophylaxis. Since no myelosuppresion was observed in the maribavir arms, if maribavir proved as effective as ganciclovir for the prevention of CMV disease, it might be the preferred agent for hematopoietic stem cell transplant recipients to avoid the hematological abnormality caused by the use of valganciclovir/ganciclovir. This agent could be an alternative for the prevention of CMV disease in SOT recipients in the future.

7.6 Role of CMV IVIG
In the current era of potent antiviral agents, there is no role for CMV IVIG in both the prevention and treatment of CMV disease. CMV IVIG does not decrease the risk for CMV infection and disease compared with placebo and provides no additional benefit when added to the antiviral therapy [56]. In addition, the combination of an antiviral drug and CMV IVIG did not modify mortality in transplant recipients with CMV pneumonia compared with antiviral drug alone [59]. Given its high cost and negligible efficacy, CMV IVIG has little role in the prevention or treatment of CMV disease, except for heart transplant recipients who might benefit from the use of CMV IVIG for transplant coronary artery disease [57,58].

7.7 Treatment
The VICTOR study has demonstrated that valganciclovir is comparable to intravenous ganciclovir for the treatment of CMV disease [62-64]. CMV IgG status of the patients, viral load at days 21 and 49, and identification of CMV resistance at day 49 are the key determinants of successful treatment of CMV disease and emergence of resistant virus. Use of valganciclovir for CMV disease in non-renal transplant recipients, severely ill patients and patients with high viral load has not been fully studied.

7.8 HHV-6
Co-morbid clinical conditions such as renal failure or marrow suppression may also dictate whether ganciclovir or foscarnet is used as therapy for HHV-6. Foscarnet may be preferable in patients with marrow suppression

since it does not possess the myelosuppressive effect of ganciclovir. A combination of ganciclovir and foscarnet might be considered for severe cases or patients with meningoencephalitis.

7.9 EBV-associated PTLD

Prophylaxis with antiviral agents might offer protective benefit for EBV-associated PTLD. In addition to reduction of immunosuppression, rituximab is an option for the treatment of CD20-positive, EBV-associated PTLD.

7.10 Polyoma virus-associated nephropathy

Cidofovir and leflunomide have been used with limited efficacy for the treatment of polyoma virus-associated nephropathy [111,120,126]. However, treatment options for polyoma virus-associated nephropathy remain suboptimal.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Hodson EM, Jones CA, Webster AC, et al. Antiviral medications to prevent cytomegalovirus disease and early death in recipients of solid-organ transplants: a systematic review of randomised controlled trials. Lancet 2005;365:2105-15

2. Ljungman P, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. Clin Infect Dis 2002;34:1094-7

3. Keenan RJ, Lega ME, Dummer JS, et al. Cytomegalovirus serologic status and postoperative infection correlated with risk of developing chronic rejection after pulmonary transplantation. Transplantation 1991;51:433-8

4. Evans PC, Soin A, Wreghitt TG, et al. An association between cytomegalovirus infection and chronic rejection after liver transplantation. Transplantation 2000;69:30-5

5. George MJ, Snydman DR, Werner BG, et al. The independent role of cytomegalovirus as a risk factor for invasive fungal disease in orthotopic liver transplant recipients. Boston Center for Liver Transplantation CMVIG-Study Group. Cytogam, MedImmune, Inc. Gaithersburg, Maryland. Am J Med 1997;103:106-13

6. Van Den Berg AP, Klompmaker IJ, Haagsma EB, et al. Evidence for an increased rate of bacterial infections in liver transplant patients with cytomegalovirus infection. Clin Transplant 1996;10:224-31

7. Basgoz N, Preiksaitis JK. Post-transplant lymphoproliferative disorder. Infect Dis Clin North Am 1995;9:901-23

8. Singh N, Paterson DL, Gayowski T, et al. Cytomegalovirus antigenemia directed pre-emptive prophylaxis with oral versus I.V. ganciclovir for the prevention of cytomegalovirus disease in liver transplant recipients: a randomized, controlled trial. Transplantation 2000;70:717-22

9. Gane E, Saliba F, Valdecasas GJ, et al. Randomised trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients. The Oral Ganciclovir International Transplantation Study Group [corrected]. Lancet 1997;350:1729-33

10. Meyers JD, Reed EC, Shepp DH, et al. Acyclovir for prevention of cytomegalovirus infection and disease after allogeneic marrow transplantation. N Engl J Med 1988;318:70-5

11. Balfour HH Jr, Chace BA, Stapleton JT, et al. A randomized, placebo-controlled trial of oral acyclovir for the prevention of cytomegalovirus disease in recipients of renal allografts. N Engl J Med 1989;320:1381-7

12. Barkholt L, Lewensohn-Fuchs I, Ericzon BG, et al. High-dose acyclovir prophylaxis reduces cytomegalovirus disease in liver transplant patients. Transpl Infect Dis 1999;1:89-97

13. Prentice HG, Gluckman E, Powles RL, et al. Impact of long-term acyclovir on cytomegalovirus infection and survival after allogeneic bone marrow transplantation. European Acyclovir for CMV Prophylaxis Study Group. Lancet 1994;343:749-53

14. Winston DJ, Wirin D, Shaked A, et al. Randomised comparison of ganciclovir and high-dose acyclovir for long-term cytomegalovirus prophylaxis in liver-transplant recipients. Lancet 1995;346:69-74

15. Soul-Lawton J, Seaber E, On N, et al. Absolute bioavailability and metabolic disposition of valaciclovir, the L-valyl ester of acyclovir, following oral administration to humans. Antimicrob Agents Chemother 1995;39:2759-64

16. Lowance D, Neumayer HH, Legendre CM, et al. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. International Valacyclovir Cytomegalovirus Prophylaxis Transplantation Study Group. N Engl J Med 1999;340:1462-70

17. Mar EC, Cheng YC, Huang ES. Effect of 9-(1,3-dihydroxy-2-propoxymethyl)guanine on human cytomegalovirus replication in vitro. Antimicrob Agents Chemother 1983;24:518-21

18. Tocci MJ, Livelli TJ, Perry HC, et al. Effects of the nucleoside analog 2′-nor-2′-deoxyguanosine on human cytomegalovirus replication. Antimicrob Agents Chemother 1984;25:247-52

19. Singh N, Yu VL, Mieles L, et al. High-dose acyclovir compared with short-course preemptive ganciclovir therapy to prevent cytomegalovirus disease in liver transplant recipients. A randomized trial. Ann Intern Med 1994;120:375-81

20. Merigan TC, Renlund DG, Keay S, et al. A controlled trial of ganciclovir to prevent cytomegalovirus disease after heart transplantation. N Engl J Med 1992;326:1182-6

21. Yang CW, Kim YO, Kim YS, et al. Clinical course of cytomegalovirus (CMV) viremia with and without ganciclovir treatment in CMV-seropositive kidney transplant recipients. Longitudinal follow-up of CMV pp65 antigenemia assay. Am J Nephrol 1998;18:373-8

22. Koetz AC, Delbruck R, Furtwangler A, et al. Cytomegalovirus pp65 antigen-guided preemptive therapy with ganciclovir in solid organ transplant recipients: a prospective, double-blind, placebo-controlled study. Transplantation 2001;72:1325-7

23. Brennan DC, Garlock KA, Lippmann BA, et al. Control of cytomegalovirus-associated morbidity in renal transplant patients using intensive monitoring and either preemptive

or deferred therapy. J Am Soc Nephrol 1997;8:118-25

24. Paya CV, Wilson JA, Espy MJ, et al. Preemptive use of oral ganciclovir to prevent cytomegalovirus infection in liver transplant patients: a randomized, placebo-controlled trial. J Infect Dis 2002;185:854-60

25. Pescovitz MD, Rabkin J, Merion RM, et al. Valganciclovir results in improved oral absorption of ganciclovir in liver transplant recipients. Antimicrob Agents Chemother 2000;44:2811-5

26. Singh N. Late-onset cytomegalovirus disease as a significant complication in solid organ transplant recipients receiving antiviral prophylaxis: a call to heed the mounting evidence. Clin Infect Dis 2005;40:704-8

27. Paya C, Humar A, Dominguez E, et al. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant 2004;4:611-20

28. Limaye AP, Bakthavatsalam R, Kim HW, et al. Late-onset cytomegalovirus disease in liver transplant recipients despite antiviral prophylaxis. Transplantation 2004;78:1390-6

29. Park JM, Lake KD, Arenas JD, et al. Efficacy and safety of low-dose valganciclovir in the prevention of cytomegalovirus disease in adult liver transplant recipients. Liver Transpl 2006;12:112-6

30. Rubin RH, Kemmerly SA, Conti D, et al. Prevention of primary cytomegalovirus disease in organ transplant recipients with oral ganciclovir or oral acyclovir prophylaxis. Transpl Infect Dis 2000;2:112-7

31. Limaye AP, Corey L, Koelle DM, et al. Emergence of ganciclovir-resistant cytomegalovirus disease among recipients of solid-organ transplants. Lancet 2000;356:645-9

32. Arthurs SK, Eid AJ, Pedersen RA, et al. Delayed-onset primary cytomegalovirus disease and the risk of allograft failure and mortality after kidney transplantation. Clin Infect Dis 2008;46:840-6

33. Limaye AP, Raghu G, Koelle DM, et al. High incidence of ganciclovir-resistant cytomegalovirus infection among lung transplant recipients receiving preemptive therapy. J Infect Dis 2002;185:20-7

34. Limaye AP. Ganciclovir-resistant cytomegalovirus in organ transplant recipients. Clin Infect Dis 2002;35:866-72

35. Li F, Kenyon KW, Kirby KA, et al. Incidence and clinical features of ganciclovir-resistant cytomegalovirus disease in heart transplant recipients. Clin Infect Dis 2007;45:439-47

36. Eid AJ, Arthurs SK, Deziel PJ, et al. Emergence of drug-resistant cytomegalovirus in the era of valganciclovir prophylaxis: therapeutic implications and outcomes. Clin Transplant 2008;22:162-70
   • **This study documented that the emergence of drug resistant virus adversely affected outcomes.**

37. Drew WL, Miner RC, Marousek GI, et al. Maribavir sensitivity of cytomegalovirus isolates resistant to ganciclovir, cidofovir or foscarnet. J Clin Virol 2006;37:124-7

38. Mossad SB, Lard M, Krishnamurthi V, et al. Clinical and virological outcomes of adding leflunomide to ganciclovir or foscarnet for treatment of CMV viremia in transplant recipients [abstract 1561]. Am J Transplant 2006;6:589-90

39. Ozaki KS, Camara NO, Nogueira E, et al. The use of sirolimus in ganciclovir-resistant cytomegalovirus infections in renal transplant recipients. Clin Transplant 2007;21:675-80

40. Shapira MY, Resnick IB, Chou S, et al. Artesunate as a potent antiviral agent in a patient with late drug-resistant cytomegalovirus infection after hematopoietic stem cell transplantation. Clin Infect Dis 2008;46:1455-7

41. Hodson E, Craig J, Strippoli G, et al. Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. Cochrane Database Syst Rev2008;CD003774

42. Boivin G, Goyette N, Gilbert C, et al. Absence of cytomegalovirus-resistance mutations after valganciclovir prophylaxis, in a prospective multicenter study of solid-organ transplant recipients. J Infect Dis 2004;189:1615-8

43. Walker JK, Scholz LM, Scheetz MH, et al. Leukopenia complicates cytomegalovirus prevention after renal transplantation with alemtuzumab induction. Transplantation 2007;83:874-82

44. Weng FL, Patel AM, Wanchoo R, et al. Oral ganciclovir versus low-dose valganciclovir for prevention of cytomegalovirus disease in recipients of kidney and pancreas transplants. Transplantation 2007;83:290-6

45. Levitsky J, Singh N, Wagener MM, et al. A survey of CMV prevention strategies after liver transplantation. Am J Transplant 2008;8:158-61

46. Baliga RS, Kadambi PV, Javaid B, et al. A nationwide survey of cytomegalovirus prophylaxis and tratment in the transplant community. Am J Transplant 2005;4:495

47. Sun HY, Wagener MM, Singh N. Prevention of post-transplant cytomegalovirus disease and related outcomes with valganciclovir: a systematic review. Am J Transplant 2008; In press

48. Limaye AP, Bakthavatsalam R, Kim HW, et al. Impact of cytomegalovirus in organ transplant recipients in the era of antiviral prophylaxis. Transplantation 2006;81:1645-52
   • **This study highlights the clinical impact of late-onset CMV disease on post-transplant outcomes with the use of antiviral prophylaxis.**

49. Biron KK, Harvey RJ, Chamberlain SC, et al. Potent and selective inhibition of human cytomegalovirus replication by 1263W94, a benzimidazole L-riboside with a unique mode of action. Antimicrob Agents Chemother 2002;46:2365-72

50. Wolf DG, Courcelle CT, Prichard MN, et al. Distinct and separate roles for herpesvirus-conserved UL97 kinase in cytomegalovirus DNA synthesis and encapsidation. Proc Natl Acad Sci USA 2001;98:1895-900

51. Krosky PM, Baek MC, Coen DM. The human cytomegalovirus UL97 protein kinase, an antiviral drug target, is required at the stage of nuclear egress. J Virol 2003;77:905-14

52. Chou S. Cytomegalovirus UL97 mutations in the era of ganciclovir and maribavir. Rev Med Virol 2008;18:233-46

53. Chou S, Marousek GI. Maribavir antagonizes the antiviral action of ganciclovir on human cytomegalovirus. Antimicrob Agents Chemother 2006;50:3470-2

54. Lalezari JP, Aberg JA, Wang LH, et al. Phase I dose escalation trial evaluating the pharmacokinetics, anti-human cytomegalovirus (HCMV) activity, and safety of 1263W94 in human

immunodeficiency virus-infected men with asymptomatic HCMV shedding. Antimicrob Agents Chemother 2002;46:2969-76

55. Winston DJ, Young JA, Pullarkat V, et al. Maribavir prophylaxis for prevention of cytomegalovirus infection in allogeneic stem-cell transplant recipients: a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. Blood 2008;111:5403-10

56. Hodson EM, Jones CA, Strippoli GF, et al. Immunoglobulins, vaccines or interferon for preventing cytomegalovirus disease in solid organ transplant recipients. Cochrane Database Syst Rev 2007;3:CD005129

57. Valantine HA, Luikart H, Doyle R, et al. Impact of cytomegalovirus hyperimmune globulin on outcome after cardiothoracic transplantation: a comparative study of combined prophylaxis with CMV hyperimmune globulin plus ganciclovir versus ganciclovir alone. Transplantation 2001;72:1647-52

58. Potena L, Holweg CT, Chin C, et al. Acute rejection and cardiac allograft vascular disease is reduced by suppression of subclinical cytomegalovirus infection. Transplantation 2006;82:398-405

59. Erard V, Guthrie KA, Smith J, et al. Cytomegalovirus pneumonia (CMV-IP) after hematopoietic cell transplantation (HCT): outcomes and factors associated with mortality [abstract no. V-1379]. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy; 17 – 20 September 2007; Chicago

60. Cytomegalovirus. Green M, Avery RK, Preiksaitis J (editors). Am J Transplant 2004;4(Suppl 10):51-8

61. Preiksaitis JK, Brennan DC, Fishman J, et al. Canadian society of transplantation consensus workshop on cytomegalovirus management in solid organ transplantation final report. Am J Transplant 2005;5:218-27

62. Pescovitz MD, Hartmann A, Humar A, et al. Management of post transplant CMV disease: lessons Learned from the VICTOR Trial [abstract No. 15]. American Transplant Congress; 31 May – 4 June 2008; Toronto, Canada

63. Asberg A, Humar A, Rollag H, et al. Oral valganciclovir is noninferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant 2007;7:2106-13

64. Hartmann A, Humar A, Rollag H, et al. oral valganciclovir and intravenous ganciclovir in the treatment of CMV disease have comparable long term outcomes in organ transplant recipients: the VICTOR Study [abstract No. 1465]. American Transplant Congress; 31 May – 4 June 2008; Toronto, Canada

65. Waldman WJ, Knight DA, Blinder L, et al. Inhibition of cytomegalovirus in vitro and in vivo by the experimental immunosuppressive agent leflunomide. Intervirology 1999;42:412-8

66. John GT, Manivannan J, Chandy S, et al. Leflunomide therapy for cytomegalovirus disease in renal allograft recepients. Transplantation 2004;77:1460-1

67. John GT, Manivannan J, Chandy S, et al. A prospective evaluation of leflunomide therapy for cytomegalovirus disease in renal transplant recipients. Transplant Proc 2005;37:4303-5

68. Ljungman P, Singh N. Human herpesvirus-6 infection in solid organ and stem cell transplant recipients. J Clin Virol 2006;37(Suppl 1):S87-91

69. Tanaka M, Taguchi J, Hyo R, et al. Human herpesvirus-6 encephalitis after unrelated cord blood transplantation. Leuk Lymphoma 2005;46:561-6

70. Yamane A, Mori T, Suzuki S, et al. Risk factors for developing human herpesvirus 6 (HHV-6) reactivation after allogeneic hematopoietic stem cell transplantation and its association with central nervous system disorders. Biol Blood Marrow Transplant 2007;13:100-6

71. Fujimaki K, Mori T, Kida A, et al. Human herpesvirus 6 meningoencephalitis in allogeneic hematopoietic stem cell transplant recipients. Int J Hematol 2006;84:432-7

72. Zerr DM, Corey L, Kim HW, et al. Clinical outcomes of human herpesvirus 6 reactivation after hematopoietic stem cell transplantation. Clin Infect Dis 2005;40:932-40

73. Seeley WW, Marty FM, Holmes TM, et al. Post-transplant acute limbic encephalitis: clinical features and relationship to HHV6. Neurology 2007;69:156-65

74. Chamberlain MC, Chowdhary S. Post-transplant acute limbic encephalitis: clinical features and relationship to HHV6. Neurology 2008;70:491-2; author reply 2-3

75. De Bolle L, Michel D, Mertens T, et al. Role of tzzzhe human herpesvirus 6 u69-encoded kinase in the phosphorylation of ganciclovir. Mol Pharmacol 2002;62:714-21

76. Bapat AR, Bodner AJ, Ting RC, et al. Identification and some properties of a unique DNA polymerase from cells infected with human B-lymphotropic virus. J Virol 1989;63:1400-3

77. Tokimasa S, Hara J, Osugi Y, et al. Ganciclovir is effective for prophylaxis and treatment of human herpesvirus-6 in allogeneic stem cell transplantation. Bone Marrow Transplant 2002;29:595-8

78. Galarraga MC, Gomez E, De Ona M, et al. Influence of ganciclovir prophylaxis on citomegalovirus, human herpesvirus 6, and human herpesvirus 7 viremia in renal transplant recipients. Transplant Proc 2005;37:2124-6

79. Razonable RR, Brown RA, Humar A, et al. Herpesvirus infections in solid organ transplant patients at high risk of primary cytomegalovirus disease. J Infect Dis 2005;192:1331-9

80. Wang FZ, Linde A, Hagglund H, et al. Human herpesvirus 6 DNA in cerebrospinal fluid specimens from allogeneic bone marrow transplant patients: does it have clinical significance? Clin Infect Dis 1999;28:562-8

81. Zerr DM, Gupta D, Huang ML, et al. Effect of antivirals on human herpesvirus 6 replication in hematopoietic stem cell transplant recipients. Clin Infect Dis 2002;34:309-17

82. Tiacci E, Luppi M, Barozzi P, et al. Fatal herpesvirus-6 encephalitis in a recipient of a T-cell-depleted peripheral blood stem cell transplant from a 3-loci mismatched related donor. Haematologica 2000;85:94-7

83. Singh N, Paterson DL. Encephalitis caused by human herpesvirus-6 in transplant recipients: relevance of a novel neurotropic virus. Transplantation 2000;69:2474-9

84. Akhyani N, Fotheringham J, Yao K, et al. Efficacy of antiviral compounds in human herpesvirus-6-infected glial cells. J Neurovirol 2006;12:284-93

85. Prichard M, Daily S, Perry A, et al. Maribavir inhibits the replication of human herpesvirus 6 and the activity of the U69 protein kinase. J Antiviral 2008;78:A29

86. Epstein–Barr virus and lymphoproliferative disorders after transplantation. Green M,

Avery RK, Preiksaitis J (editors). Am J Transplant 2004;4(Suppl 10):59-65

87. Liebowitz D. Epstein–Barr virus and a cellular signaling pathway in lymphomas from immunosuppressed patients. N Engl J Med 1998;338:1413-21

88. Shahinian VB, Muirhead N, Jevnikar AM, et al. Epstein–Barr virus seronegativity is a risk factor for late-onset posttransplant lymphoroliferative disorder in adult renal allograft recipients. Transplantation 2003;75:851-6

89. Walker RC, Marshall WF, Strickler JG, et al. Pretransplantation assessment of the risk of lymphoproliferative disorder. Clin Infect Dis 1995;20:1346-53

90. Aris RM, Maia DM, Neuringer IP, et al. Post-transplantation lymphoproliferative disorder in the Epstein–Barr virus-naive lung transplant recipient. Am J Respir Crit Care Med 1996;154:1712-7

91. Caillard S, Lelong C, Pessione F, et al. Post-transplant lymphoproliferative disorders occurring after renal transplantation in adults: report of 230 cases from the French Registry. Am J Transplant 2006;6:2735-42

92. Swinnen LJ, Costanzo-Nordin MR, Fisher SG, et al. Increased incidence of lymphoproliferative disorder after immunosuppression with the monoclonal antibody OKT3 in cardiac-transplant recipients. N Engl J Med 1990;323:1723-8

93. Bustami RT, Ojo AO, Wolfe RA, et al. Immunosuppression and the risk of post-transplant malignancy among cadaveric first kidney transplant recipients. Am J Transplant 2004;4:87-93

94. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant 2004;4:222-30

95. Smith JM, Rudser K, Gillen D, et al. Risk of lymphoma after renal transplantation varies with time: an analysis of the United States Renal Data System. Transplantation 2006;81:175-80

96. McDiarmid SV, Jordan S, Kim GS, et al. Prevention and preemptive therapy of posttransplant lymphoproliferative disease in pediatric liver recipients. Transplantation 1998;66:1604-11

97. Davis CL, Harrison KL, McVicar JP, et al. Antiviral prophylaxis and the Epstein–Barr virus-related post-transplant lymphoproliferative disorder. Clin Transplant 1995;9:53-9

98. Darenkov IA, Marcarelli MA, Basadonna GP, et al. Reduced incidence of Epstein–Barr virus-associated posttransplant lymphoproliferative disorder using preemptive antiviral therapy. Transplantation 1997;64:848-52

99. Funch DP, Walker AM, Schneider G, et al. Ganciclovir and acyclovir reduce the risk of post-transplant lymphoproliferative disorder in renal transplant recipients. Am J Transplant 2005;5:2894-900

100. Humar A, Hebert D, Davies HD, et al. A randomized trial of ganciclovir versus ganciclovir plus immune globulin for prophylaxis against Epstein–Barr virus related posttransplant lymphoproliferative disorder. Transplantation 2006;81:856-61
•   An important study that delineates the effect of antiviral prophylaxis on EBV-related PTLD.

101. Opelz G, Daniel V, Naujokat C, et al. Effect of cytomegalovirus prophylaxis with immunoglobulin or with antiviral drugs on post-transplant non-Hodgkin lymphoma: a multicentre retrospective analysis. Lancet Oncol 2007;8:212-8

102. Elstrom RL, Andreadis C, Aqui NA, et al. Treatment of PTLD with rituximab or chemotherapy. Am J Transplant 2006;6:569-76

103. Jain AB, Marcos A, Pokharna R, et al. Rituximab (chimeric anti-CD20 antibody) for posttransplant lymphoproliferative disorder after solid organ transplantation in adults: long-term experience from a single center. Transplantation 2005;80:1692-8

104. Milpied N, Vasseur B, Parquet N, et al. Humanized anti-CD20 monoclonal antibody (Rituximab) in post transplant B-lymphoproliferative disorder: a retrospective analysis on 32 patients. Ann Oncol 2000;11(Suppl 1):113-6

105. Blaes AH, Peterson BA, Bartlett N, et al. Rituximab therapy is effective for posttransplant lymphoproliferative disorders after solid organ transplantation: results of a phase II trial. Cancer 2005;104:1661-7

106. Oertel SH, Verschuuren E, Reinke P, et al. Effect of anti-CD 20 antibody rituximab in patients with post-transplant lymphoproliferative disorder (PTLD). Am J Transplant 2005;5:2901-6

107. Choquet S, Leblond V, Herbrecht R, et al. Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. Blood 2006;107:3053-7

108. Gonzalez-Barca E, Domingo-Domenech E, Capote FJ, et al. Prospective phase II trial of extended treatment with rituximab in patients with B-cell post-transplant lymphoproliferative disease. Haematologica 2007;92:1489-94

109. Trappe RU, Choquet S, Reinke P, et al. Salvage therapy for relapsed posttransplant lymphoproliferative disorders (PTLD) with a second progression of PTLD after Upfront chemotherapy: the role of single-agent rituximab. Transplantation 2007;84:1708-12

110. Trappe R, Riess H, Babel N, et al. Salvage chemotherapy for refractory and relapsed posttransplant lymphoproliferative disorders (PTLD) after treatment with single-agent rituximab. Transplantation 2007;83:912-8

111. Kuypers DR, Vandooren AK, Lerut E, et al. Adjuvant low-dose cidofovir therapy for BK polyomavirus interstitial nephritis in renal transplant recipients. Am J Transplant 2005;5:1997-2004

112. Rinaldo CH, Hirsch HH. Antivirals for the treatment of polyomavirus BK replication. Expert Rev Antiinfect Ther 2007;5:105-15
•   A thorough and insightful review of treatment options for polyoma virus nephropathy.

113. Trofe J, Hirsch HH, Ramos E. Polyomavirus-associated nephropathy: update of clinical management in kidney transplant patients. Transpl Infect Dis 2006;8:76-85

114. Hirsch HH, Knowles W, Dickenmann M, et al. Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. N Engl J Med 2002;347:488-96

115. Hirsch HH, Brennan DC, Drachenberg CB, et al. Polyomavirus-associated nephropathy in renal transplantation: interdisciplinary analyses and recommendations. Transplantation 2005;79:1277-86

116. Randhawa PS, Finkelstein S, Scantlebury V, et al. Human polyoma virus-associated interstitial nephritis in the allograft kidney. Transplantation 1999;67:103-9

117. Sener A, House AA, Jevnikar AM, et al. Intravenous immunoglobulin as a treatment for BK virus associated nephropathy: one-year follow-up of renal

allograft recipients. Transplantation 2006;81:117-20

118. Randhawa PS. Anti-BK virus activity of ciprofloxacin and related antibiotics. Clin Infect Dis 2005;41:1366-7; author reply 7

119. Chandraker A, Ali S, Drachenberg CB, et al. Use of fluoroquinolones to treat BK infection in renal transplant recipients [abstract 1564]. Am J Transplant 2004;4:587

120. Araya CE, Lew JF, Fennell RS III, et al. Intermediate-dose cidofovir without probenecid in the treatment of BK virus allograft nephropathy. Pediatr Transplant 2006;10:32-7

121. Vats A, Shapiro R, Singh Randhawa P, et al. Quantitative viral load monitoring and cidofovir therapy for the management of BK virus-associated nephropathy in children and adults. Transplantation 2003;75:105-12

122. Lim WH, Mathew TH, Cooper JE, et al. Use of cidofovir in polyomavirus BK viral nephropathy in two renal allograft recipients. Nephrology (Carlton) 2003;8:318-23

123. Kadambi PV, Josephson MA, Williams J, et al. Treatment of refractory BK virus-associated nephropathy with cidofovir. Am J Transplant 2003;3:186-91

124. Lopez V, Sola E, Gutierrez C, et al. Anterior uveitis associated with treatment with intravenous cidofovir in kidney transplant patients with BK virus nephropathy. Transplant Proc 2006;38:2412-3

125. Farasati NA, Shapiro R, Vats A, et al. Effect of leflunomide and cidofovir on replication of BK virus in an in vitro culture system. Transplantation 2005;79:116-8

126. Faguer S, Hirsch HH, Kamar N, et al. Leflunomide treatment for polyomavirus BK-associated nephropathy after kidney transplantation. Transpl Int 2007;20:962-9

127. Josephson MA, Gillen D, Javaid B, et al. Treatment of renal allograft polyoma BK virus infection with leflunomide. Transplantation 2006;81:704-10

128. Singh N, Wannstedt C, Keyes L, et al. Efficacy of valganciclovir administered as preemptive therapy for cytomegalovirus disease in liver transplant recipients: impact on viral load and late-onset cytomegalovirus disease. Transplantation 2005;79:85-90

129. Kusne S, Grossi P, Irish W, et al. Cytomegalovirus PP65 antigenemia monitoring as a guide for preemptive therapy: a cost effective strategy for prevention of cytomegalovirus disease in adult liver transplant recipients. Transplantation 1999;68:1125-31

130. Kelly J, Hurley D, Raghu G. Comparison of the efficacy and cost effectiveness of pre-emptive therapy as directed by CMV antigenemia and prophylaxis with ganciclovir in lung transplant recipients. J Heart Lung Transplant 2000;19:355-9

131. Singh N, Yu VL. Severing the Gordian knot of prevention of cytomegalovirus in liver transplant recipients: the principle is the sword. Liver Transpl 2005;11:891-4

132. Weller S, Blum MR, Doucette M, et al. Pharmacokinetics of the acyclovir pro-drug valaciclovir after escalating single- and multiple-dose administration to normal volunteers. Clin Pharmacol Ther 1993;54:595-605

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