Herpesvirus Infections in Solid Organ Transplant Patients at High Risk of Primary Cytomegalovirus Disease

Raymund R. Razonable,1 Robert A. Brown,1 Atul Humar,2 Emma Covington,3 Emma Alecock,3 Carlos V. Paya,1 and the PV16000 Study Group

1Division of Infectious Diseases, Mayo Clinic College of Medicine, Rochester, Minnesota; 2University of Toronto, Toronto, Canada; 3Roche Products, Welwyn Garden City, Herts, United Kingdom

The epidemiology of infections with 5 human herpesviruses (HHVs) (HHV-6, HHV-7, HHV-8, varicella zoster virus [VZV], and Epstein-Barr virus [EBV]) was investigated during the first year after solid organ transplantation in 263 patients who received oral ganciclovir or valganciclovir prophylaxis. HHV-6B DNAemia was uncommon, HHV-6A DNAemia was not observed, and HHV-7 DNAemia was prevalent. HHV-6 and HHV-7 DNAemia were not significantly associated with cytomegalovirus (CMV) disease, although a trend toward higher incidence of CMV disease was observed in HHV-6 DNAemic patients. VZV and HHV-8 DNAemia were not detected. EBV infection was common, although incidence of high-level EBV DNAemia was low, especially in patients who received valganciclovir prophylaxis. EBV-related posttransplant lymphoproliferative disease was not observed up to 12 months after transplantation. Compared with historic data, data from the present study suggest that antiviral prophylaxis may lower the incidence, prevalence, or level of DNAemia for infection with HHV-6, HHV-8, VZV, and EBV but not for infection with HHV-7.

Adaptation to allow for latency is the hallmark of human herpesviruses (HHVs) [1]. This characteristic could lead to viral reactivation, which accounts for clinical disease when the immune system is suppressed, such as after solid organ transplantation (SOT) [1, 2]. Among the 8 HHVs, cytomegalovirus (CMV) is the most significant in terms of effect on SOT outcomes and, hence, is the subject of major prevention efforts [1, 2].

CMV-seronegative recipients of organs from seropositive donors (CMV D+/R− patients) are at the highest risk of acquiring CMV disease [2]. In addition, CMV D+/R+ patients are at higher risk of acquiring other viral infections, possibly as a result of virus-virus and virus-host interactions, which lead to an enhanced immunosuppressive state [2]. For example, the interaction between CMV, HHV-6, and HHV-7 results in increased predisposition to CMV disease [2, 3].

CMV is also believed to influence the other herpesviruses. Its association with Epstein-Barr virus (EBV) can result in uncontrolled EBV replication that leads to B cell proliferation and posttransplant lymphoproliferative disorder (PTLD) [1, 4–6]. Although primary EBV infection is the major risk factor for PTLD, CMV D+/R− SOT patients are known to have a higher risk of developing this complication [5, 6]. Accordingly, it is recommended that patients be monitored carefully, because of their EBV-PTLD predisposition [7]. An interaction between CMV and HHV-8 has also been suggested on the basis of the results of an in vitro study that reported the ability of CMV to activate HHV-8 replication [8]. Hence, in vivo, HHV-8 replication could be enhanced by CMV, and this could result in Kaposi sarcoma and nonneoplastic HHV-8–related syndromes.
[9–12]. Several anecdotal reports have also described that varicella zoster virus (VZV) infection occurs more frequently in SOT patients with CMV infection and disease [13], although these observations have not been confirmed in a large cohort of patients.

Oral ganciclovir and valganciclovir prophylaxis are equally effective at reducing the incidence of CMV disease in CMV D+/R⁻ SOT patients [14]. In addition to preventing CMV disease, anti-CMV prophylaxis is believed to reduce the incidence of infections with non-CMV herpesviruses. Indeed, it is well accepted that oral ganciclovir, valganciclovir, and other antiviral agents are effective at preventing herpes simplex virus (HSV)–1 and HSV-2 infection [15]. However, compelling data that demonstrate this added benefit, as it pertains to other herpesviruses, are limited. Hence, the present study was undertaken to specifically evaluate the epidemiology of infections with 5 herpesviruses—EBV, VZV, HHV-6, HHV-7, and HHV-8—in patients who received oral ganciclovir or valganciclovir prophylaxis.

PATIENTS AND METHODS

Study design, patient population, and clinical samples. Two hundred sixty-three (72%) of the 364 CMV D+/R⁻ kidney, kidney-pancreas, liver, or heart transplant patients who participated in the PV16000 trial, which compared the efficacy of valganciclovir (900 mg once daily; n = 168) with that of oral ganciclovir (1000 mg 3 times daily; n = 95) for prevention of CMV disease, were included in the present study [14]; failure to obtain consent from patients for specific virologic studies is the reason for non-inclusion of 28% of patients. The demographic characteristics and the outcomes (CMV disease) of the 263 patients included in the present study were similar to those of the entire patient population [14]. All patients initiated anti-CMV prophylaxis within 10 days after SOT and continued treatment until day 100. In accordance with the study protocol, peripheral blood samples were collected from the 263 patients before anti-CMV prophylaxis (on days 2 and 3 after SOT for the vast majority of patients), during anti-CMV prophylaxis (on days 14, 42, 70, and 100 after SOT), and at serial time points after anti-CMV prophylaxis (at months 4, 4.5, 6, 8, and 12 after SOT). A total of 2232 blood samples were collected (mean, 8.5 samples/patient [86% of anticipated blood samples]); the samples were stored at −70°C until use in the present study.

Viral nucleic acid quantification. All 2232 blood samples were quantified for EBV, VZV, HHV-6, HHV-7, and HHV-8 DNAemia (viral load) at the Mayo Clinic research laboratory (Rochester, MN) by a technologist who was blinded to the outcome of the trial. Viral DNA was extracted from 200 μL of whole blood by use of the IsoQuick Method (ORCA Research) and was eluted in 100 μL of DNase-free and RNase-free water. Five microliters of the eluted DNA was added to 15 μL of Mastermix Solution (Roche Molecular Biochemicals) containing primers and probes that amplify and detect the viruses under investigation (immediate early gene of HHV-6, U10 and U11 of HHV-7, gene 29 of VZV, late membrane protein of EBV, and major capsid protein of HHV-8), as reported elsewhere [16–21]. Viral load was quantified by use of a LightCycler (Roche Molecular Biochemicals); the details of the assays and a clinical evaluation of them have been reported elsewhere [16–21].

Correlation with clinical data. During the PV16000 trial [14], clinical events during the first year after SOT were prospectively recorded in a database that was maintained by the sponsor (Roche). These data were retrieved for correlation in the present study, in which the presence and degree of viremia were assessed for association with the clinical data.

Statistical analysis. The incidence and prevalence of EBV, VZV, HHV-6, HHV-7, and HHV-8 DNAemia were calculated. Incidence was determined for all patients and for specific organ transplant groups. Prevalence was determined on the basis of the total number of patients tested at each time point. Viremia was classified arbitrarily as low level if it was <1000 copies/mL and as high level if it was ≥1000 copies/mL; this value was derived from a study [22] that defined it as the clinically significant level of viremia (for HHV-6 and HHV-7). The values are presented as proportions, means, medians, and/or ranges. The association between HHV-6, HHV-7, EBV, VZV, and HHV-8 DNAemia and CMV disease and other outcomes, such as PTLD and Kaposi sarcoma, if present, was investigated. Statistical analysis was performed by use of the χ² test or Fisher’s exact test, as appropriate, and the level of significance was P < .05.

RESULTS

HHV-6. The majority (86.3%) of CMV D+/R⁻ patients who received oral ganciclovir or valganciclovir prophylaxis did not exhibit HHV-6 DNAemia. Only 36 patients (13.7%) developed HHV-6 DNAemia (median peak viral load [range], 103 copies/mL [5–910,500 copies/mL]); all were classified as being infected with variant B. Among the 36 patients, the majority (89%) had low-level HHV-6 DNAemia (5–450 copies/mL); only 4 patients had high-level HHV-6 DNAemia (1096–910,500 copies/mL). In almost half (47%) of the HHV-6 DNAemic patients, the virus was detected at only 1 time point.

The onset of HHV-6 DNAemia occurred before anti-CMV prophylaxis in 9 patients, during anti-CMV prophylaxis in 15 patients, and after cessation of anti-CMV prophylaxis in 12 patients. There were no significant differences in the degree of HHV-6 DNAemia between patients who received oral ganciclovir and those who received oral valganciclovir (median peak viral load, 33 vs. 117 copies/mL, respectively; P = .31). During the first year after SOT, the prevalence of HHV-6 DNAemia was <10%, and that of high-level HHV-6 DNAemia was <2% (figure 1A).
HHV-6 DNAemia was more common among kidney and/or pancreas transplant patients (table 1). No clinical syndrome was directly attributed to HHV-6 DNAemia. No significant correlation was observed between HHV-6 DNAemia and acute graft rejection or CMV disease, although there was a trend toward a higher incidence of CMV disease in patients with HHV-6 DNAemia: 10 (27.8%) of 36 patients with HHV-6 DNAemia developed CMV disease, compared with 36 (15.9%) of 227 patients without HHV-6 DNAemia ($P = .08$). However, this trend did not correlate with the degree of HHV-6 DNAemia.

**HHV-7.** The majority (64.3%) of CMV D+/R− patients had at least 1 episode of HHV-7 DNAemia, including 34 patients (12.9%) who were HHV-7 DNAemic before initiation of anti-CMV prophylaxis. The majority of episodes of HHV-7 DNAemia (70.4%) were low level; only 50 patients (29.6%) had HHV-7 DNAemia ≥1000 copies/mL. The highest incidence of HHV-7 DNAemia was observed among kidney and/or pancreas transplant patients (table 1), and there were no significant differences in incidence and degree of HHV-7 DNAemia between patients who received oral ganciclovir and those who received oral valganciclovir.

The prevalence of HHV-7 DNAemia was highest at months 4.5 and 6 after SOT (figure 1B). There was no correlation between the presence and degree of HHV-7 DNAemia and acute graft rejection or CMV disease. CMV disease occurred in 50 (17.8%) of 295 patients with HHV-7 DNAemia and in 16 (17.0%) of 94 patients without HHV-7 DNAemia ($P = .88$). CMV disease occurred in 23 (19.3%) of 119 patients with HHV-7 DNAemia of 1–999 copies/mL and in 7 (14.0%) of 50 patients with HHV-7 DNAemia ≥1000 copies/mL.

**EBV.** The majority (56.3%) of patients had at least 1 episode of EBV DNAemia during the first year after SOT.

---

**Figure 1.** First-year prevalence of human herpesvirus (HHV)-6 (A) and HHV-7 (B) DNAemia in 263 solid organ transplant patients. 0 days* denotes the time point before anti-CMV prophylaxis (which occurred on days 2 and 3 for most patients and within 10 days after transplantation for all patients).
The prevalence of EBV DNAemia is depicted in figure 2A, with the highest incidence in liver transplant patients. The incidence of EBV DNAemia varied according to the type of organ (table 1). The incidence and prevalence of HHV-6 infection during the first year after SOT relates to its ability to influence CMV disease pathogenesis. An association between HHV-6 DNAemia and acute graft rejection has also been suggested [39], but this was not observed in the present study. Whether the lack of a significant association between HHV-6 DNAemia and these outcomes is a result of ganciclovir-associated disruption of the phenomenon of β-herpesvirus interactions deserves further study.

The present study, high incidence and prevalence of HHV-6 DNAemia were observed, despite oral ganciclovir or valganciclovir prophylaxis. This observation concurs with that of a pre-

### Table 1. First-year incidence of human herpesvirus (HHV)-6, HHV-7, and Epstein-Barr virus (EBV) infection in 263 cytomegalovirus (CMV)-seronegative recipients of a liver, heart, kidney, or pancreas from a CMV-seropositive donor.

<table>
<thead>
<tr>
<th>Organ</th>
<th>HHV-6</th>
<th>HHV-7</th>
<th>EBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver (n = 121)</td>
<td>14 (11.6)</td>
<td>77 (63.6)</td>
<td>72 (59.5)</td>
</tr>
<tr>
<td>Heart (n = 45)</td>
<td>2 (4.4)</td>
<td>19 (42.2)</td>
<td>22 (48.9)</td>
</tr>
<tr>
<td>Kidney (n = 92)</td>
<td>18 (19.6)</td>
<td>69 (75.0)</td>
<td>52 (56.5)</td>
</tr>
<tr>
<td>Kidney-pancreas (n = 5)</td>
<td>2 (40.0)</td>
<td>4 (80.0)</td>
<td>2 (40.0)</td>
</tr>
<tr>
<td>All patients (n = 263)</td>
<td>36 (13.7)</td>
<td>169 (64.3)</td>
<td>148 (56.3)</td>
</tr>
</tbody>
</table>

**Note:** Data are no. (%) of patients. Any level of viral load was included in the calculation.

Incidence of EBV DNAemia varied according to the type of SOT, with the highest incidence in liver transplant patients (table 1). The prevalence of EBV DNAemia is depicted in figure 2A. Forty-one (16.8%) of 244 patients had EBV DNAemia before anti-CMV prophylaxis. Shortly after the start of antiviral prophylaxis (day 14), the prevalence of EBV DNAemia peaked at 26.2% but then progressively declined to reach the lowest point at the end of prophylaxis (figure 2A). The prevalence of EBV DNAemia was similar between patients who received oral ganciclovir (range, 12.0%–25.0%) and those who received oral valganciclovir (10.5%–26.8%). EBV DNAemia was low level in most patients. EBV DNAemia ≥1000 copies/mL was detected in only 7.6% of patients (figure 2B). EBV DNAemia ≥5000 copies/mL was detected in 6.3% of oral ganciclovir recipients and in 1.2% of oral valganciclovir recipients (P = .03) (figure 2B). No correlation was observed between EBV and CMV, and no cases of EBV-associated PTLD at 1 year were reported.

**VZV and HHV-8.** VZV DNAemia was not detected in any patient. However, there was one reported episode of clinical herpes zoster, in a 69-year-old male patient at day 22 after transplant. The patient did not require specific treatment (in addition to the valganciclovir prophylaxis he was already receiving). There were no cases of HHV-8 DNAemia or Kaposi sarcoma during the first year after transplantation.

**Discussion**

The present molecular surveillance study has demonstrated that, among CMV D+/R− SOT patients who received oral ganciclovir or valganciclovir prophylaxis, EBV and HHV-7 DNAemia were common; HHV-6B DNAemia was infrequent; and HHV-6A, VZV, and HHV-8 DNAemia were not observed during the first year after SOT. The incidence of high-level EBV DNAemia was low, especially among patients who received valganciclovir prophylaxis. A significant interaction among β-herpesviruses was not observed, although a nonsignificant trend toward a higher incidence of CMV disease was observed among HHV-6 DNAemic patients. These data provide insights into the epidemiology of HHV infections in CMV D+/R− SOT patients during the current era of transplantation medicine, in which use of antiviral prophylaxis for prevention of CMV disease is widespread. Collectively, these data suggest that antiviral prophylaxis may have direct or indirect efficacy against other herpesviruses.

The incidence and prevalence of HHV-6 infection during this 1-year observational study were comparably lower than those indicated by historical data. In previous studies, HHV-6 occurred in 30%–66% of patients [23–27]. In a study of CMV D+/R− liver transplant patients who did not receive anti-CMV prophylaxis, HHV-6 DNAemia occurred in 36% of patients during the first 8 weeks after transplantation [26]. Although the differences in incidence among studies could be accounted for by patient characteristics and the lack of a standardized HHV-6 assay, it is also reasonable to hypothesize that the low incidence of HHV-6 DNAemia in the present study may relate to the use of antiviral prophylaxis. This hypothesis is supported by a study of bone marrow transplant patients [28], in which ganciclovir prophylaxis was effective at preventing HHV-6 DNAemia and by an in vitro study [29] in which the EC50 values of ganciclovir were 0.65 µg/mL for HHV-6A and 1.33 µg/mL for HHV-6B—both of which are achievable with antiviral prophylaxis. Notably, other studies demonstrated higher and varying EC50 values for both variants, with HHV-6B being described as the less-susceptible variant [30, 31].

Indeed, the detection of HHV-6B in 12% of our patients (and the lack of HHV-6A) suggests that oral ganciclovir or valganciclovir prophylaxis may be effective at preventing HHV-6A, but not HHV-6B, reactivation. Whether the incomplete inhibition of HHV-6B replication relates to systemic ganciclovir levels or to undefined viral and host factors is unclear. The lack of a significant difference in HHV-6 DNAemia between patients who received oral ganciclovir and those who received oral valganciclovir implies a mechanism other than drug levels. Indeed, even the use of intravenous (iv) ganciclovir, which achieves concentrations higher than the EC50 value for HHV-6A or -B, is unable to completely suppress HHV-6 DNAemia [21].

The major clinical significance of HHV-6 DNAemia after SOT relates to its ability to influence CMV disease pathogenesis [21, 26, 27, 32–38]. In the present study, a nonsignificant trend toward a higher incidence of CMV disease was observed. An association between HHV-6 DNAemia and acute graft rejection has also been suggested [39], but this was not observed in the present study. Whether the lack of a significant association between HHV-6 DNAemia and these outcomes is a result of ganciclovir-associated disruption of the phenomenon of β-herpesvirus interactions deserves further study.

In the present study, high incidence and prevalence of HHV-7 DNAemia were observed, despite oral ganciclovir or valganciclovir prophylaxis. This observation concurs with that of a pre-
A first-year prevalence of Epstein-Barr virus (EBV) DNAemia in 263 solid organ transplant (SOT) patients who received oral ganciclovir (black bars) or valganciclovir (white bars) prophylaxis. B, First-year incidence of high-level EBV DNAemia in 263 SOT patients who received oral ganciclovir (black bars) and valganciclovir (white bars) prophylaxis. Higher levels of EBV DNAemia (>5000 copies/mL) were observed to be significantly more common among patients who received oral ganciclovir prophylaxis than among those who received oral valganciclovir prophylaxis ($P = .03$). 0 days* denotes the time point before anti-CMV prophylaxis (which occurred on days 2 and 3 for most patients and within 10 days after transplantation for all patients).

In a previous study, which reported that the prevalence of HHV-7 viremia was not affected by oral or iv ganciclovir [40]. In a study of 92 kidney transplant patients, the baseline and peak prevalences of HHV-7 DNAemia (22% and 54%, respectively) were not significantly affected by the use of oral or iv ganciclovir [40]. Indeed, in the present study, the prevalence of HHV-7 DNAemia increased during the period of anti-CMV prophylaxis, and the onset of viremia occurred during anti-CMV prophylaxis in 62% of HHV-7 DNAemic patients. Collectively, these observations imply that HHV-7 is not affected by oral ganciclovir or valganciclovir prophylaxis.

The lack of an effect of ganciclovir on HHV-7 is further supported by an in vitro study that showed that HHV-7 is much less sensitive to ganciclovir than is HHV-6 [29]. The EC$_{50}$ value of ganciclovir for HHV-7 is $>7$ µg/mL—a level that is unattainable with standard oral ganciclovir or valganciclovir [29]. Therefore, these observations highlight the contrasting susceptibilities to ganciclovir among the 3 β-herpesviruses: CMV is
the most susceptible, HHV-6 is modestly susceptible, and HHV-7 is the least susceptible to ganciclovir [29, 41].

The clinical significance of HHV-7 infection in SOT has not been fully defined, although it has been suggested as a cofactor in the pathogenesis of CMV disease and graft rejection [21, 26, 27, 32–38]. However, the present study did not find significant associations between HHV-7 DNAemia and these clinical outcomes. This suggests that prolonged anti-CMV prophylaxis may disrupt the interaction among these viruses and that the disruption of CMV–HHV-7 interaction is likely affected through its ability to influence the natural history of CMV, but not HHV-7, infection.

Despite ganciclovir or valganciclovir prophylaxis, the majority of CMV D+/R− SOT patients had at least 1 episode of EBV DNAemia. Many patients have detectable EBV DNAemia at baseline, and this likely represents the detection of both the latent and lytic phases; the detection of latent EBV in blood is not uncommon in healthy individuals [42]. Nonetheless, there are findings in the present study that imply that anti-CMV prophylaxis exerted beneficial anti-EBV effects: (1) the low incidence of higher levels of EBV replication and (2) the control of the increasing prevalence of EBV DNAemia during the early period after SOT. Both findings could have accounted for the lack of EBV-associated PTLD during the first year after SOT.

The declining prevalence of EBV DNAemia during anti-CMV prophylaxis and its transient resurgence soon after cessation of prophylaxis further suggest that anti-CMV prophylaxis is effective at directly controlling EBV replication. Indeed, during this period, the majority of EBV DNAemic patients had low-level EBV viremia. In addition, there appears to be an association between EBV replication and the type of antiviral prophylaxis, since the incidence of EBV DNAemia ≥5000 copies/mL was significantly higher among patients who received oral ganciclovir than among those who received oral valganciclovir. This finding would suggest that the higher level of ganciclovir attained after valganciclovir administration may be more effective at reducing EBV replication. Overall, these data concur with numerous observations that anti-CMV prophylaxis may be effective at curtailing the risk of EBV-related diseases [43, 44]. For early PTLD, the cumulative time receiving ganciclovir was significantly associated with lower risk—for every 30 days of ganciclovir received, the risk of PTLD was lowered by ~30% [44]. It has even been suggested that the nonuse of anti-CMV prophylaxis in CMV D+/R− pancreas transplant patients was a major factor in the incidence of PTLD in these patients [45]. Our data, when interpreted with findings of previous studies, suggest that prolonged anti-CMV prophylaxis with oral ganciclovir or valganciclovir could also prevent higher levels of EBV replication and that valganciclovir may offer an important advantage in this regard.

VZV infection is a frequent complication after SOT, but systematically conducted studies of its molecular epidemiology have been limited. In most studies that used polymerase chain reaction, VZV viremia was common in patients with clinical zoster [46, 47], but whether VZV viremia occurs in asymptomatic transplant patients has not been investigated. In a study of 869 SOT patients [48], the incidence of clinical zoster was 8.6%, and the median onset was 9 months after SOT. On the basis of this study, we anticipated that patients in the present study could exhibit VZV DNAemia during the first year after SOT. However, there were no cases of VZV DNAemia, and only 1 case of clinical zoster was detected. The lack of VZV viremia and the remarkably low incidence of clinical zoster could have resulted from the effective anti-CMV prophylaxis. This is further supported by a previous study, which suggested that anti-CMV prophylaxis (compared with other antiviral prophylaxis) was protective against VZV [48].

Although HHV-8 infection is associated with Kaposi sarcoma and lymphoproliferative disorders [49], its full spectrum in SOT has not been fully defined. Recent data suggest the association of HHV-8 infection with nonneoplastic syndromes, such as transplant-associated gammapathy [50] and febrile syndrome with myelosuppression [51, 52]. In the present study, which attempted to determine the molecular epidemiology of HHV-8 and assess its clinical correlation in a large cohort of patients from multiple international centers, HHV-8 DNAemia and Kaposi sarcoma were not observed during the first year after SOT. This failure to detect HHV-8 DNA highlights the restricted distribution of this virus (since a large number of patients in the present study originated from regions with low HHV-8 endemicity) and/or that HHV-8 is an uncommon pathogen. Whether the use of oral ganciclovir or valganciclovir prophylaxis accounted for this failure to detect HHV-8 is not clear, and we suggest that studies be aimed at providing an answer to this question in areas in which HHV-8 is endemic.

Several limitations of the present study need to be emphasized in the hope of guiding the direction of future studies. First, the lack of a placebo control limited the analysis of anti-HHV efficacy. Second, the comparison of our results with historical data was limited by the lack of standardized assays. The assays used for viral quantification use different samples and experimental conditions, and, hence, the viral load outputs may not be similar. The availability of a standardized assay that could be used by many centers would be ideal. Third, serologic testing for the viruses was not performed, and our results were interpreted under the assumption, on the basis of data from the general population, that the majority of patients (and their donors) had been previously infected with these viruses (with the exception of HHV-8). Fourth, the PV16000 trial did not control for immunosuppression among transplant centers and patient populations. Hence, the present study could not detect the influence of specific immunosuppressive regimens on viral re-
activation. Our analysis, however, did not find differences in the incidence of viral reactivation between centers in North America and those in Europe, Australia, and New Zealand (data not shown). Further attempts to analyze center-dependent rates of virus reactivation were limited by low numbers of patients \((n < 10)\) in the majority (86%) of participating centers. Finally, assessment of long-term outcomes—specifically, chronic graft dysfunction and mortality—was not performed. In future studies, it will be important to determine whether the beneficial effects of antiviral prophylaxis on graft function and patient survival [53] relate not only to its ability to prevent CMV but also to its preventive effect on the other viruses. In this context, we suggest that clinical trials involving preemptive antiviral therapy, particularly when this approach is to be compared with antiviral prophylaxis, should incorporate monitoring for other viruses as part of its outcomes. This head-to-head trial could provide the answer to whether antiviral prophylaxis indeed offers its advantage by preventing infections with other herpesviruses.

Among CMV D+/R SOT patients who received oral ganciclovir or valganciclovir prophylaxis for 100 days, infections with EBV and HHV-7 were common, whereas infections with HHV-6, HHV-8, and VZV were either uncommon or not observed. Although EBV infection was common, the degree of EBV replication was low, especially among patients who received valganciclovir, and no cases of PTLD were reported. Whether the replication was low, especially among patients who received valganciclovir or valganciclovir prophylaxis for 100 days, infections with EBV and HHV-7 were common, whereas infections with HHV-6, HHV-8, and VZV were either uncommon or not observed. Although EBV infection was common, the degree of EBV replication was low, especially among patients who received ganciclovir, and no cases of PTLD were reported. Whether the reduced degree of EBV replication during the early period after SOT will translate into reduced incidence of late-onset PTLD remains to be seen. An interaction among the \(\beta\)-herpesviruses—HHV-6, HHV-7, and CMV—was not observed. This could have resulted from the presence of antiviral prophylaxis to disrupt the natural history of CMV and possibly HHV-6, but not HHV-7, infection. Hence, the results of the present study suggest that anti-CMV prophylaxis may also have direct or indirect efficacy against other members of the herpesvirus family.

**PV16000 STUDY GROUP**

A complete list of the members of the Valganciclovir Solid Organ Transplant Study Group follows, in alphabetical order, by country: Australia—Josie Eris (Royal Prince Alfred Hospital, Camperdown), Anne Keogh (St. Vincent’s Hospital, Darlinghurst), Tim Mathew (Queen Elizabeth Hospital, Woodville), Geoff McCaughan (Royal Prince Alfred Hospital, Camperdown), Kathy Nicholls (Royal Melbourne Hospital, Parkville), and Simone Strasser (Royal Prince Alfred Hospital, Camperdown); Canada—Atul Humar (Toronto General Hospital, Toronto), Richard Lalonde (Montreal Chest Institute, Montreal), Paul Marotta (London Health Sciences Center University Campus, London), Jutta Preiksaitis (University of Alberta Hospital, Edmonton), and Eric Yoshida (Vancouver Hospital and Health Sciences Center, Vancouver); France—Iradj Gandjbakch (Pitié-Salpetrière Hospital, Paris), Yvon Lebranchu (Bretonneau Hospital, Tours), Christophe Legendre (Saint-Louis Hospital, Paris), and Faouzi Saliba (Hopital Paul Brousse, Villejuif); Ireland—Oscar Traynor (St. Vincent’s University Public Hospital, Dublin); Italy—Paolo Angeli (Azienda Ospedaliera Di Padova, Padova) and Francesco Menichetti (Ospedale Cisanello, Pisa); New Zealand—Ed Gane (Auckland Hospital, Auckland); United Kingdom—Ali Bakran (Royal Liverpool University Hospital, Liverpool), John Forsythe (Edinburgh Royal Infirmary, Edinburgh), Nigel Heaton (Kings College Hospital, London), Peter Lodge (St. James Hospital, Leeds), Derek Manas (Freeman Hospital, Newcastle Upon Tyne), Peter Morris (Churchill Hospital, Oxford), Jayan Parameshwar (Pawpworth Hospital, Pawpworth Everard), and Nizar Yonan (Wythenshawe Hospital, Manchester); and United States—Barbara Alexander (Duke University Medical Center, Durham, NC), Emily Blumberg (Hospital of the University of Pennsylvania, Philadelphia, PA), Daniel C. Brennan (Barnes Jewish Hospital, St. Louis, MO), Robert Brown (Columbia Presbyterian Medical Center, New York, NY), Ronald W. Busuttil (UCLA School of Medicine, Los Angeles, CA), Ken Chavin (Medical University South Carolina, Charleston, SC), David Conti (Albany Medical Center, Albany, NY), Angelo DeMattos (Oregon Health Sciences University, Portland, OR), Ed Dominguez (University of Nebraska Medical Center, Omaha, NE), Howard J. Eisen (Temple University School of Medicine, Philadelphia, PA), Dan Fishbein (University of Washington, Seattle, WA), Thomas Fishbein (Mt. Sinai Medical Center, New York, NY), Robert Fisher (Medical College of Virginia Hospital, Richmond, VA), Richard Freeman (New England Medical Center, Boston, MA), Chris Freise (University of California, San Francisco, San Francisco, CA), Marquis Hart (UC San Diego Medical Center, San Diego, CA), Thomas Heftron (Emory University, Atlanta, GA), Ray E. Hershberger (Oregon Health Sciences University, Portland, OR), Richard J. Howard (University of Florida, Gainesville, FL), Sandra A. Kemmerly (Alton Ochsner Medical Institution, New Orleans, LA), Richard Knight (Mt. Sinai Medical Center, New York, NY), Bernard Kubak (UCLA School of Medicine, Los Angeles, CA), Shimon Kusne (University of Pittsburgh, Pittsburgh, PA), Steven Mawhorter (Cleveland Clinical Foundation, Cleveland, OH), Martin Mullen (Loyola University Medical Center, Maywood, IL), Carlos Paya (UC San Diego Medical Center, San Diego, CA), Thomas Hefton (Emory University, Atlanta, GA), Efficiency (University of Virginia Hospital, Richmond, VA), Richard Pirsch (University of Wisconsin Medical School, Madison, WI), Timothy L. Pruett (University of Virginia Health Systems, Charlottesville, VA), Jeffrey Punch (University of Michigan Medical Center, Ann Arbor, MI), John Rabkin (Oregon Health Sciences University, Portland, OR), Robert Rubin (Massachusetts General Hospital, Boston, MA), John Scandling (Stanford University Medical Center, Palo Alto, CA), Michael Shapiro (Hackensack University Medical Center, Hackensack, NJ), Randi Silibovsky (Albert Einstein Medical Center, Philadelphia, PA), Kenneth...
Washburn (University of Texas Health Service Center, San Antonio, TX), and Sam Weinstein (LifeLink Transplant Institute, Tampa, FL).

References


