Risk Factors for Cytomegalovirus Viremia and Disease Developing after Prophylaxis in High-Risk Solid-Organ Transplant Recipients

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Background. Cytomegalovirus (CMV) D+/R− solid-organ transplant (SOT) recipients carry increased risk of developing CMV disease; however, other risk factors in these patients have not been delineated.

Methods. We examined 20 demographic and clinical variables for their association with the development of CMV disease, as defined by an independent endpoint committee (IEC) and also by the investigator (investigator treated [IT]), or CMV viremia within 12 months of transplant in D+/R− transplant recipients who received prophylaxis with valganciclovir or oral ganciclovir for 100 days.

Results. Recipients with low creatinine clearance (Ccr < 40 mL/min) at screening had a significantly increased hazard of developing IEC-defined CMV disease (hazards ratio [HR] = 4.28, confidence interval [CI] 1.69, 10.83). Females were twice as likely (HR = 2.19, CI 2.1, 3.99) to develop IEC-defined CMV disease than males. These variables were associated with an increased risk of IEC-defined CMV disease in time-dependent models. Recipients with blood group A were also more likely to develop IEC-defined CMV disease than those with group O (HR = 2.36 CI 1.24, 4.51) in the logistic regression model only. Prophylactic drug, organ type, recipient age, rejection episodes, and maintenance immunosuppression regimen were not associated with IEC-defined CMV disease. Female sex was the only variable associated with the development of CMV viremia (odds ratio [OR] = 1.65; CI 1.03, 2.65) and IT CMV disease (OR = 1.78; CI 1.08, 2.93).

Conclusions. Low Ccr at screening and blood type A are risk factors for IEC-defined CMV disease, and female sex was a risk factor for IEC- and IT-defined CMV disease and viremia in high-risk SOT recipients. These variables should perhaps be considered when optimizing treatment.

Keywords: Cytomegalovirus, Solid organ transplantation, Prophylaxis, Valganciclovir.

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patients given anti-CMV prophylaxis have not been well studied. The aim of this study was to identify risk factors for CMV disease and viremia in D+/R− SOT recipients who participated in a large, randomized, double-blind trial of valganciclovir prophylaxis (11). Identification of risk factors for CMV disease in the high risk D+/R− SOT recipient population will help optimize disease prevention.

**MATERIALS AND METHODS**

We analyzed data collected from 364 patients from a multicenter trial (PV 16000 trial) comparing valganciclovir and oral ganciclovir in SOT (11). This double-blind, double-dummy, randomized controlled trial was conducted at 57 centers worldwide (US, n=35; Canada, n=5; Europe, n=11; Australia/New Zealand, n=6) and was approved by the independent ethics committees/institutional review boards of participating centers. It was conducted in accordance with the Declaration of Helsinki, and all patients provided written informed consent. The study was performed under the supervision of an independent drug safety monitoring board.

**Patients and Prophylactic Regimen**

Eligible patients were previously unexposed to CMV (CMV antibody negative). Patients were 13 or more years of age with an absolute neutrophil count greater than 1,000 cells/µL and creatinine clearance (Cr) greater than 25 mL/min (liver and heart recipients) or greater than 15 mL/min with improving renal function (kidney and kidney-pancreas recipients), who received a first heart, liver, kidney, kidney-pancreas, kidney-heart, or kidney-liver allograft or second kidney allograft from a CMV-positive donor (D+/R−). Patients were randomized (2:1) to receive valganciclovir 900 mg once daily or oral ganciclovir 1,000 mg three times daily. Kidney recipients were, by design, limited to 120 subjects to ensure enrolment of sufficient numbers of nonrenal transplant. Assigned anti-CMV treatment was to begin within 10 days posttransplant (as soon as the subject was able to take oral medication) and continued through day 100 posttransplant. No intravenous anti-CMV prophylaxis was allowed. In patients with impaired renal function, both study medication doses were adjusted according to calculated Cr using a protocol-defined algorithm (11).

**Assessments**

Patients were assessed at screening, first day of study drug administration (baseline), posttransplant days 14, 28, 42, 56, 70, 84, and 100, and months 4, 4.5, 5, 6, 8, 10, and 12. Patients were screened from 4 days before to 12 days after transplant. Patients received the first dose of study medication between 0 and 12 days posttransplant (mean of 4.2 days posttransplant for valganciclovir or 4.3 days for ganciclovir). Blood sampling for CMV viral load occurred at the time points specified above and immediately before treatment of suspected CMV disease. CMV viremia was detected by a shell vial culture, antigenemia assay, or Food and Drug Administration (FDA)-approved DNA/RNA-based assay at each study center and also centrally (LabCorp, Burlington, NC, or Mechelen, Belgium) using an FDA-approved or fully validated DNA/RNA-based method as previously described (12, 13).

**End Points**

We analyzed clinical and biochemical variables for their association with three different CMV endpoints. To maximize objective endpoint determinations, the PV16000 trial used a blinded independent endpoint committee (IEC) that retrospectively defined the development of CMV disease based on predetermined protocol definitions. These criteria were either (1) CMV syndrome (presence of CMV in blood and fever ≥38°C on ≥2 occasions, ≥24 hours apart within a 7-day period) and one or more of the following: malaise, two successive measurements of leukopenia 24 or more hours apart, atypical lymphocytosis 5% or greater, thrombocytopenia, or elevation of hepatic transaminases to twice or more than the upper limit of normal (nonliver-transplant recipients) or (2) tissue-invasive CMV (evidence of localized CMV infection [biopsy proven or other appropriate specimen] and evidence of organ dysfunction). The incidence of this IEC-defined CMV disease within 12 months of transplant served as the first risk-factor endpoint. The second endpoint for our risk factor analysis was the incidence of investigator-treated CMV disease within 12 months of transplant. This was defined as the presence of a positive CMV culture or DNA assay or tissue biopsy and symptoms suggestive of CMV that lead the investigator to treat the patient with intravenous ganciclovir. The third endpoint for our risk factor analysis was the incidence of CMV viremia within 12 months of transplant as measured by at least one CMV viral load above the detection limit (>400 copies/mL in plasma using the Cobas Amplicor CMV Monitor Test, Roche, Basel, Switzerland).

**Statistical Analyses**

All statistical analyses were performed on an intent-to-treat (ITT) basis; the ITT population comprised all D+/R− patients randomized to either treatment group. Logistic regression models were fitted to describe the incidence of CMV disease and CMV viremia against clinical covariates. Cox proportional hazards models were used to model time to CMV disease or viremia.

**TABLE 1.** Demographic and clinical variables examined for association with cytomegalovirus (CMV) disease and CMV viremia

| Covariate                          | Age | Sex | Weight | Race/ethnicity | Country | Treatment group | Organ transplant type | Creatinine clearance at screening | Number of human leukocyte antigen mismatches | Acute rejection at any time up to 12 months posttransplant | Antilymphocyte antibodies before or during the study | Immunosuppressive regimen | Recipient and donor Rhesus typing | Recipient and donor ABO typing |
|-----------------------------------|-----|-----|--------|---------------|---------|----------------|----------------------|-------------------------------|------------------------------------------|--------------------------------------------|-----------------------------------------------|--------------------------------|---------------------------|-----------------------------|-----------------------------|

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against clinical covariates. A stepwise method (a mixture of forward and backward inclusions) was used to test covariates individually for inclusion in the final models. Covariates were included in the models if there was a $-2 \log$ change compared with the chi-square statistic for the appropriate degrees of freedom (forward inclusion). After the development of a model, covariates were deleted from the model (backward elimination) by testing at the 5% significance level. The final model contained variables that were significant in the model plus treatment arm and organ–transplant-type variables. The latter two were included whether they were significant in the model or not. This was done so parameter estimates were adjusted for treatment group and to test for treatment/covariate interactions.

### Clinical Covariates Tested in Statistical Models

To identify variables independently associated with CMV disease/viremia, we used the statistical models above to examine a number of clinical variables (Table 1). The following covariates were tested for significance in the models: treatment arm, age, sex, race, country, organ-transplant type, weight, Ccr at screening, number of HLA mismatches, recipient and donor ABO typing, recipient and donor Rhesus typing, number of immunosuppressives or specific combinations of immunosuppressive drugs received at baseline, patients who had experienced an acute rejection, and patients who had received antilymphocyte antibody (ALAs) treatment (OKT3, antithymocyte globulin preparations, and interleukin-2 receptor antagonists were not included in this variable). Ccr at screening was the value obtained nearest to the first day that study drug is taken and no more than 5 days before the first day of study drug administration.

### RESULTS

In total, 372 patients were randomized to treatment and had completed the 12-month study period (or died or...
withdrew before the 12-month visit). The ITT population comprised 364 patients (8 patients who were not D/H11001/H11002 were excluded). The ITT population included 185 liver (including 2 liver-kidney transplants), 120 kidney, 11 kidney-pancreas, and 56 heart recipients.

Sixty-four (17.6%) recipients developed IEC-defined CMV disease up to 12 months posttransplant (Table 2). When analyzed by variable, the highest incidence of CMV disease occurred in patients with reduced Ccr at screening (Ccr < 40 mL/min, 29%), in females (26%), in recipient blood type A (23%), and in patients who received ALA treatment, although this was not statistically significant (23%) (Table 2). At 12 months posttransplant, 30% of all study subjects had investigator–treated-defined CMV disease, and 49% had developed CMV viremia.

### Risk Factors for Independent Endpoint Committee-Defined CMV Disease and time to Development of CMV Disease up to 12 Months after Transplant

#### Logistic regression analyses

The effect of various demographic and clinical variables on the risk of developing IEC-defined CMV disease is presented in Table 3. Three variables were significantly associated with IEC-defined CMV disease: reduced Ccr (<40 mL/min), female sex, and recipient ABO type A (compared with blood type O) (Table 3).

Patients with low Ccr (<40 mL/min) at screening had the highest incidence of IEC-defined CMV disease (29%, Table 2). The odds ratio for Ccr of less than 40 mL/min versus 40 to 70 mL/min was 4.28 (95% confidence interval [CI] 1.69, 10.83), suggesting that the odds of developing CMV disease was between 1.7 times and 10.8 times higher on average for patients with reduced Ccr compared with those with higher Ccr at screening. The incidence of IEC-defined CMV disease in females and males was 26% and 15%, respectively (Table 2), and the odds of developing IEC-defined CMV disease was between 1.21 and 3.99 times higher for females (Table 3). The odds ratio for recipient ABO typing comparing type A with type O was 2.36 (95% CI 1.24, 4.51); the incidence of IEC-defined CMV disease in these blood groups was 23% and 13%, respectively (Table 2).

There was no statistically significant relationship between the incidence of IEC-defined CMV disease up to 12 months posttransplant in any of the other variables tested. Adjusting for treatment randomization group and the organ transplanted did not significantly alter the results, indicating that the population’s risk of IEC-defined CMV disease was unrelated to these factors.

There was no statistically significant relationship between the number of immunosuppressives at baseline (none–mono/dual/triple/quadruple–quintuple) or specific combinations of immunosuppressives at baseline and IEC-defined CMV disease up to 12 months posttransplant. However, patient numbers in each subcategory were relatively small, precluding the necessary power to detect any between-category differences.
differences. There were also no apparent differences in IEC-defined CMV rates between patients who did versus those who did not receive any of the following at baseline: mycophenolate mofetil (MMF), cyclosporine, prednisolone (prednisone), tacrolimus, MMF/prednisolone or tacrolimus, or MMF/prednisolone.

In total, 123 patients had an acute rejection episode during the study. This subset had a slightly higher IEC-defined CMV disease rate compared with those without acute rejection (20.3% vs. 16.2%). However, acute rejection was not independently associated with CMV disease in the model.

ALA treatment (muromonab-CD3 [OKT3], antilymphocyte immunoglobulin, or antithymocyte immunoglobulin either before or during the study was received by 64 patients. This patient subset had a slightly higher IEC-defined CMV disease rate than those who did not receive ALA (23.4% vs. 16.3%). However, ALA treatment also was not independently associated with CMV disease in the multivariable models.

Cox proportional hazard analyses
The effect of various demographic and clinical variables on the time to development of IEC-defined CMV disease is presented in Table 4. Low Ccr at screening and female sex were identified as the only significant risk factors. The hazard ratio for Ccr comparing less than 40 mL/min versus 40 to 70 mL/min was 3.38 (95% CI 1.62, 7.03), indicating that the hazard of developing CMV disease was between 1.6 and approximately 7 times higher for patients with Ccr of less than 40 mL/min compared with Ccr 40–70 mL/min. The hazard ratio for sex, comparing females to males, was 1.89 (95% CI 1.13, 3.16).

There was no statistically significant relationship between the incidence of investigator-treated CMV disease up to 12 months posttransplant and any of the other variables tested. Adjusting for treatment randomization group and the organ transplanted did not significantly alter the results, indicating that the population’s risk of CMV disease was unrelated to these factors.

### Risk Factors for Investigator-Treated CMV Disease and Time to Development of CMV Disease up to 12 Months after Transplant

#### Logistic regression analyses
The effects of the selected demographic and clinical variables were also modeled to investigate the risk of developing investigator-treated CMV disease within 12 months of transplant. Only female sex was significantly associated with investigator-treated CMV disease (Table 3). The incidence of CMV disease in females and males was 38.1% and 26.6%, respectively (Table 2). The odds ratio for sex, comparing female with male, was 1.78 (95% CI, 1.08, 2.93), suggesting that the odds of developing investigator-treated CMV disease was between 1.1 and 2.9 times higher for females.

There was no statistically significant relationship between the incidence of investigator-treated CMV disease up to 12 months posttransplant and any of the other variables tested. Adjusting for treatment randomization group and the organ transplanted did not significantly alter the results, indicating that the population’s risk of CMV disease was unrelated to these factors.

### Cox proportional hazard analyses
The effect of various demographic and clinical variables on the time to development of IEC-defined CMV disease is presented in Table 4. As for the logistic regression analyses, female sex was identified as the only significant risk factor. The hazard ratio for sex, comparing females to males, was 1.70 (95% CI 1.12, 2.49). The effect of sex on time to investigator-treated CMV disease was statistically significant at the 5% level when tested without treatment group and organ transplant group present in the model. However, in the final model, sex did not achieve signifi-
Risk Factors for CMV Viremia and Time to Development of CMV Viremia up to 12 Months after Transplant

Logistic regression analyses.

The effect of various demographic and clinical variables on the risk of developing CMV viremia is presented in Table 5. Sex was the only covariate significantly related to the incidence of CMV viremia. The odds ratio for females versus males was 1.44 (95% CI 1.04, 1.99). Females had a higher proportion of CMV viremia (57.7%) when compared with male patients (45.3%) (data not shown). Again, treatment arm and organ-transplant type were not independent risk factors affecting the incidence of CMV viremia (Table 5).

Cox proportional hazard analyses.

The effect of various demographic and clinical variables on the time to developing of CMV viremia is presented in Table 6. Female sex was the only significant variable; the hazard ratio for females versus males was 1.65 (95% CI 1.03, 2.65). Females had a higher incidence of CMV viremia. The odds ratio for females versus males was 1.44 (95% CI 1.04, 1.99). When fitted to the model, organ type or treatment group were not statistically significant predictors, again indicating that these factors did not influence the population’s risk for CMV viremia within 12 months of transplant (Table 6).

DISCUSSION

CMV remains an important opportunistic pathogen in the immunocompromised host and a significant cause of morbidity and mortality in SOT recipients (14). Despite the introduction of more effective antiviral agents into clinical practice, the direct and indirect consequences of CMV infection and disease continue to have major detrimental effects on transplant outcomes (15).

In this study, where all subjects received prophylaxis with either ganciclovir or valganciclovir, IEC-defined CMV disease occurred in a total of 64 (17.6%) high-risk D+/R− transplant recipients up to 12 months posttransplant. We identified low Ccr at screening, female sex, and ABO blood type A as significant risk factors for IEC-defined CMV disease. In contrast, female sex was identified as the only significant risk factor for investigator-treated CMV disease. Interpretation of results using investigator-treated disease is, however, limited by the lack of uniform definition for CMV disease and potential investigator bias in treatment of these patients. The rigorous use of the IEC-defined endpoint overcomes these problems and makes this study unique.

Low Ccr at screening and female sex were also significant risk factors for time to development of IEC-defined CMV disease. These results suggest that low Ccr is an important factor in determining CMV disease. Reduced Ccr may confer a higher susceptibility to viral infection overall. Patients with chronic renal failure mount much reduced responses to vaccinations (16) and are more susceptible to infections in general (17). This may explain why patients with low Ccr have higher rates of CMV infection, as seen in this study. Alternatively, if recipients for whom the initial dose of

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**TABLE 5.** Odds ratio for effects of covariates on incidence cytomegalovirus viremia in logistic regression model

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Pairwise comparison</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>Ganciclovir vs. valganciclovir</td>
<td>1.04</td>
<td>(0.67, 1.62)</td>
</tr>
<tr>
<td>Organ type</td>
<td>Heart vs. kidney</td>
<td>1.32</td>
<td>(0.70, 2.51)</td>
</tr>
<tr>
<td></td>
<td>Heart vs. liver</td>
<td>0.92</td>
<td>(0.50, 1.68)</td>
</tr>
<tr>
<td></td>
<td>Kidney vs. liver</td>
<td>0.70</td>
<td>(0.43, 1.11)</td>
</tr>
<tr>
<td>Sex</td>
<td>Female vs. male</td>
<td>1.65a</td>
<td>(1.03, 2.65)</td>
</tr>
</tbody>
</table>

* Odds ratio significantly different from 1 (*P*<0.05). CI, confidence interval.

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**TABLE 6.** Hazard ratios for covariate effects on time to cytomegalovirus viremia in Cox proportional hazard model

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Pairwise comparison</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>Ganciclovir vs. valganciclovir</td>
<td>1.19</td>
<td>(0.87, 1.62)</td>
</tr>
<tr>
<td>Organ type</td>
<td>Heart vs. liver</td>
<td>0.87</td>
<td>(0.57, 1.33)</td>
</tr>
<tr>
<td></td>
<td>Kidney vs. liver</td>
<td>0.73</td>
<td>(0.52, 1.03)</td>
</tr>
<tr>
<td>Sex</td>
<td>Female vs. male</td>
<td>1.44a</td>
<td>(1.04, 1.99)</td>
</tr>
<tr>
<td>Age</td>
<td>≤50 vs. &gt;50 years</td>
<td>0.76</td>
<td>(0.76, 1.02)</td>
</tr>
</tbody>
</table>

* Hazard ratio significantly different from 1 (*P*<0.05).
study drug was intentionally reduced because of their reduced creatinine clearance did not have their dose increased appropriately as the renal function improved posttransplant, they may have been underexposed and may have been more susceptible to infection. However, preliminary pharmacokinetic data do not suggest that this occurred (data not shown). There may also be relationships between $C_{cr}$ and other variables that have not been completely characterized in our study. For instance, patients with $C_{cr}$ of less than 40 mL/min received, on average, a higher number of immunosuppressives at baseline compared with patients with higher $C_{cr}$, although immunosuppressive regimens were not associated with CMV disease. Therefore, although $C_{cr}$ may appear to be an important factor in determining CMV disease, inconsistent adjustment of prophylactic drug dosing as renal function improves after transplantation may explain some of our findings. It may also be that low $C_{cr}$ is confounded with immunosuppressive regimen. Moreover, there is the difficulty in satisfactorily characterizing immunosuppressive regimen over time or indeed at any one time point. The number of immunosuppressive drugs received is only a crude way to summarize the data; however, testing numerous drug combinations in the model leads to problems with multiple significance testing (18).

In our study, female sex was also significantly associated with the development of IEC-defined CMV disease and time to development of disease. Female recipients of kidney, liver, and kidney-pancreas transplants had a higher incidence of CMV disease than their male counterparts. Further studies are warranted to determine whether female recipients of these allograft types need more aggressive CMV prophylaxis or whether females are less sensitive to ganciclovir or valganciclovir. Only female sex was associated with a significantly higher risk of CMV viremia and time to development of viremia. There are some preliminary molecular data suggesting that plasmids constructed with CMV virus transduce more readily under estrogen-rich conditions (19), and it is possible that estrogen makes the immediate to early CMV genes more sensitive or more active. These data may provide mechanistic support to our clinical findings.

Over the past 10 years, several new potent immunosuppressive drugs have been introduced into clinical transplantation, and opportunistic infections resulting from their use continue to produce serious complications (20). Some studies have associated the use of immunosuppressives in SOT with CMV disease, whereas others have not. Using multivariate analysis, Kuypers et al. (20) identified the use of tacrolimus, MMF, and steroids as independent risk factors for CMV disease in kidney-transplant recipients. However, Schnitzler et al. (10), in a study of 470 kidney-transplant recipients, failed to identify immunosuppressives as a significant risk factor for CMV disease. In our study, neither the number of immunosuppressives at baseline (none–mono/dual/triple/quadruple–quintuple) nor specific combinations of immunosuppressives at baseline was statistically significantly associated with the development or time to development of CMV disease or CMV viremia. These results may be confounded by the fact that immunosuppressive regimens change over time for each patient, and CMV reactivation may be dependent upon the immunosuppressive treatment at only one point in time. However, it should also be noted that the numbers of patients in each subcategory were relatively small, and there may not have been sufficient power to detect any between-category difference.

A number of reports have associated ALA treatment in SOT recipients with an increased risk of CMV disease (21–24). Portela et al. (23) identified the use of the ALA treatment (muromab-CD3 [OKT3]) as a significant risk factor for the development of CMV infection in CMV seropositive but not seronegative liver-transplant recipients who were not receiving specific CMV prophylaxis. In our study, ALA treatment was associated with a high incidence of CMV disease (Table 2), but this factor was not independently associated with CMV disease or viremia in the multivariate models used in this analysis.

Recipient-donor HLA mismatch has also been associated with the development of CMV disease in SOT recipients (25). The incidence of CMV disease has been strongly associated with HLA-DR mismatching in CMV seropositive kidney-transplant donors after ganciclovir prophylaxis (10). In our study, none of the HLA mismatch analyses showed any relationship between HLA status and CMV disease. However, it should be noted that only 56% of patients randomized had HLA typing data for both donor and recipient available, perhaps making the lack of HLA matching effect on CMV disease in our study a function of small sample size and a type II statistical error. Interestingly, acute rejection was not associated with CMV disease in our study. Previous studies have found an association between acute rejection and CMV disease (6).

In the current study, organ-transplant type or prophylactic group to which patients were randomized was not significantly associated with the development of CMV disease or viremia. The incidence of CMV disease at 12 months posttransplant was similar to oral ganciclovir (17.2%) and oral ganciclovir (18.4%) prophylaxis (11).

Primary CMV infection occurs in CMV seronegative transplant recipients who have no preexisting immunity and in the past has been associated with severe morbidity because extensive viral replication may occur before antiviral immune responses are mounted (26). Development of effective prophylactic regimens against this potentially life-threatening infection represents a significant advance in improving the overall care of SOT recipients, especially for the $D+/R-$ combination. However, our study reveals that, even with these effective regimens, CMV disease can still occur. We have identified risk factors for CMV disease for the $D+/R-$ recipients who receive effective ganciclovir or valganciclovir prophylaxis (low $C_{cr}$, female sex, and blood type A), and these should be considered when optimizing treatment.

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