Pharmacodynamics of Oral Ganciclovir and Valganciclovir in Solid Organ Transplant Recipients

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Background. A randomized, double-blind study was conducted to evaluate the pharmacokinetics of ganciclovir following oral administration of ganciclovir or valganciclovir for prophylaxis of cytomegalovirus (CMV) disease in solid organ transplant recipients (n = 240/372).

Methods. The correlations between individual exposure to ganciclovir during prophylaxis, with CMV viremia incidence during and after treatment, CMV disease up to 12 months posttransplant, and hematological toxicity were assessed.

Results. Mean daily areas under the curve (AUCs) of ganciclovir from valganciclovir and oral ganciclovir were 46.3 ± 15.2 and 28.0 ± 10.9 µg·h/ml (mean ± SD), respectively. Viremia was suppressed during prophylaxis when exposure to ganciclovir was 40–50 µg·h/ml, AUCs typical of those achieved in valganciclovir-treated patients. The development of viremia 1 month after ending prophylaxis was also reduced with higher ganciclovir AUC (median predicted incidence, 20% and 10% at AUCs of 33 and 50 µg·h/ml, respectively). The development of CMV disease within 1 year of transplant was 17.6% and independent of prophylactic exposure to ganciclovir. There was only a weak tendency to increased neutropenia and leukopenia with higher ganciclovir exposure.

Conclusions. The greater systemic exposure to ganciclovir delivered by valganciclovir was associated with delayed development of viremia. There was only a weak association between AUC and hematological toxicity.

Keywords: Cytomegalovirus, Valganciclovir, Ganciclovir, Pharmacodynamics, Solid organ transplant.

(Cytomegalovirus (CMV) is a leading cause of disease in immunocompromised subjects, including solid organ transplant (SOT) recipients (1). Ganciclovir has been the current standard of care for prevention of CMV disease and intravenous (IV) ganciclovir is indicated for the prevention of CMV disease in at-risk transplant recipients, while the oral formulation is indicated in SOT recipients. However, IV ganciclovir is inconvenient for long-term use (>3 months), requiring IV catheters and frequent home health visits (2).

Oral ganciclovir was developed to offer an alternative to long-term IV therapy and is effective in SOT recipients (3–5). However, it has low bioavailability (6–10%), which may limit the viral suppression achievable with this formulation (6) and predispose to the development of ganciclovir-resistant CMV (7). Furthermore, a dosage of 1000 mg tid as 6–12 capsules/day is needed to deliver plasma ganciclovir exposures that are 40–50% of those achieved with the standard 5 mg/kg daily dosage of IV ganciclovir (2, 8).

Valganciclovir is an L-valyl ester prodrug of ganciclovir that delivers ganciclovir with a bioavailability of approximately 60%, up to 10-fold higher than oral ganciclovir. Moreover, the convenient once-daily oral dosing regimen offered by valganciclovir provides comparable plasma ganciclovir exposure to that achieved with 5 mg/kg IV ganciclovir (2).

A recent randomized, double-blind study showed that valganciclovir was as effective as oral ganciclovir up to 6 months posttransplant for the prevention of CMV viremia and disease in high-risk donor positive/recipient negative (D+/R-) SOT recipients (9). The aim of this study was to investigate the relationship between systemic exposure to ganciclovir and prevention of viremia, prevention of CMV disease and the occurrence of hematologic adverse events.
MATERIALS AND METHODS

This randomized, double-blind, double-dummy study was conducted at 57 centers and was approved by the Independent Ethics Committees/Institutional Review Boards of each participating center in accordance with the Declaration of Helsinki; all patients provided written informed consent. The study was supervised by an independent Drug Safety Monitoring Board.

SOT recipients with a CMV serostatus of D+/R- were eligible for inclusion in the study if they were ≥13 years of age with adequate hematological and renal function, and were receiving a first heart, liver, kidney, kidney-pancreas, kidney-heart or kidney-liver allograft or second kidney allograft. Patients were excluded if they: 1) had a history of CMV infection or disease; 2) had received anti-CMV therapy within the past 30 days; or 3) had severe, uncontrolled diarrhea or evidence of malabsorption. Patients enrolled at each study center were stratified by allograft type and were randomized in a 2:1 ratio to receive valganciclovir 900 mg once daily or oral ganciclovir 1000 mg tid for 100 days. Dose was adjusted in patients with renal impairment, according to estimated creatinine clearance from data in renally impaired patients (10), and in cases of suspected drug-related toxicity. Immunosuppression was administered according to the standard practice at each individual study center.

CMV Viremia and Disease

Blood sampling for CMV viral load occurred posttransplant at days 14, 28, 42, 56, 70, 84 and 100, months 4, 4.5, 5, 6, 8, 10 and 12, and at the onset of suspected CMV disease. CMV viral load was determined centrally (LabCorp) using an FDA-approved and fully validated DNA/RNA-based method as previously described (11, 12).

Patients were monitored for signs and symptoms of CMV disease (CMV syndrome and/or tissue-invasive CMV) throughout the 12-month study period. To ensure consistent reporting of CMV disease, all investigator-reported cases were submitted to an independent blinded Endpoint Committee who made a final, retrospective decision regarding the diagnosis of CMV disease based on clinical judgment and predetermined protocol definitions. CMV syndrome was defined as the presence of CMV in blood and fever (>38°C on two occasions, >24 hr apart) and one or more of the following: malaise, leukopenia at two successive measurements at least 24 hours apart, atypical lymphocytosis, thrombocytopenia, or elevated hepatic enzymes. Tissue-invasive CMV was defined by evidence of localized CMV infection (biopsy-proven) and evidence of organ dysfunction.

Hematological Adverse Events

All adverse events were monitored up to month 6, and drug-related adverse events to month 12. For hematological abnormalities, anemia was defined as a hemoglobin <8 g/dL. Patients were considered neutropenic if they had at least one incidence of an absolute neutrophil count of <1000 cells/µL within 4 months. Leukopenia was defined as a white blood cell count of <3500/µL or a decrease in white blood cell count of 20% if it was <4000/µL prior to the development of clinical symptoms.

Pharmacokinetic/Pharmacodynamic Assessment

Systemic exposure to ganciclovir, from either valganciclovir or oral ganciclovir, was measured on two occasions (usually three timepoints per visit: 1–3 h, 5–12 h, and 24 h postdose). The visits were 6 weeks apart, either days 28 and 70 or 42 and 84. Ganciclovir population pharmacokinetics was analyzed using NONMEM software (13). In brief, the analysis was based on a two-compartment pharmacokinetic model with different absorption/metabolism and absorption parameters for valganciclovir and ganciclovir, respectively. The model was validated internally and with reference to historical studies with intensive plasma concentrations (2, 10). Body weight was used as a predictor of both central and peripheral volumes and estimated creatinine clearance as a predictor of the systemic clearance of ganciclovir. As no significant differences were noted between the two separate AUCs, an average was used for analysis.

The correlations between individual exposure (AUC<sub>0–24h</sub>) to ganciclovir during prophylaxis with the incidence of CMV viremia, CMV disease, and hematological toxicity during and after prophylaxis were assessed graphically and by logistic regression analysis. The individual AUC<sub>0–24h</sub> values were calculated using the individual posthoc parameters as obtained from the population analysis in a two-compartment model. The incidence of either one was described by a linear probabilistic function, of the form:

\[ P(\text{event}) = g\{a + b \cdot \text{AUC}\} \]

where

\[ g(x) = e^x / (1 + e^x) \]

\[ P(\text{event}) \] describes the occurrence of CMV viremia, CMV disease, or hematological toxicity during and after prophylaxis as a binary outcome. The model terms \( a \) and \( b \) represent the intercept and the slope in the generalized linear model, respectively. The influence of covariates (age, gender, treatment, etc.) was evaluated on the slope, \( \beta \). The logistic model was fitted to the data using an iteratively reweighted least squares routine as implemented in S-PLUS (v.6.1, Insightful Corporation, Seattle, WA). In order to obtain the 90th percentile prediction intervals, the outcomes of a typical study population were simulated 1000 times by randomly sampling from the multivariate normal distributions of \( \alpha \) and \( \beta \).

| TABLE 1. Baseline demographics for solid organ transplant recipients randomized to valganciclovir and oral ganciclovir (ITT population) |
|-----------------|-----------------|-----------------|
|                 | Valganciclovir (n=239) | Ganciclovir (n=125) |
| Mean age (yrs)  | 45.8             | 45.4             |
| Male/female, n (%) | 174/65 (73%/27%) | 93/32 (74%/26%) |
| Race, n (%)      |                 |                 |
| Caucasian       | 212 (89%)        | 113 (90%)        |
| Black           | 16 (6.5%)        | 7 (6%)           |
| Other           | 11 (4.5%)        | 5 (4%)           |
| Mean weight (kg) | 81.0             | 84.2             |
| Mean height (cm) | 172.4            | 172.5            |

ITT, intent-to-treat.
Simulations results were summarized by taking the 5th, 50th (median), and 95th quantile.

Statistics

The intent-to-treat (ITT) population comprised all D+/R- randomized patients. The safety population included all patients who were randomized, had received at least one dose of study medication, and had at least one safety assessment.

RESULTS

A total of 372 SOT recipients were randomized to treatment: 245 to valganciclovir (124 liver [including 2 liver-kidney], 81 kidney, 35 heart, 5 kidney-pancreas) and 127 to ganciclovir (61 liver, 39 kidney, 21 heart, 6 kidney-pancreas). The baseline demographics for all randomized patients are presented in Table 1. The ITT population included 364 patients; eight liver transplant recipients (valganciclovir, n = 6; ganciclovir, n = 2) who were not D+/R- were excluded. A total of 1181 data points describing 449 pharmacokinetic profiles from 240 patients (valganciclovir, n = 160; ganciclovir, n = 80) were used for the pharmacokinetic modeling. These patients comprised ~66% of the total study population and were well balanced with respect to demographics. The safety population comprised 370 patients (one patient in each group did not receive study medication).

Both groups were well balanced for concomitant immunosuppressive therapy. The most frequent combinations recorded at day 100 were triple therapy with mycophenolate mofetil, prednisolone, and either tacrolimus (28.3%) or cyclosporine (14.8%), or dual therapy with tacrolimus and prednisolone (20.3%). Similar proportions of patients received antilymphocytic antibodies (~6 months posttransplant) for induction or treatment of rejection (24.4% and 28.8% for ganciclovir and valganciclovir, respectively). The overall incidences of acute rejection ~6 months posttransplant were 36.0% and 29.7%, respectively.

A total of 43 patients withdrew from the study over 12 months, 14 receiving ganciclovir (11.2%) and 29 receiving valganciclovir (12.1%).

Ganciclovir Exposure

The mean daily AUC was on average 1.65 (95% CI 1.58, 1.81)-fold greater with valganciclovir (46.3 ± 15.2 µg h/ml) than ganciclovir (28.0 ± 10.9 µg h/ml). The distribution of systemic exposure to ganciclovir following administration of valganciclovir or oral ganciclovir is described in Fig. 1A.

Correlation of Systemic Exposure with CMV Viremia

Full efficacy results have been reported elsewhere (9). In brief, in the ITT population, the incidence of CMV viremia during the prophylactic period was significantly lower with valganciclovir than oral ganciclovir (2.9% vs. 10.4%; P = 0.001), but was comparable between the two groups by 6 months (valganciclovir, 39.7%; ganciclovir, 43.2%) and 12 months (valganciclovir, 48.5%; ganciclovir, 48.8%). The organ distribution for patients with pharmacokinetic samples developing CMV viremia up to day 100 and 4 months posttransplant is shown in Table 2.

FIGURE 1. (A) The number of solid organ transplant patients split by systemic ganciclovir exposure, and the relationship between systemic ganciclovir exposure and the incidence of cytomegalovirus (CMV) viremia at (B) the end of prophylaxis (day 100), (C) at month 4 posttransplant (3 weeks after cessation of prophylaxis), and (D) month 6 posttransplant (~3 months after cessation of prophylaxis) following administration of valganciclovir 900 mg once daily or oral ganciclovir 1000 mg three times daily in solid organ transplant recipients. Dosage was adjusted according to estimated creatinine clearance in patients with renal impairment.
For all patients combined who had pharmacokinetic data, there was a good correlation between systemic exposure to ganciclovir and antiviral activity during prophylaxis. The proportion of patients with AUCs $\text{H}11022/\text{H}11045/\text{H}9262 \text{g h/ml}$ developing CMV viremia on any sampling day before cessation of prophylaxis was low (3%; Fig. 1) and corresponds to a typical AUC from valganciclovir but $\text{H}11021/\text{H}10%$ of those treated with oral ganciclovir. The development of viremia during prophylaxis, and for the following month (month 4), was appreciably reduced with higher ganciclovir AUCs (Fig. 1). Most patients in the valganciclovir arm were distributed in the higher exposure groups, which is also where CMV viremia was least frequent, indicating valganciclovir to be superior to oral ganciclovir at suppressing viremia up to 4 months posttransplant.

### FIGURE 2.

Logistic regression analysis of the relationship between systemic ganciclovir exposure and the probability of any patient developing (A) cytomegalovirus viremia at the end of prophylaxis (day 100) and (B) cytomegalovirus (CMV) viremia at 4 months posttransplant (3 weeks after cessation of prophylaxis) after oral administration of valganciclovir 900 mg once daily or oral ganciclovir 1000 mg three times daily. Dosage was adjusted according to estimated creatinine clearance in patients with renal impairment. Solid lines represent median AUCs, dotted lines represent 90% prediction intervals predicted by Monte Carlo analysis and circles represent individual data points.

### TABLE 2.

Proportion of solid organ transplant recipients who developed hematological adverse events (up to 4 months posttransplant), cytomegalovirus (CMV) viremia (during prophylaxis [day 100] or 4 months [3 weeks after cessation of prophylaxis] posttransplant), or CMV disease (within 12 months posttransplant) by organ transplant type

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Patients with pharmacokinetic data</th>
<th>Hematological adverse events (%)</th>
<th>CMV viremia in patients with pharmacokinetic data (%)</th>
<th>CMV disease in patients with pharmacokinetic data (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anemia</td>
<td>Neutropenia</td>
<td>Leucopenia</td>
</tr>
<tr>
<td>Liver$^{a,b}$</td>
<td>185</td>
<td>106</td>
<td>9 (8.5)</td>
<td>16 (15.1)</td>
<td>48 (45.3)</td>
</tr>
<tr>
<td>Kidney</td>
<td>120</td>
<td>96</td>
<td>7 (7.3)</td>
<td>14 (14.6)</td>
<td>40 (41.7)</td>
</tr>
<tr>
<td>Heart$^{b}$</td>
<td>56</td>
<td>30</td>
<td>2 (6.7)</td>
<td>2 (6.7)</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>Kidney-panreas</td>
<td>11</td>
<td>8</td>
<td>2 (25.0)</td>
<td>1 (12.5)</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>Total</td>
<td>372</td>
<td>240</td>
<td>20</td>
<td>33</td>
<td>101</td>
</tr>
</tbody>
</table>

$^{a}$ Including liver-kidney.

$^{b}$ For hematological adverse events n=184 for liver and n=55 for heart transplant recipients.
ciclovir exposure during prophylaxis did not have any impact upon CMV viremia at 6 months. This is reflected in the incidence of CMV viremia in the ITT population of both treatment groups at 6 months.

Logistic regression analyses of the data are presented in Fig. 2. At day 100, an AUC of 50 \( \mu g \) h/ml predicted an average incidence of viremia of 1.3%, whereas an AUC of 25 \( \mu g \) h/ml was associated with 8 times the risk (Fig. 2). At 4 months posttransplant, the AUCs associated with a 20% and 10% chance of developing viremia were 33 \( \mu g \) h/ml and 50 \( \mu g \) h/ml, respectively. At 4 months, median exposure with ganciclovir was 44 \( \mu g \) h/ml but only 25 \( \mu g \) h/ml with ganciclovir. None of the covariates evaluated provided a statistically significant improvement.

**Correlation of Systemic Exposure with CMV Disease**

In the ITT population, by 6 months posttransplant, 12.1% and 15.2% of valganciclovir and ganciclovir recipients, respectively, had developed CMV disease. The corresponding figures at 12 months were 17.2% and 18.4%. The majority of CMV disease occurred between the end of prophylaxis and month 6 posttransplant. Only four cases of CMV disease (0.8% valganciclovir, 1.6% ganciclovir) occurred during the prophylactic period (9). Although there were insufficient CMV disease events to calculate a median time to CMV disease, the average time to CMV disease appeared shorter on the ganciclovir arm of the study (9). The organ distribution for patients with pharmacokinetic samples developing anemia, neutropenia and leukopenia up to 4 months posttransplant is shown in Table 2.

While valganciclovir yielded higher levels of ganciclovir during the 100 day period of prophylaxis than did oral ganciclovir, these higher levels did not change the incidence of CMV disease at day 180. For ganciclovir AUCs of 33–50 \( \mu g \) h/ml during prophylaxis, the risk of developing CMV disease within one year of transplant was 17.6%, and was not dependent on exposure to ganciclovir during prophylaxis.

**Correlation of Systemic Exposure with Myelotoxicity**

In the safety population, there was a trend towards a lower incidence of anemia (5.7% vs. 8.7%; \( P=0.2771 \)) but a higher incidence of leukopenia (13.5% vs. 7.1%; \( P=0.0667 \)) and neutropenia (8.2% vs. 3.1%; \( P=0.0631 \)) for valganciclovir compared with ganciclovir. The organ distribution for patients with pharmacokinetic samples developing anemia, neutropenia and leukopenia up to 4 months posttransplant is shown in Table 2.

For patients with pharmacokinetic data, few became anemic during treatment and there was no correlation between higher ganciclovir exposure and anemia (Fig. 3). There appeared to be only a weak tendency to increased neutropenia and leukopenia with higher ganciclovir exposure (Fig. 3). At 4 months posttransplant, median predicted incidences of neutropenia of 15% and 20% were associated with AUCs of 39 and 61 \( \mu g \) h/ml, respectively (Fig. 4A). Median predicted incidences of leukopenia of 40% and 50% were associated with AUCs of 34 and 62 \( \mu g \) h/ml, respectively (Fig. 4B).

**DISCUSSION**

Immunocompromised individuals are at increased risk of CMV disease, and over the past two decades a number of antiviral drugs with proven activity against CMV have been introduced into clinical practice. Ganciclovir, foscarnet and cidofovir have proven efficacy in the prevention and treatment of CMV disease (3, 14, 15); however, foscarnet and cidofovir are associated with unfavorable adverse events and as a result are considered second-line alternatives (16).

Initial studies of the bioavailability of ganciclovir delivered from oral ganciclovir demonstrated that the plasma levels attained were sufficient to inhibit the in vitro growth of CMV (17). Oral ganciclovir has since been shown to be effective in preventing CMV infection and disease in SOT recipients (3, 4, 9, 18, 19) and has been the current standard of care for the prevention of CMV disease; however, its low bioavailability limits the viral suppression achievable with this formulation (6) and may predispose to the development of resistance (7).

Valganciclovir has been developed in an attempt to increase the bioavailability of ganciclovir; valganciclovir 900 mg provides similar ganciclovir exposure to that achieved with IV ganciclovir 5 mg/kg (20, 21). The efficacy and safety of valganciclovir in the prevention of CMV in SOT recipients (9) and the treatment of CMV retinitis in AIDS patients (22) have been described. There are no data describing the pharmacodynamics of valganciclovir in SOT recipients.

Mean daily AUCs with valganciclovir and ganciclovir were 46.3 ± 15.2 \( \mu g \) h/ml and 28.0 ± 10.9 \( \mu g \) h/ml, respectively. In the current study, the greater systemic exposure to ganciclovir delivered by valganciclovir was associated with greater suppression of CMV viremia during the prophylactic period (e.g., patients with viral load >400 copies/ml while on study drug were 2.9% and 10.4% for valganciclovir and ganciclovir, respectively) and for the month following. However, there was no difference in the incidence of CMV viremia between the two groups by 6 months posttransplant. The potential long-term benefit of this greater viremia suppression during the 100 days of CMV prophylaxis is unknown and requires further study.
The risk of progression to CMV viremia and disease is dependent on viral replication (23). Our results show that CMV replication during prophylaxis was greater in patients receiving oral ganciclovir than in those receiving valganciclovir. Razonable et al. (23) have previously reported that six of seven liver transplant recipients had persistent viral replication despite the administration of oral ganciclovir. Two of these six patients subsequently developed CMV disease while receiving ganciclovir prophylaxis (23).

In our study, the higher ganciclovir exposures delivered by valganciclovir had a significantly greater effect in suppressing CMV viremia during 100 days of prophylaxis, but did not prevent CMV viremia or disease by 6 and 12 months post-transplant. This is in agreement with the clinical results, as the overall incidence of CMV viremia and disease was similar in both treatment groups; however, the average time to CMV disease and viremia appeared shorter in the ganciclovir arm. This suggests that anti-CMV prophylaxis with valganciclovir may delay the onset of CMV viremia and disease compared with oral ganciclovir, and raises the question of whether extending the duration of CMV prophylaxis beyond 100 days could further reduce CMV disease rates.

Circumstances during the initial 3 months following transplantation (i.e., when the degree of immunosuppression is generally most intense) favor the development of CMV disease (23). In our study, the majority of CMV disease occurred between the end of the prophylaxis and 6 months posttransplant. These results are consistent with those presented elsewhere. In 37 D+/R- SOT recipients receiving oral ganciclovir prophylaxis (1000 mg id) for a median of 96 days after transplantation, no patients developed CMV disease during prophylaxis. However, during a mean follow-up period of 9.4 months, CMV disease occurred in 24% (9/37) of the patients. As with our study, most of the CMV disease occurred between 3 and 6 months after transplantation (144 days median) (24).

One possible strategy to prevent the late onset of CMV disease is to prolong the duration of prophylaxis. Whether the extension of valganciclovir prophylaxis beyond three months is associated with a decreased incidence of CMV disease is...
subject to further study. However, there is preliminary evidence to suggest that prolongation of valganciclovir prophylaxis reduces the incidence of CMV disease in lung transplant recipients. Zamora et al. (25) reported on their single center experience with prolonged (up to 12 months) valganciclovir (900 mg) prophylaxis that was begun after IV ganciclovir and CMV hyperimmune globulin for 30 days in R− patients, and after 100 days in D+/R− lung transplant recipients. In 32 patients tolerating prophylaxis, there were no cases of CMV disease and only two cases of asymptomatic viremia.

A potential impediment to the use of anti-CMV prophylaxis is the occurrence of hematological adverse events. In our study, few patients became anemic and there was no correlation between higher ganciclovir exposure and anemia. There appeared to be only a weak tendency to increased neutropenia and leukopenia with higher ganciclovir exposure.

The suboptimal plasma concentrations achieved with oral ganciclovir have been associated with the development of ganciclovir-resistant CMV in SOT recipients (7). From our trial, data on the incidence of ganciclovir resistant CMV have been published (26). At the end of prophylaxis, the incidence of CMV UL97 mutations was 0% and 1.9% with valganciclovir and oral ganciclovir, respectively (p = NS). The lack of resistance mutations in CMV from ganciclovir–treated patients may be attributable to the increased exposure to ganciclovir achieved with valganciclovir (26).

In conclusion, the greater systemic exposure of ganciclovir delivered by valganciclovir 900 mg/day was associated with enhanced suppression of CMV viremia and disease during prophylaxis, and delayed development of viremia and disease when therapy was curtailed. There was only a weak association between increased ganciclovir exposure and the development of hematological adverse events. Additional studies are required to understand the association between enhanced viremia suppression and long-term outcomes in SOT.

REFERENCES