High-Dose Acyclovir for Cytomegalovirus Prophylaxis in Seropositive Abdominal Transplant Recipients

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Abstract
Background: Following abdominal solid organ transplant (aSOT), valganciclovir (VGC) is recommended for cytomegalovirus (CMV) prophylaxis. This agent is associated with efficacy concerns, toxicity, and emergence of ganciclovir resistance. Objective: To evaluate the incidence of high-dose acyclovir (HD-A) prophylaxis failure in seropositive aSOT recipients (R+). Methods: This was a retrospective, single-center study of R+ transplanted without lymphocyte-depleting induction between January 1, 2000, and June 30, 2013, discharged with 3 months of HD-A prophylaxis (800 mg 4 times daily). The primary outcome was incidence of prophylaxis failure. Secondary outcomes were incidence of biopsy-proven tissue-invasive disease and prophylaxis failure for each allograft subgroup. Results: A total of 1525 patients met inclusion criteria: 944 renal (RTX), 108 simultaneous pancreas-kidneys (SPK), 462 liver (LTX), and 11 pancreas (PTX) transplant recipients. The composite rate of HD-A prophylaxis failure was 7%; incidence of tissue-invasive disease was 0.4%. Failure rates were 4.5%, 6.1%, 11%, and 20% in the RTX, SPK, LTX, and PTX populations, respectively; tissue-invasive disease rates were 0.2%, 0%, 0.7%, and 10%. Failure occurred more frequently in the LTX and PTX populations (P < 0.0001, HR = 2.6; P = 0.04 HR = 4.4). Incidence of tissue-invasive disease was minimal and not different in the RTX, LTX and SPK populations (P = 0.34). When evaluating recipients of seronegative allografts (D−), the composite failure rate was 3.4% with no significant difference between allograft subgroups (P = 0.45). Conclusion: HD-A may be a reasonable prophylaxis alternative for D−/R+ recipients, in the absence of lymphocyte-depleting induction, if low incidence viremia is tolerable. Future studies are needed to determine the long-term impact of CMV viremia in the setting of this prophylaxis approach.

Keywords
antivirals, transplantation, prophylaxis, renal transplant, drug-related problems

Introduction
Cytomegalovirus (CMV) is the most common opportunistic infection following abdominal solid organ transplantation (aSOT).¹ Universal prophylaxis is a recommended preventive strategy.² Antiviral agents for prophylaxis are selected based on patient risk extrapolated from donor (D) and recipient (R) serostatus. Patients whose CMV status is D+/R− are at high risk, all R+ patients are moderate-risk, and patients without serological exposure (D−/R−) are considered low risk for CMV infection. Valganciclovir (VGC) is the preferred antiviral for prophylaxis in moderate- and high-risk patients; however, it is associated with significant cytotoxicity, particularly in the liver transplant population that is predisposed to functional hyposplenism.³⁴ Additionally, VGC dose reduction to avoid cytotoxicity has been associated with the emergence of CMV resistance.⁵ Recent literature suggests that patients stratified into a low-moderate risk subgroup may obtain sufficient prophylaxis with less toxic therapies, such as high-dose acyclovir (HD-A).⁶

Objective
The objective of this study was to evaluate the effect of HD-A (defined as acyclovir 800 mg orally 4 times daily, renally adjusted per manufacturer recommendations) on
incidence of CMV reactivation and disease in R+ recipients who did not receive lymphocyte-depleting induction at the time of transplant.

Methods

Design

Data were collected using retrospective analysis of electronic medical records at the University of Wisconsin Hospital. The UW is a 550-bed tertiary care, academic medical center with a well-established transplant program with 50 years of practice experience. This study was deemed exempt from review by the local institutional review board.

Patients

Patients were included if they received a primary kidney (RTX), simultaneous kidney-pancreas (SPK), liver (LTX), or pancreas (PTX) transplant at our institution within the defined study period (January 1, 2000, to June 30, 2013); were CMV IgG seropositive (R+) at the time of transplant; received induction therapy with an IL-2 receptor antagonist or no induction therapy; and were discharged on HD-A for a planned duration of 3 months. The study window was selected because of a relative stability in both CMV molecular diagnostics and protocolized immunosuppression during this 14-year period. Patients were excluded if they received aSOT at an outside institution, if they were less than 18 years old at the time of transplant, if they received multivisceral transplant or any other abdominal transplant combination other than kidney-pancreas, or if they received a transplant outside of the study period. Patients with CMV quantitative polymerase chain reaction (QNAT PCR of plasma) results from outside institutions were excluded to avoid interlaboratory variability, particularly at the breakpoint of negativity and positive-below-quantifiable measurements.

Outcomes

The primary outcome was incidence of prophylaxis failure. For the purpose of this study, overall prophylaxis failure was defined as any positive CMV QNAT PCR or biopsy-proven tissue-invasive disease between 14 and 100 days following aSOT. At our center, standardized protocol does not call for CMV PCR testing during universal prophylaxis unless there is clinical concern for CMV syndrome. Therefore, any detectable viremia was included to capture all occurrences. Secondary outcomes included incidence of biopsy-proven tissue-invasive disease alone as well as analysis of prophylaxis failure for each allograft subgroup in the first 3 months posttransplantation.

Statistical Analysis

Baseline patient characteristics were compared using the Kruskal-Wallis test for continuous variables and the χ² or Fisher’s exact test for categorical variables. Kaplan-Meier methods were used to estimate occurrence of prophylaxis failure. Both univariate and multivariable Cox proportional hazards models were used to evaluate factors potentially associated with prophylaxis failure.

Results

A total of 1525 patients met inclusion criteria: 944 RTX, 108 SPK, 462 LTX, and 11 PTX recipients. Baseline patient characteristics at the time of transplant based on allograft subgroup are reported in Table 1. The composite rate of HD-A prophylaxis failure was 7%, whereas the incidence of tissue-invasive disease was 0.4%. Rates of prophylaxis failure were 4.5%, 6.1%, 11%, and 20% in the RTX, SPK, LTX, and PTX populations, respectively. Incidence rates of tissue-invasive disease were 0.2%, 0%, 0.7%, and 10% in the same respective order (Table 2). The mean time to prophylaxis failure overall was 62.2 ± 22.8 days (median = 62 days; Figure 1). Prophylaxis failure was fairly well distributed across the study period, with a mean of 8.2 ± 4 cases/year (median = 7.5 cases/year). Failure occurred at nearly a 3-fold higher rate in the LTX population than the RTX population (P < 0.0001; hazard ratio [HR] = 2.6; 95% CI = 1.7-3.9) and a 5-fold higher rate in the PTX population than the RTX population (P = 0.03; HR = 4.9; 95% CI = 1.2-20.6). There was no significant difference in failure between the RTX and SPK groups (P = 0.5; HR = 1.4; 95% CI = 0.6-3.2). The incidence of tissue-invasive disease was minimal in all allograft types except in the PTX group (10%, P = 0.001). The incidence of tissue-invasive disease was not significantly different between the RTX, SPK, and LTX groups (P = 0.34).

At our center, VGC tolerance issues in the LTX subgroup are common. To elucidate risk factors associated with HD-A failure in this population, a multivariable analysis was conducted evaluating previously described and presumed risk factors, including primary liver disease, recipient of intraoperative blood products, donor CMV serostatus, and postoperative ventilation time. CMV D− was associated with a decreased risk of prophylaxis failure (P < 0.0001; HR = 0.18; 95% CI = 0.08-0.39). Primary liver disease and receipt of intraoperative blood products were not associated with prophylaxis failure. Risk of failure increased 1.05-fold for each week of mechanical ventilation postoperatively (P = 0.04).

Because of the significant degree of risk mitigation in the presence of a seronegative donor in the LTX group, the above analysis was completed for the entire D−/R+ cohort of patients. Rates of D− recipients did not differ significantly between groups (RTX, 44.4%; SPK, 54.3%; LTX, 46.2%; PTX, 18.2%; P = 0.076). In the D−/R+ patient population,
the rate of prophylaxis failure was 3.4%. Rates of prophylaxis failure were 2.3%, 3.8%, 4.9%, and 0% in the RTX, SPK, LTX, and PTX groups, respectively, and not significantly different between groups ($P = 0.45$). D+ was associated with an increased risk of prophylaxis failure compared with D− and continued to be most pronounced in the LTX group (RTX HR = 3.3, $P = 0.005$, 95% CI = 1.4-7.5; LTX HR = 5.5, $P < 0.001$, 95% CI = 2.6-12.5). These findings trended in the pancreas population as well but did not reach statistical significance (SPK HR = 2.9, $P = 0.1972$, 95% CI = 0.57-15.2). When the D+ population was excluded, there was no incidence of breakthrough viremia in the PTX subgroup.

**Discussion**

Universal prophylaxis with VGC is guideline endorsed for D+/R− and R+ transplant recipients of all allograft types; however, the majority of the literature supporting this recommendation is extrapolated from the high-risk D+/R− population.2,3 Additionally, tolerability in the way of cytotoxic effects and efficacy differences have been described between allograft types.7-9 Attempts to decrease cytotoxicity and its associated sequelae via dose reduction protocols have been associated with emerging ganciclovir-resistant CMV.6 Successful prophylaxis regimens that are less toxic and more cost-effective are needed. Acyclovir 400 mg twice daily is used in the CMV D−/R− population to prevent herpes simplex viral reactivation. Studies have suggested that higher doses of acyclovir, similar to that used for varicella zoster infection, may have some efficacy in preventing CMV.6 Indeed, the prodrug valacyclovir is endorsed by consensus guidelines as a prophylactic option for RTX.2,3 Acyclovir is not associated with the leukopenic effects of VGC, even in high doses, although appropriate hydration is required to prevent crystal nephropathy.

<table>
<thead>
<tr>
<th>Table 1. Demographics.</th>
<th>RTX</th>
<th>SPK</th>
<th>PTX</th>
<th>LTX</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>944</td>
<td>108</td>
<td>11</td>
<td>462</td>
<td></td>
</tr>
<tr>
<td>Recipient age (years)</td>
<td>53.5±12.99</td>
<td>41.2±8.25</td>
<td>42.8±9.3</td>
<td>55.1±9.06</td>
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<tr>
<td>Donor age (years)</td>
<td>44.5±14.47</td>
<td>30.9±13.32</td>
<td>30.7±12.03</td>
<td>42.7±16.69</td>
<td>0.0001</td>
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<tr>
<td>Recipient sex (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>59</td>
<td>36</td>
<td>27</td>
<td>59</td>
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</tr>
<tr>
<td>Recipient weight (kg)</td>
<td>81.2±18.5</td>
<td>69.7±14.07</td>
<td>73.7±16.73</td>
<td>85.6±21.21</td>
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<tr>
<td>Recipient race (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>73</td>
<td>86</td>
<td>100</td>
<td>90</td>
<td>0.0001</td>
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<tr>
<td>African American</td>
<td>13</td>
<td>12</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>11</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Donor CMV status (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>40.9</td>
<td>44</td>
<td>82</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>33.1</td>
<td>53</td>
<td>18</td>
<td>45</td>
<td>0.08*</td>
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<tr>
<td>Indeterminate</td>
<td>0.2</td>
<td>3</td>
<td>0</td>
<td>0.8</td>
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<tr>
<td>Unknown</td>
<td>25.8</td>
<td>0</td>
<td>0</td>
<td>1.7</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: CMV, cytomegalovirus; LTX, liver transplant; PTX, pancreas transplant; RTX, kidney transplant; SPK, simultaneous kidney-pancreas transplant.

*Indeterminate and unknown removed in calculation of $P$ value.

<table>
<thead>
<tr>
<th>Table 2. Prophylactic Failure by Allograft Subgroup.</th>
<th>All R+ (n = 1525)</th>
<th>RTX (n = 944)</th>
<th>SPK (n = 108)</th>
<th>PTX (n = 11)</th>
<th>LTX (n = 462)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>107 (7%)</td>
<td>42 (4.5%)</td>
<td>6 (6.1%)</td>
<td>2 (20%)</td>
<td>50 (11%)</td>
<td>0.000026</td>
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<tr>
<td>Tissue invasive</td>
<td>6 (0.4%)</td>
<td>2 (0.2%)</td>
<td>0 (0%)</td>
<td>1 (10%)</td>
<td>3 (0.7%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Tissue invasive (PTX outlier removed)</td>
<td>5 (0.3%)</td>
<td>2 (0.2%)</td>
<td>0 (0%)</td>
<td>—</td>
<td>3 (0.7%)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>All D+/R+ (n = 579)</th>
<th>RTX (n = 312)</th>
<th>SPK (n = 57)</th>
<th>PTX (n = 2)</th>
<th>LTX (n = 208)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>18 (3.2%)</td>
<td>7 (2.3%)</td>
<td>2 (3.8%)</td>
<td>0 (0%)</td>
<td>10 (4.9%)</td>
</tr>
</tbody>
</table>

Abbreviation: CMV, cytomegalovirus; D, donor; LTX, liver transplant; PTX, pancreas transplant; R, recipient; RTX, kidney transplant; SPK, simultaneous kidney-pancreas transplant.
The composite rate of HD-A prophylaxis failure was 7% in our R+ population. This is high considering that previously published literature reports of failure rates of standard-dose VGC (SD-VGC, 900 mg daily) are essentially nonexistent in RTX in the setting of good compliance, even in the D+/R− population. When HD-A was evaluated based on allograft subgroup, rates of failure in our RTX and SPK population seem to be similar to, if not lower than, previously published rates of failure of low-dose VGC in D+/R− (LD-VGC, 450 mg daily). Low-dose VGC has been investigated in an attempt to attenuate toxicity and cost concerns related to the use of SD-VGC; however, the association with the development of ganciclovir-resistant CMV may negate any potential benefits.

The use of HD-A prophylaxis could be considered in the RTX and SPK population over LD-VGC because rates of prophylaxis failure are similar and HD-A would not drive CMV ganciclovir resistance.

LTX are predisposed to VGC toxicity partly because of functional hyposplenism prior to transplantation and may benefit from alternative prophylaxis strategies to a greater degree than other allograft types. Additionally, rates of SD-VGC prophylaxis failure have been described to be as high as 4% after liver transplantation. The use of HD-A prophylaxis could be considered in the RTX and SPK population over LD-VGC because rates of prophylaxis failure are similar and HD-A would not drive CMV ganciclovir resistance.

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Interestingly, although the rate of prophylaxis failure was higher in the LTX subgroup, the rate of tissue-invasive disease was minimal and was not significantly different from the RTX and SPK subgroups. This raises the question of the clinical significance of breakthrough viremia in the R+ population. One of the main concerns associated with CMV infection are the indirect effects on long-term graft outcomes, which have been described, even in the setting of asymptomatic viremia. However, the preemptive monitoring approach to prophylaxis, which utilizes standardized laboratory monitoring in place of antiviral drug therapy, is guideline endorsed and has been associated with decreased risk of long-term graft complications, despite being associated with a high incidence of asymptomatic viremia. Reischig et al argue that favorable long-term outcomes of preemptive monitoring over universal prophylaxis with VGC are attributable to the reduction in late-onset disease and are attainable in the setting of close monitoring. Indeed, it has been shown that the presence of limited viral replication allows reconstitution of CMV-specific T-cell responses that result in prevention of late-onset CMV disease. Although this prophylaxis strategy could also solve issues related to tolerability and drug resistance, the logistics of preemptive monitoring are burdensome. The use of HD-A could fill the need for relatively nontoxic and non-labor-intensive prophylaxis strategies. Further studies are needed to elucidate the impact of low-level viremia in the setting of HD-A on long-term graft outcomes for R+ recipients.

This study had a number of limitations, particularly the retrospective, nonrandomized, and uncontrolled nature of the study design as well as the lack of a VGC comparator group. We attempted to control for these limitations to the extent possible. To ensure that all prophylaxis failure was captured, we had a very broad definition of CMV viremia, including any patient with any detectable virus even if below the limit of quantification. This may explain the high incidence of viremia in our study overall. However, the definition of end-organ disease was narrow, limited to biopsy-proven results, to encompass the entire clinical spectrum from both conservative to liberal disease definitions. By including all allograft subgroups, we corroborated previously published work by McKeen et al, who demonstrated the potential success of HD-A in a small population of LTX. Our study suggests that these findings may be applicable to all allograft subgroups.
Although there were significant differences in population demographics between subgroups, none of the demographics that have been previously shown to correlate with CMV disease (e.g., Hispanic race) were present in any population to a significant extent (Table 1). Unlike Singh et al, we did not find any association between primary disease and CMV infection in the LTX group, although we did find an association between prolonged mechanical ventilation time and prophylaxis failure, perhaps speaking to a degree of functional immunosuppression in ventilated patients. Indeed, one of the most important confounders between subgroups when considering prophylaxis failure or incidence of CMV infection is the degree of immunosuppression for each recipient. The initial step in treating CMV infection is to reduce the overall immunosuppressive burden to allow reconstitution of host immune responses. In our study, the patient-specific baseline immunosuppression regimen was not available; however, it is our institutional protocol in all allograft subgroups to utilize triple drug immunosuppression, including a calcineurin inhibitor, mycophenolate, and a glucocorticoid, for at least the first 3 months posttransplantation regardless of allograft type. Per institutional protocol the RTX, SPK, and PTX patients who met inclusion criteria for this study would have received basiliximab induction. Basiliximab induction is not standard practice in the LTX population. By limiting the study population to R+ patients receiving either an IL-2 receptor antagonist or no induction therapy, the impact of variation in baseline immunosuppressive burden in the first 3 months should be minimal. However, the selection of our low-moderate risk subgroup limits the clinical applicability of our results to this population alone. To avoid the need for inter-allograft comparisons, a control group of patients receiving VGC prophylaxis would be ideal. Unfortunately, our institutional protocol of HD-A for moderate-risk recipients precluded adequate sample size for the comparator.

Of note, although we did evaluate HD-A prophylaxis failure in R+ isolated-pancreas recipients, the sample size was small because of our institutional practice to utilize thymoglobulin induction in this allograft type. In this small group, both breakthrough viremia and end-organ disease occurred frequently and at a significantly higher rate than in the RTX population. However, when the D+ population was excluded, there was no incidence of breakthrough viremia. These results suggest that even in one of the most immunogenic abdominal organ transplants—isolated pancreas—comprehensive CMV risk stratification based on induction and donor/recipient serostatus can allow for the use of HD-A prophylaxis.

**Conclusion**

Because of the toxicity, cost, and association with ganciclovir-resistant CMV, alternative prophylaxis strategies to VGC are needed. HD-A is well tolerated and has demonstrated historical efficacy as a prophylaxis agent, even for D+/R− aSOT recipients. Our study indicates that HD-A may be an alternative for D−/R+ aSOT recipients, in the absence of lymphocyte-depleting induction, if low-incidence viremia is tolerable. Future studies are needed to determine the long-term impact of CMV viremia in the setting of this prophylaxis strategy, particularly as compared with those receiving the standard of care.

**Declaration of Conflicting Interests**

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