A Retrospective Comparison of the Safety and Efficacy of 3 months vs. 6 months Valganciclovir for Cytomegalovirus Prophylaxis in Renal Transplant Recipients

Investigators:

Ashley Masys, BScPharm, ACPR(c)
Pharmacy Resident, Pharmacy Department
The Ottawa Hospital, Ottawa, ON

Marie-Josée Deschênes, B. Pharm, M.Sc.
Clinical Pharmacist Specialist
The Ottawa Hospital, Ottawa, ON

Alyssa Dalton BScPharm, RPh, ACPR
Clinical Pharmacist
The Ottawa Hospital, Ottawa, ON

Dr. Todd Fairhead, MD, FRCP, M.Sc.
Nephrology Transplant Specialist
The Ottawa Hospital, Ottawa, ON

Pierre Giguere, B. Pharm, M.Sc.
Clinical Pharmacist Specialist
The Ottawa Hospital, Ottawa, ON
Conflict of interest: No conflict of interest to disclose.

Institution: The Ottawa Hospital, 501 Smyth Rd, Ottawa, ON K1H 8L6

Contact Information: Ashley Masys email: amasys@toh.ca
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Abstract

Background: Antiviral prophylaxis has been shown to be effective in reducing the risk of CMV disease in renal transplant recipients and reducing all-cause mortality in solid organ transplant recipients. Extending valganciclovir prophylaxis from 100 to 200 days was associated with a further reduction of CMV disease post-renal transplant. Longer valganciclovir prophylaxis can induce leukopenia, increase risk of other infections, and lead to alteration in immunosuppression, which may lead to rejection. It is currently unknown how the extension from 3 to 6-month prophylaxis with valganciclovir has impacted outcomes in our institution.

Methods: A retrospective chart review was conducted from January 1st 2010 to May 31st 2014 (followed until May 31st 2015). Patients were included if they had received a renal transplant and were prescribed 3 months (group 1; from January 2010 to December 2011) or 6 months (group 2; from January 2012 to May 2014) of valganciclovir and were at least 18 years of age at time of transplant.

Results: Both groups experienced high rates of leukopenia; 78% in 3-month prophylaxis group compared to 85% in 6-month prophylaxis group (P = 0.284). There is a statistically insignificant increase in patients who developed CMV viremia in 6-month prophylaxis group (19.8%) compared to the 3-month group (14.3%). There was one patient in 3-month prophylaxis group (2.0%) and three patients in 6-month prophylaxis group (3.5%) (P=0.633) who experienced acute rejection.

Conclusion: The change of TOH Renal Transplant Protocol to extend duration of CMV prophylaxis from 3 to 6 months for high-risk recipients did not result in statistically significant change in incidence of leukopenia; CMV viremia; or rates of graft rejection.
Introduction

Cytomegalovirus (CMV), a beta human herpesvirus, is one of the most common infections in solid organ transplant recipients. (1) In organ transplant recipients, CMV infection is defined as the “evidence of CMV replication regardless of symptoms.” (1) CMV disease is defined as the “evidence of CMV infection with attributable symptoms”. (1) CMV disease can be further categorized as a “viral syndrome with fever, malaise, leukopenia, and/or thrombocytopenia or as tissue-invasive disease”. (1)

At The Ottawa Hospital (TOH), donor and recipient CMV serology is determined prior to transplantation, as serostatus is a key predictor for infection and management. (1) Seronegative recipients who receive organs from seropositive donors (D+/R-) and patients who receive highly immunosuppressing treatment regimens, such as antilymphocyte therapy, are at the highest risk of CMV disease. (2)

Although the infection is usually asymptomatic or has mild symptoms, in the immunocompromised patient, CMV infection can lead to increased morbidity and mortality through reactivation of latent CMV infection or by acquiring a primary CMV infection. (3) Kidney transplant recipients may develop encephalitis, pneumonitis, hepatitis, uveitis, retinitis, colitis, opportunistic infections and/or graft rejection from CMV infection within four weeks after CMV replication (HR 1.58; 95% CI, 1.16-2.16, p=0.02). (4,5,6)

The use of prophylaxis is effective in reducing the risk of CMV disease in kidney transplant recipients (RR 0.42, 95% CI 0.31-0.57) and has been shown to be effective in reducing all-cause mortality in solid organ transplant recipients (RR 0.63, 95% CI 0.43-0.92). (2) Two approaches have been successful in preventing CMV disease in kidney transplant
recipients: preemptive prophylaxis and universal prophylaxis. (1) Preemptive prophylaxis requires regular blood work and laboratory monitoring to detect early CMV viral replication. Diagnostic assays are highly variable; therefore, clinical practice guidelines do not define the threshold for starting therapy.

Universal prophylaxis involves providing prophylactic antiviral medications, such as valganciclovir, to recipients at high-risk of CMV. Duration of prophylaxis for high-risk patients ranges between 3 to 6 months. The International Consensus Guidelines on the Management of Cytomegalovirus in Solid-Organ Transplantation recommends specific prophylaxis strategy based on donor and recipient serostatus. (1)

Short-course prophylaxis (≤3 months) has been associated with late-onset CMV infection (18-31%) and disease. (5) The IMPACT study, a randomized, double blind, controlled trial, compared the efficacy and safety of 200 days to 100 days of valganciclovir prophylaxis in high-risk kidney transplant recipients. Results showed that transplant recipients who received 200 days of prophylaxis developed fewer confirmed CMV disease in the 12 months post-transplant (16.1% vs 36.8%; p< 0.001) and CMV viremia at 12 months (37.4% vs 50.9%; p = 0.015). (7,8) There was no significant difference in the rate of biopsy-proven acute rejection and no significant difference in adverse events between the groups.

Leukopenia is a well-established side effect of valganciclovir. (9) The incidence of leukopenia in renal transplant recipients is 20.3% when receiving dose-adjusted valganciclovir in conjunction with mycophenolate mofetil and tacrolimus. (9) Results from the IMPACT trial showed a statistically insignificant higher rate of leucopenia in transplant recipients who received 200 days of prophylaxis compared to those who received 100 days of prophylaxis. (7)
Leukopenia associated with valganciclovir has led to both dose-reduction of anti-rejection medications and valganciclovir, putting patients at increased risk of graft-rejection. (10)

On average 75 renal transplants are performed annually at TOH. Approximately 30-50% of recipients will be started on valganciclovir (or ganciclovir) for CMV prophylaxis. In January 2012, following the IMPACT study results, TOH CMV prophylaxis protocol was changed to extend the duration of CMV prophylaxis from 3 to 6 months for renal transplant recipients. As per TOH protocol (Appendix II), D+/R- recipients, as well as, R+ patients receiving thymoglobulin will receive 6 months of oral valganciclovir, which is dose adjusted for glomerular function rate with Cockcroft-Gault formula.

The primary objective of this study is to retrospectively examine the impact of extending prophylaxis from 3 months to 6 months on the rate of leukopenia. This study also looked at the proportion of patients who experienced graft rejection, and CMV viremia in those receiving valganciclovir for 3 months vs 6 months within 12 months post-transplant. Furthermore, this study assessed the duration, frequency, and severity of leukopenia (time from first leukopenic event to recovery of WBC) in those receiving valganciclovir for 3 months vs 6 months within 12 months post-transplant.
Methodology

A retrospective chart review of renal transplant patients at TOH from January 1, 2010 to May 31, 2014 was conducted. Renal transplant recipients age 18 years or older at time of transplant from January 1, 2010 to Dec 31, 2011 (3 months valganciclovir) and January 1, 2012 until May 31, 2014 (6 months valganciclovir), prescribed valganciclovir (or IV ganciclovir) for CMV prophylaxis were included in the study. Patients transferred to another center within the first 12 months of transplant and recipients with early-onset graft loss requiring nephrectomy within 1 month of transplant were excluded.

This study was approved by The Ottawa Health Science Network Research Ethics Board. Data was collected from the TOH electronic medical record database, the Ambulatory Transplant Clinic Database, and hand-written paper medical charts at the renal transplant clinic.

In this study, leukopenia was defined as a white blood cell count less than $3.5 \times 10^6$ as per TOH laboratory value. This cut-off was also used in the IMPACT trial. CMV viremia was defined as PCR > 500 copies/mL based on expert consensus at TOH.

In order to better characterize leukopenia, different outcome measures were assessed. First, the time to first episode was collected to better characterize at which point in time leukopenia occurred in each group. Secondly, the nadir of each leukopenic episode was collected to better characterize the severity of leukopenia. Lastly, the number of episodes of leukopenia, the duration of each episode, and the time at which these occurred was calculated to further characterize severity and frequency of leukopenia.

In a prior preliminary observation of CMV prophylaxis with valganciclovir post renal transplant at TOH, the proportion of patients with leukopenia was 58% and 38% for 6-month
and 3-month prophylaxis, respectively. (11) Given that 150 patients are expected during the pre-determined sampling period, an alpha value preset at 0.05, the power to detect a 20% difference was estimated at 70%.

Proportions were compared using chi-square test. Cox regression analysis was performed to assess time to first leukopenia between groups. Student’s t-test or Wilcoxon analyses were used for comparisons of continuous variables where appropriate. All statistical tests were performed using SPSS v20 with a p value of less than 0.05 considered significant.
Results

A total of 145 high-risk patients were identified and 135 patients were included in the final analysis. Four patients were excluded because they were deceased within 6 months post-transplant; four were excluded because they were transferred to other clinics, and two were excluded because they had a nephrectomy. (See Figure 1) Overall, the two groups have similar baseline characteristics (Table 1). There appeared to be a trend towards higher use of thymoglobulin use in the 3-month group that was not statistically significant.

Both groups experienced high rates of leukopenia; 78% in the 3-month group compared to 85% in the 6-month group (P = 0.284). The estimated rates of leukopenia were 58% and 38% for 6-month and 3-month prophylaxis, respectively. The rates of leukopenia are significantly higher than the estimated rates.

Within one-year post transplant the highest number of leukopenic episodes was nine and the lowest nadir observed was $0.4 \times 10^9$ cells. Overall, the lowest nadirs were experienced in the five leukopenic episodes which ranged from $0.4-1.1 \times 10^9$ cells. The nadirs of the later leukopenic episodes were not as low and ranged from $2.0 – 2.8 \times 10^9$ cells. Patients who received 6 months prophylaxis had lower nadirs in the first three episodes compared to those who received 3 months prophylaxis; however, this was only significant in the second nadir episode.

There was no difference in number of episodes of leukopenia between 3 months and 6 months of prophylaxis ($-0.538 [-1.21, 0.135; p=0.340]$). There was no statistical difference in duration of leukopenia. The median duration of leukopenia was 3 days [IQR 9] in the 3-month group compared to 4 days [IQR 21] in the 6-month group for the 1st episode. (see Table 3)
Overall, subsequent episodes had a median duration that ranged from 14 to 20 days. There appears to be a trend towards shorter median duration of leukopenia amongst patients treated with 3 months of prophylactic therapy in most of the episodes as depicted by the wide interquartile range. (see Table 3)

No difference was observed with regards to time to first leukopenia (OR 0.945 (0.635, 1.406)). Most patients developed the first episode of leukopenia within the first 30 days of valganciclovir. Patients who received thymoglobulin were twice as likely to experience leukopenia (OR 1.895(1.215, 2.954; p=0.005)). Only thymoglobulin was found to be associated with the occurrence of the first leukopenia episode. (see Figure 3)

In the first three months’ post-transplant, patients who received only 3 months of CMV prophylaxis had more leukopenic episodes per patient compared to patients who had received 6 months of prophylaxis (0.76 vs 1.06). (see Table 4) As expected, three to six months following transplant, patients who received 6 months of valganciclovir had more leukopenic episodes per patient. Interestingly, there was no difference in number of leukopenic episodes per patient six to twelve months following transplant.

There is a no difference in patients who developed CMV viremia in the 6-month group (19.8%) compared to the 3-month group (14.3%). There was one patient in the 3-month group (2.0%) and three patients in 6-month group (3.5%) (P=0.633) who experienced acute rejection. (see Table 2)
Discussion

The optimal duration of CMV prophylaxis with valganciclovir is currently unknown. This study showed no statistical difference in rates of leukopenia, acute rejection or development of CMV between 3 and 6-month prophylaxis in high-risk patients receiving valganciclovir. As depicted in Table 4, 3-month prophylaxis reduces the chance of leukopenia after 3 months compared to 6 month prophylaxis.

Compared to the IMPACT trial (7), patients included in this study had much higher rates of leukopenia and less CMV viremia. The IMPACT trial reports 19% vs 4% of patients in the 200 day valganciclovir group compared to the 100 day group experienced leukopenia. (7) Despite using the same definition of leukopenia, the rate of leukopenia is dramatically lower than what our patients experienced. One hypothesis for our high rate of leukopenia is the inclusion of patients who received thymoglobulin. The IMPACT trial reports that 33% vs 32% of patients in the 200 day group compared to the 100 day group received leukopenia. Our patients had more than double the use of thymoglobulin. This could explain why we are seeing more than twice as much leukopenia compared to their study. In our study, thymoglobulin use appears to be the driving force for leukopenia in patients in both groups. The high use of thymoglobulin in our study may help to explain why the time to first episode was so short. Lastly, the rate of leukopenia was higher than the preliminary analysis.

The lowest nadirs were experienced in the first five leukopenic episodes. This could again be a reflection of the short-term effect of thymoglobulin. Patients who had multiple episodes of leukopenia (over 5 episodes), experienced higher nadirs in the later episodes.
Duration of leukopenia had a very large range. There was a trend for a shorter median duration in the 3-month prophylaxis group. Some episodes were very short and led to consecutives episodes, whereas others were very long. One episode lasted 146 days which was likely the reflection of lack of bloodwork monitoring.

The time to first episode of leukopenia was driven by use of thymoglobulin. Leukopenia arose quickly, almost 50% of patients at 30 days regardless of groups. Figure 3, illustrates that the time to first episode was driven by thymoglobulin.

Compared to the IMPACT trial (7), patients included in this study had much less CMV viremia. The IMPACT trial reported 37% vs 51% of CMV viremia in the 200 day group compared to the 100 day group. (7) The IMPACT trial included high risk (D+/R-) kidney allograft recipients, whereas we also included D+/R+ patients who received thymoglobulin. This could explain why there was less CMV viremia in our patient population. Our definition of CMV viremia is viral load > 500 copies/mL whereas the IMPACT trial defined CMV viremia as viral load > 600 copies/mL. The slight variation in definition is not thought to have impacted our results.

There are many possible confounding parameters when assessing leukopenia and CMV viremia rates. These include, but are not limited to patient compliance and lack of consistency with dose adjustments. Monitoring for leukopenia and CMV viremia at the TOH ambulatory renal transplant clinic is based on clinical judgement. Thus, different practitioners may select to do blood work on some patients more frequently than others thereby affecting the results.

There are several limitations to this retrospective chart review. Due to the retrospective nature of the study, as well as the fact that most data was collected from hand-written paper
charts, there may be inaccuracies in the data collection. The small sample size limits the ability to control for other variables that could potentially mask any differences.
Conclusion

The change of TOH Renal Transplant Protocol to extend duration of CMV prophylaxis from 3 to 6 months for high-risk recipients did not result in statistically significant change in incidence of leukopenia; CMV viremia; or rates of graft rejection. Shorter prophylaxis may reduce late onset leukopenia. Further analysis is required to explain the high rates of leukopenia experienced by high-risk renal transplant recipients at TOH.
Appendix I: Figures and Tables

Figure 1: Flow Diagram of Study Enrollment

- Exclusions
  - Transfers to other clinics ($N = 4$)
  - Nephrectomy ($N = 2$)
  - Deceased within 6 months post-transplant ($N = 4$)

145 patients identified

3-month prophylaxis ($N = 49$)  
6-month prophylaxis ($N = 86$)
Table 1: Patient baseline demographics

<table>
<thead>
<tr>
<th></th>
<th>3-month prophylaxis (N=49)</th>
<th>6-month prophylaxis (N=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>32 (65.3)</td>
<td>43 (50.0)</td>
</tr>
<tr>
<td><strong>CMV serology positive, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor</td>
<td>36 (81.8)</td>
<td>69 (81.2)</td>
</tr>
<tr>
<td>Recipient</td>
<td>31 (63.3)</td>
<td>43 (50.0)</td>
</tr>
<tr>
<td><strong>Donor status, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased donor</td>
<td>34 (69.4)</td>
<td>53 (61.6)</td>
</tr>
<tr>
<td><strong>Thymoglobulin administered, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37 (75.5)</td>
<td>58 (67.4)</td>
<td></td>
</tr>
<tr>
<td><strong>G-CSF administered, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (6.1)</td>
<td>5 (5.8)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2: Results

<table>
<thead>
<tr>
<th></th>
<th>3-month prophylaxis (N=49)</th>
<th>6-month prophylaxis (N=86)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia, n (%)</td>
<td>38 (77.6%)</td>
<td>73 (84.9%)</td>
<td>0.284</td>
</tr>
<tr>
<td>Rejection, n (%)</td>
<td>1 (2.0%)</td>
<td>3 (3.5%)</td>
<td>0.633</td>
</tr>
<tr>
<td>CMV viremia, n (%)</td>
<td>7 (14.3%)</td>
<td>17 (19.8%)</td>
<td>0.423</td>
</tr>
</tbody>
</table>
Figure 2: Time to first episode of leukopenia in patients using 3-month versus 6-month valganciclovir prophylaxis

Probability of having the first episode of leukopenia

OR 0.945 (0.635, 1.406)
Figure 3: Time to first episode of leukopenia in patients having received thymoglobulin or not

![Figure 3: Time to first episode of leukopenia in patients having received thymoglobulin or not](image)

Probability of having the first episode of leukopenia

OR 1.895 (1.215, 2.954)

- No thymoglobulin
- Thymoglobulin administered
Table 3: Median duration of leukopenia per group

<table>
<thead>
<tr>
<th>Episodes</th>
<th>3-month Prophylaxis</th>
<th>6-month Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>25th Percentile</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>7</td>
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<td>4</td>
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<td>5</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>
Table 4: Number of leukopenic episodes per patient

<table>
<thead>
<tr>
<th>Group</th>
<th>0-3 months post transplant</th>
<th>3-6 months post transplant</th>
<th>6-12 months post transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total number of leukopenic episodes</td>
<td>Episode per patient</td>
<td>Total number of leukopenic episodes</td>
</tr>
<tr>
<td>1</td>
<td>37</td>
<td>0.76</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>91</td>
<td>1.06</td>
<td>73</td>
</tr>
</tbody>
</table>
Appendix II: TOH Renal Transplant Protocol – CMV Prophylaxis

CMV prophylaxis

1. CMV positive donor to CMV negative recipient: valganciclovir 900 mg po daily (dose adjusted for GFR, see below). Use IV ganciclovir 5 mg/kg Q24h (dose adjusted for GFR, see below) if unable to tolerate oral medication or if has DGF requiring dialysis. Total duration: 6 months.

2. CMV positive recipient receiving Thymoglobulin: valganciclovir 900 mg po daily (dose adjusted for GFR, see below). Use IV ganciclovir 5 mg/kg Q24h (dose adjusted for GFR, see below) if unable to tolerate oral medication or if has DGF requiring dialysis. Total duration: 6 months.

Table 5: Intravenous Ganciclovir Dosing:

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>PROPHYLACTIC DOSE</th>
<th>TREATMENT DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 80</td>
<td>5 mg/kg Q24h</td>
<td>5 mg/kg Q12h</td>
</tr>
<tr>
<td>50-79</td>
<td>2.5 mg/kg Q24h</td>
<td>2.5 mg/kg Q12h</td>
</tr>
<tr>
<td>25-49</td>
<td>1.25 mg/kg Q24h</td>
<td>2.5 mg/kg Q24h</td>
</tr>
<tr>
<td>&lt; 25</td>
<td>0.625 mg/kg Q24h</td>
<td>1.25 mg/kg Q24h</td>
</tr>
<tr>
<td>DIALYSIS</td>
<td>0.625 mg/kg post-HD</td>
<td>1.25 mg/kg post-HD</td>
</tr>
</tbody>
</table>
Table 6: Oral Valganciclovir Dosing:

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>PROPHYLACTIC DOSE</th>
<th>TREATMENT DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60</td>
<td>900 mg daily</td>
<td>900mg PO BID</td>
</tr>
<tr>
<td>40-59</td>
<td>450 mg daily</td>
<td>450mg PO BID</td>
</tr>
<tr>
<td>25-39</td>
<td>450 mg q2days</td>
<td>450mg PO daily</td>
</tr>
<tr>
<td>&lt; 25</td>
<td>450 mg 2x per week</td>
<td>450mg PO Q2 days</td>
</tr>
<tr>
<td>DIALYSIS</td>
<td>100 mg 3x per week post- dialysis (oral solution)</td>
<td>200 mg 3x per week post- dialysis (oral solution)</td>
</tr>
</tbody>
</table>
References


