Cytomegalovirus Prophylaxis in Renal Transplant Patients: High Dose, Best Dose?

September 6th, 2019

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Disclosures
• No conflicts of interest to disclose

Objectives
• Understand the manifestations and implications of Cytomegalovirus (CMV) infection in solid organ transplant patients
• Summarize different strategies for preventing CMV
• Apply CMV prophylaxis study results to the clinical setting in dose decision making for renal transplant patients

Meet the patient...
• JC is a 40 year old male who is day 9 status post renal transplant. His past medical history is significant for diabetes mellitus, hypothyroidism, and polycystic kidney disease.

Meet the patient...
The decision is made to give JC prophylactic valganciclovir. Which regimen would you recommend?
A. 450 mg daily for 3 months
B. 450 mg daily for 6 months
C. 900 mg daily for 3 months
D. 900 mg daily for 6 months

What is Cytomegalovirus?
• Herpesviridae family double stranded DNA virus
• 60 to 70% of people in United States are exposed
• Immunocompetent patients are asymptomatic and latent infection is established
Acute Infection

- CMV establishes lifelong latency after primary infection
- Re-activation of latent infection can occur in immunocompromised patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>Acquired immunodeficiency syndrome</th>
<th>Solid organ transplant (SOT)</th>
<th>Bone marrow transplant</th>
</tr>
</thead>
</table>

Infection vs End Organ Disease

- **Infection**:
  - Evidence of CMV replication with virus isolation or detection of viral proteins or nucleic acid in any body fluid or tissue specimens
  - Often referred to as CMV viremia
  - Commonly diagnosed by serum polymerase chain reaction testing (PCR)

- **Disease**:
  - Evidence of CMV infection with attributable symptoms
  - Viral syndrome
  - End organ disease
  - Diagnosed with tissue biopsy
  - Presents with viral syndrome

Diagnostics

<table>
<thead>
<tr>
<th>Variables</th>
<th>pp65 antigenemia assay</th>
<th>CMV PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Processing</td>
<td>Polymorphonuclear cells</td>
<td>Blood or other body fluids</td>
</tr>
<tr>
<td>Turnaround time</td>
<td>6 hours</td>
<td>2-3 hours</td>
</tr>
<tr>
<td>Prevention of Disease</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Units of measurement</td>
<td>Number of CMV infected cells per total number of cells</td>
<td>IU/mL</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>98%</td>
<td>95%</td>
</tr>
<tr>
<td>Specificity</td>
<td>98%</td>
<td>95%</td>
</tr>
<tr>
<td>Advantages</td>
<td>Rapid diagnosis, assess severity</td>
<td>Rapid diagnosis, assess severity, risk of CMV disease</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Subjective interpretation of results, not useful in leukopenia</td>
<td>Wide viral threshold for predicting CMV disease, no standardization, may detect latent CMV</td>
</tr>
</tbody>
</table>

Which transplant patients are at the highest risk for CMV?

- Degree of immunosuppression with lymphocyte depleting agents
- Allograft rejection
- Serostatus

<table>
<thead>
<tr>
<th>Serostatus</th>
<th>D+/R-</th>
<th>D+/R+</th>
<th>D-/R+</th>
<th>D-/R-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viremia</td>
<td>11.9%</td>
<td>4.6%</td>
<td>0.2%</td>
<td>0%</td>
</tr>
<tr>
<td>Disease</td>
<td>23.8%</td>
<td>12.0%</td>
<td>4.2%</td>
<td>2.8%</td>
</tr>
</tbody>
</table>

Incidence of SOT CMV Disease without Prophylaxis

- **Direct**
  - End organ disease
  - Allograft rejection

- **Indirect**
  - Bacteremia
  - Invasive fungal infection
  - Epstein-Barr Virus associated malignancy
  - Vascular thrombosis
  - Diabetes mellitus

Sequela of CMV Infection

Available at: https://online.seterra.com/en-an/vgp/3801.
Preventive Strategies

- **Universal prophylaxis**
  - Valganciclovir (VGCV) to all patients or a subset at risk for three to six months
  - CMV viral load check weekly to detect replication
  - Treatment dose VGCV if viral load meets threshold

- **Preemptive therapy**
  - CMV viral load check weekly to detect replication for eight to twelve weeks after the end of prophylactic therapy

- **Surveillance after prophylaxis**
  - CMV viral load check weekly to detect replication for eight to twelve weeks after the end of prophylactic therapy
  - VGCV 900 mg twice daily for 21 days as treatment
  - Hospitalization $625 ± 2446
  - Provider time $438 ± 20
  - CMV PCR $1343 ± 297

Guidelines

Management of CMV in SOT

- **Preventive Strategies**
  - Prophylaxis may be preferred in donor and/or recipient seropositive patients whose risk for CMV may be increased
  - A longer duration of prophylaxis (ie, 6 months) may be more effective (weak, moderate LOE)
  - Prophylaxis may be preferred in donor and/or recipient seropositive patients whose risk for CMV may be increased

- **Surveillance**
  - Use of surveillance after prophylaxis may be considered in patients at increased risk for post-prophylaxis CMV disease for eight to twelve weeks after prophylaxis

Comparison of CMV Prophylaxis Strategies

- **Outcomes**
  - Safety
  - Prophylaxis
  - Preemptive

- **Prevention of Disease**
  - Good
  - Good

- **Resistance**
  - Uncommon
  - Uncommon

- **Prevention of other herpes viruses**
  - Herpes simplex virus, varicella zoster virus
  - Does not prevent

- **Prevention of rejection**
  - May prevent
  - Unknown

- **Graft survival**
  - May improve
  - May improve

- **Cost**
  - Increased drug cost
  - Increased laboratory cost

CMV Prophylaxis Options

- **Valganciclovir, ganciclovir, and valacyclovir can all be used in renal transplant patients**
- **VGCV is most commonly used**

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Treatment Dose</th>
<th>Maintenance/Preventive Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60</td>
<td>900 mg every 12 h</td>
<td>900 mg once daily</td>
</tr>
<tr>
<td>40 - 59</td>
<td>450 mg every 12 h</td>
<td>450 mg once daily</td>
</tr>
<tr>
<td>25 - 39</td>
<td>450 mg once daily</td>
<td>450 mg every 2 days</td>
</tr>
<tr>
<td>10 - 24</td>
<td>450 mg every 2 days</td>
<td>450 mg twice weekly</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>350 mg 3 times a week after HD</td>
<td>100 mg 3 times a week after HD</td>
</tr>
</tbody>
</table>
### Valganciclovir Pharmacokinetics

**Absorption**
- Well absorbed
- High fat meal increases AUC by 30%

**Distribution**
- 0.7 L/kg

**Metabolism**
- 80% bioavailable
- Converted to GCV by intestinal mucosal cells
- Half-life: 5 hours
- 80% excreted in urine

**Elimination**
- Half-life: 6 hours
- 80% excreted in urine
- AUC increases by 30%

**Adverse Effects**
- Anemia 31%
- Thrombocytopenia <22%
- Neutropenia 3-19%
- Increased SCr 12-50%
- Tremor 12-28%

In an international survey on CMV management, 24% of respondents acknowledged using low dose VGCV prophylaxis in high-risk patients.

### Low Dose vs Standard Dose Pharmacokinetics

<table>
<thead>
<tr>
<th>AUC 0-24 hrs (mcg/hr/mL)</th>
<th>VGCV 450 mg daily</th>
<th>VGCV 900 mg daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>30</td>
<td>60</td>
<td>120</td>
</tr>
<tr>
<td>60</td>
<td>120</td>
<td>240</td>
</tr>
</tbody>
</table>

### Controversies in CMV Prophylaxis

**Which strategy is appropriate?**
- Prophylaxis vs preemptive

**Which dose is appropriate?**
- 900 mg daily vs 450 mg daily

**Do doses need to be renally adjusted?**
- Dose of 450 mg daily in CrCl <60 mL/min

Increased risk of breakthrough infection among CMV D+/R- renal transplant recipients receiving 450 mg VGCV prophylaxis.

### Introduction

Design: Single-center, retrospective cohort study

**Objective:** Evaluate prevalence of CMV infection and disease in D+/R- renal transplant patients receiving high dose vs low dose VGCV prophylaxis.

**Endpoints:** Rates of CMV infection and disease

**Inclusion Criteria:**
- ≥ 18 years of age
- D+/R- serostatus
- Induction with ATG
- Standard maintenance immunosuppressive therapy

**Intervention:**
- VGCV 450 mg vs 900 mg daily for six months

**Monitoring:**
- CMV screening, if symptomatic or abnormal labs using PCR based assays

**Definitions:**
- Infection: active viral replication as detected by PCR
- Disease: infection with attributable symptoms to CMV
- Late onset (LO) CMV: any case of CMV infection or disease after discontinuation of prophylaxis

### Results

- Median age, years (IQR): 53.2 (33.9 – 58.8) vs 54.2 (46.8 – 58.7)
- Deceased donor, n (%): 29 (64.4) vs 35 (77.8)
- Mean follow up in days: 320 (103) vs 357 (25.5)
- Mean tacrolimus trough at 30 days: 9.7 ± 2.3 vs 10 ± 2.4

*Goal tacrolimus level with thymoglobulin induction at day 30: 5 to 10 ng/mL

**SD:** standard deviation

### Conclusion


Introduction

Methods

Results

Conclusion


Rates of CMV Infection and Disease

VGCV 450 mg

VGCV 900 mg

p = 0.18

40%

26.7%

Primary Composite

Components

450 mg VGCV, n = 45

900 mg VGCV, n = 45

p value

Breakthrough infection, n (%) 6 (13.3) 1 (2.2) 0.11

Late onset infection or disease, n (%) 12 (26.7) 11 (24.4) 0.86

• No difference
  • Overall survival or graft loss at six and twelve months
  • GCV resistant CMV infection
  • Acute rejection in first six months
  • Patients on 900 mg VGCV were more likely to experience leukopenia (75% vs 44.4%, p <0.01)

Conclusions

• Increased rates of breakthrough infection and a single case of GCV-resistant infection in patients taking 450 mg VGCV was observed
• VGCV 900 mg was associated with increase risk of leukopenia and rejection compared with VGCV 450 mg

Comments

• 450 mg group had significantly shorter follow up
• Conclusions were drawn from non-significant findings
• Higher rates of leukopenia compared to literature
• Trial stopped prior to reaching power due to identified trends
• No routine screening
• No PCR diagnostics definition

Evaluation of VGCV 450 mg versus 900 mg for prevention of CMV disease in D+/R- renal transplant recipients


Introduction

Methods

Results

Conclusion

Design

Multicenter, retrospective cohort study

Objective

Compare the efficacy and safety of six months of VGCV 450 mg with 900 mg in high risk renal transplant patients

Endpoints

12 month CMV disease rates

Inclusion Criteria

18 to 75 years old, D+/R-, induction with ATG or interleukin-2 antagonist, maintenance on tacrolimus and mycophenolic acid

Intervention

VGCV 450 mg vs 900 mg daily for 6 months

Monitoring

CMV screening if symptomatic or abnormal labs using PCR based assays

Definitions

Disease: viral syndrome or tissue invasive
  Viral syndrome: CMV viremia PCR or pp65 and one of the following: >38°C, flu symptoms, leukopenia on 2 successive measurements
  Tissue invasive: presence of localized CMV infection in a biopsy along with symptoms of organ dysfunction

BPAR: biopsy proven acute rejection
1. Introduction

Multivariate logistic regression
- Low dose VGCV prophylaxis had a 57% lower risk of developing CMV disease compared to those receiving high dose
- No difference in rates of BPAR, graft loss, patient survival, opportunistic infection, and new onset diabetes mellitus after transplantation
- Higher rates of leukopenia in the 900 mg group reported at months 5 and 6 (20.6% vs 9.9; \( p = 0.034 \)), but no differences in grades of leukopenia
- Using low dose VGCV can provide $14,000 in savings per patient

Components of Primary Outcome

<table>
<thead>
<tr>
<th>Component</th>
<th>450 mg VGCV, n = 19</th>
<th>900 mg VGCV, n = 26</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral syndrome, n (%)</td>
<td>13 (68.4)</td>
<td>24 (92.3)</td>
<td>0.055</td>
</tr>
<tr>
<td>Tissue invasive disease, n (%)</td>
<td>6 (31.6)</td>
<td>2 (7.7)</td>
<td>0.055</td>
</tr>
</tbody>
</table>

Conclusions

- Low and standard dose VGCV regimens provide similar efficacy in preventing CMV disease in D+/R- renal transplant patients
- VGCV 450 mg may have a higher risk of tissue invasive disease than 900 mg
- VGCV 900 mg is associated with significantly lower white blood cell counts at months five and six, but no difference in rates of discontinuation observed

Comments

- One year follow up
- Did not report rates of CMV viremia
- VGCV dose reductions due to adverse events were not recorded
- Trend towards higher breakthrough CMV on 900 mg dose after discontinuation
- D+/R- only

High rates of inappropriate VGCV dosing for CMV prophylaxis after renal transplantation

Design
- Retrospective, single center cohort study

Objective
- Evaluate routine prescribing frequency for all GFR classes in relation to under dosing/recommended dosing or over dosing due to current recommendations

Endpoints
- Occurrence of CMV viremia and infection at days 30 and 60

Inclusion Criteria
- > 18 years old renal transplant patients

Intervention
- VGCV 900 mg daily

Definitions
- CMV viremia: CMV PCR > 750 copies/mL
- CMV infection: positive PCR with clinical symptoms
Introduction

All patients, n = 635

Under dosing, n = 426

Recommended Dose, n = 137

Overdosing, n = 43

Mean age, years ± SD
51 ± 14
49 ± 14
54 ± 13
55 ± 13

Decreased donor, n (%) 465 (73.2) 299 (71.4) 106 (77.4) 37 (86.0)

D+/R-, n (%) 103 (16.2) 75 (17.9) 21 (15.9) 5 (11.6)

Mean prophylaxis duration, days ± SD
129 ± 68
127 ± 67
134 ± 69
135 ± 71

Mean prophylaxis daily dose, mg ± SD
248 ± 152
227 ± 119
315 ± 210
256 ± 160

Basiliximab indication therapy, n (%) 468 (73.7) 347 (81.5) 91 (66.4) 29 (67.4)

Methods

Results

Conclusion

**Design**
Retrospective, single center cohort study

**Objective**
Investigate if, and to what extent, different dosages of (val)ganciclovir prophylaxis affect the risk of breakthrough during prophylaxis.

**Endpoints**
CMV breakthrough within 90 days based on prophylactic score.

**Inclusion Criteria**
≥18 years old with heart, lung, liver, or kidney transplants anticipated to receive prophylaxis for at least 90 days.

**Intervention**
VGCV 450 mg every other day for renal transplants; VGCV 900 mg daily for all other SOT.

**Monitoring**
Once monthly CMV PCR for 90 days.

**Definitions**
CMV breakthrough: CMV infection within the first 90 days post transplant.

CMV infection: 2 consecutive PCRs > 273 IU/mL within 14 days of each other or 1 CMV PCR > 2,730 IU/mL.

**Results**

<table>
<thead>
<tr>
<th>Breakthrough, n=38</th>
<th>No breakthrough, n=547</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median day 15 prophylaxis score, IQR</td>
<td>78.7</td>
<td>100.3</td>
</tr>
</tbody>
</table>

- Trend toward increased rates of prophylaxis breakthrough rates with lungs and kidneys over hearts and livers (p = 0.067)
- For every 10% more days spent during follow up with a prophylaxis score <90, the risk of breakthrough infection increased by 15% (HR, 1.15; 95% CI, 1.07 to 1.24; p <0.01)
- D+/R- serostatus patients were more likely to develop a breakthrough infection compared with D+/R+ or D-/R+ (16.1% vs 4.6% vs 2.2%, p <0.01)

**Conclusions**

- SOT patients receiving prophylactic doses of VGCV below manufacturer recommended are at an increased risk of experiencing prophylaxis breakthrough
- Low-dose VGCV may be suboptimal in preventing breakthrough CMV infection in solid organ transplant patients

**Comments**

- Definition of breakthrough
- Various SOT types
- Monitoring of immunosuppressants not recorded
- Follow up period of 90 days
- No value at 90 days
- Baseline dose for renal transplant patients

**Applying to Clinical Practice**

<table>
<thead>
<tr>
<th>Renal Transplant Recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>D+/R-</td>
</tr>
<tr>
<td>D+/R+</td>
</tr>
<tr>
<td>D-/R+</td>
</tr>
<tr>
<td>D-/R-</td>
</tr>
</tbody>
</table>

Close follow up for renal dose adjustment is recommended.
Meet the patient…

JC is a 40 year old male who is day 9 status post renal transplant. His past medical history is significant for diabetes mellitus, hypothyroidism, and polycystic kidney disease.

Vitals:
- Temp: 99.5°F
- HR: 94 bpm
- BP: 109/64 mmHg
- RR: 18
- Weight: 75 kg

Serostatus: D-/R+*

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Creatinine (mg/dL)</th>
<th>Estimated Creatinine Clearance (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>1.5</td>
<td>125</td>
</tr>
</tbody>
</table>

*D/R: donor/recipient

The decision is made to give JC prophylactic valganciclovir. Which regimen would you recommend?

- A. 450 mg daily for 3 months
- B. 450 mg daily for 6 months
- C. 900 mg daily for 3 months
- D. 900 mg daily for 6 months

Conclusions

- Low dose CMV prophylaxis may be appropriate in D+/R+ and D-/R+ renal transplant patients
- Standard dose VGCV should be continued for D+/R- renal transplant patients
- There is not sufficient data to apply these findings to other SOT patients

Acknowledgements

- Dr. Andrew Hunter, PharmD, BCPS (AQ-ID)
- Dr. Dusten Rose, PharmD, BCIDP, AAHIVP
- Dr. Terry Jaso, PharmD, BCPS (AQ-ID)
- Dr. Julia Sapozhnikov, PharmD

Questions?
Appendix A: Abbreviations

CMV: cytomegalovirus
D/R: donor/recipient serostatus
SOT: solid organ transplant
PCR: polymerase chain reaction
VGCV: valganciclovir
AUC: area under the curve
GCV: ganciclovir
SCr: serum creatinine
ATG: anti-thymocyte globulin
LO CMV: late onset CMV
SD: standard deviation
IQR: interquartile range
BPAR: biopsy proven acute rejection
GFR: glomerular filtration rate
CG-CrCl: Cockcroft-Gault creatinine clearance
Appendix B: Gabardi, et al. Figure

Kaplan-Meier plot of time to CMV disease up to month 12 after transplantation
Appendix C: Rissling, et al. Figures

Different dosing frequencies according to CG-CrCl on day 30

VGCV dosing frequency in relation to CrCl on day 30 post transplant
Appendix D: Khurana, et al. Figure

Average prophylaxis scores for renal transplant patients from days 15 to 89