Management of CMV: Immune Monitoring, New therapies, Vaccines

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Disclosure

• Consulting, Honoraria or research support
  – Astellas, Roche, Oxford Immunotec, Merck
Objectives

• Immune monitoring for CMV
• Antiviral resistance and new treatments
• CMV vaccine
Management of CMV in the Modern Era

- CMV disease risk is highest in donor-positive, recipient-negative (D+/R-) serostatus SOT patients who lack cellular and humoral immunity to CMV.
- CMV disease risk is lowest in the D-/R- setting, provided these patients are given CMV negative blood or leukodepleted blood products.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Donor (D) / Recipient (R) Serologic Status (+/-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>D+/R-</td>
</tr>
<tr>
<td>Intermediate*</td>
<td>D+/R+, D-/R+</td>
</tr>
<tr>
<td>Low</td>
<td>D-/R-</td>
</tr>
</tbody>
</table>

* D+/R+ generally at higher risk than D-/R+

CMV PREVENTION: UNIVERSAL PROPHYLAXIS

- Antiviral therapy from the time of transplant to all patients or a subgroup of patients

- This strategy mostly used in high risk (D+/R-) or R+ patients who receive polyclonal ab induction
CMV PREVENTION: PRE-EMPTIVE THERAPY

CMV disease

TEST

initiate pre-emptive therapy

0 4 8 12 weeks
Pros and Cons of Prevention Strategies

Prophylaxis (GCV)
- Easy to administer
- Leukopenia
- Cost
- Optimum duration of prophylaxis unknown
- Late disease still occurs after prophylaxis

Pre-emptive
- Less pill burden, side effects, cost
- Compliance with routine monitoring
- Some patients have rapid doubling times for CMV (may develop disease before viremia detection or before antivirals started)
- Immunomodulatory effects of CMV
TIME to CMV DISEASE UP to 6 MONTHS (n=364)

364 D+/R- SOT patients

GCV vs VGCV

• May present with atypical symptoms (no fever – malaise, fatigue); diagnosis can be missed
• Patient may not be followed by primary center or may not be followed as closely

How do we deal with late onset disease?

**OPTIONS**

- Do nothing – accept the risk of late onset disease and treat as it arises

- Prolong prophylaxis – Is more better?
  - ? push disease further, high NNT

- Use better prophylaxis?

- Careful virologic monitoring of high-risk patients after completing prophylaxis
Humar et al. Am J Transpl 2010
Monitoring after prophylaxis: hybrid strategy

CMV disease

- Compliance
- Rapid increase in viremia
- Delay in starting therapy
- Does everyone require monitoring?

0 4 8 12 months

TEST = + + + + + + + + + = =

Prophylaxis

initiate pre-emptive therapy
Case

• 60 y/o man post DD liver transplant for EtOH cirrhosis, CMV D+/R- and about to finish 3 months antiviral prophylaxis.

• Could we use immune monitoring to predict his risk of CMV disease (after prophylaxis)?
Immune Monitoring: personalizing CMV prevention
Host response to CMV: the basis for immune monitoring

**Innate immunity**
- TLR-2 / TLR-4
- Complement deficiency
- Mannose binding Lectin Deficiency
- Activated NK

**Adaptive immunity**
- Neutralizing antibody production
- CD4+ T cells
- Cytotoxic CD8 T-cells
- TNF-α
- IL-2
- IFN-γ

Host Response to CMV
Cell-mediated immune response to CMV

Proteins studied

Strength of reactivities detected

Strong reactivity

Subdominant reactivities

Occasional weak reactivities

pp65 (UL83)
pp50 (UL44)
IE-1 (UL122)
gB (UL55)
IE-2 (UL123)
gH (UL75)
pp28 (UL99)
pp150 (UL32)
pp71 (UL82)
US2
US3
US6
US11
UL16
UL18

Gandhi MK, Lancet ID 2004; 4: 725
Quantiferon-CMV Assay (ELISA based)

- **Peptides**
  - Quantiferon-CMV assay: CMV epitopes (peptides) restricted through various HLA class I alleles

- **Quantiferon assay**
  - Part 1: overnight stimulation of blood with CMV CD8+ T-cell synthetic peptide epitopes (2 μg/mL of each of 22 peptides)
  - Part 2: Quantification of IFN-γ production by standard ELISA.
CMI: STUDY PROTOCOL

n=127 D+/R- patients [Canada, US, Europe]

Manuel et al. CID 2013
<table>
<thead>
<tr>
<th></th>
<th>Total (n=127)</th>
<th>CMV disease (n=29)</th>
<th>No CMV disease (n=98)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of transplant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>68 (53%)</td>
<td>12 (41%)</td>
<td>56 (57%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Kidney-pancreas</td>
<td>10 (8%)</td>
<td>2 (7%)</td>
<td>8 (8%)</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>27 (25%)</td>
<td>7 (24%)</td>
<td>20 (20%)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>14 (11%)</td>
<td>5 (17%)</td>
<td>9 (9%)</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>4 (3%)</td>
<td>1 (3%)</td>
<td>3 (3%)</td>
<td></td>
</tr>
<tr>
<td>Other*</td>
<td>4 (3%)</td>
<td>2 (7%)</td>
<td>2 (2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Induction therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>17 (13%)</td>
<td>4 (14%)</td>
<td>13 (13%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>60 (47%)</td>
<td>11 (38%)</td>
<td>49 (50%)</td>
<td></td>
</tr>
<tr>
<td>Thymoglobulin</td>
<td>47 (37%)</td>
<td>14 (48%)</td>
<td>33 (34%)</td>
<td></td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>3 (2%)</td>
<td>0 (0%)</td>
<td>3 (3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>101 (79%)</td>
<td>24 (82%)</td>
<td>77 (77%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>113 (89%)</td>
<td>25 (89%)</td>
<td>88 (89%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>9 (7%)</td>
<td>4 (14%)</td>
<td>5 (5%)</td>
<td>0.10</td>
</tr>
<tr>
<td>MMF/MPA</td>
<td>103 (81%)</td>
<td>23 (79%)</td>
<td>80 (81%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>7 (5%)</td>
<td>1 (3%)</td>
<td>6 (6%)</td>
<td>0.57</td>
</tr>
<tr>
<td>mTOR inhibitors</td>
<td>8 (6%)</td>
<td>3 (10%)</td>
<td>5 (5%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Other</td>
<td>3 (2%)</td>
<td>1 (3%)</td>
<td>2 (2%)</td>
<td>0.66</td>
</tr>
</tbody>
</table>
CMV D+/R-

Time Post-Transplant

Antiviral prophylaxis

D/C Prophylaxis

Prolong Prophylaxis or Monitor more closely

Monitor CMI
Clinical Scenarios where CMV T-cell immunity assays can be useful

• D+/R- patient at the end of 3-6 months prophylaxis
  - Should prophylaxis be continued?

• Patient with low-level viremia below threshold for preemptive therapy
  - Should therapy be started?

• Patient recovered from CMV disease
  - Should further monitoring be done?
  - Should there be secondary prophylaxis?
**Summary**

- Assays aimed at measuring T-cell immunity may prove useful for many clinical scenarios.

- Assays need to be further developed for the clinical setting.

- CMI does not replace viral load testing but could provide more tailored management and prevention strategies in the individual patient.
Case 2

- 46 y.o. woman 6 mos post-DLTx
- CMV D+/R- received 6 months of Valganciclovir prophylaxis
- On MMF 1000mg bid, Tacrolimus, Prednisone
- CMV viremia at month 8 – 25,000 IU/mL, started on Ganciclovir
- Initial decrease to 10,000 IU/mL, then increase to 16,000 IU/mL
- Reduced MMF, increased dose of GCV 10mg/kg bid but unable to tolerate d/t leukopenia
- Unable to tolerate foscarnet d/t renal insufficiency
- Started on CMX001 100mg twice weekly
CMX001 mutation: A594T
CMV Antiviral Resistance

• Suspect when increasing or high-level CMV viremia or progressive clinical disease is observed during prolonged antiviral therapy.

• Risk factors for drug resistance are:
  – Prolonged low-dose oral prophylaxis
  – Increased intensity of immunosuppression
  – A lack of prior CMV immunity (D+/R-)
  – Lung transplantation

• Resistance risk:
  – Boivin (2004) reported ~ 1%-2% risk with 3 months prophylaxis.
  – May be higher in sub-populations, Limaye et al and Li et al reporting rates of 5% to 10% in D+/R- lung transplant recipients.
GCV Mechanism of Action

GCV

GCV-MP

GCV-DP

GCV-TP

Viral Protein Kinase (UL97)

Cellular Enzymes

Inhibits Viral DNA Polymerase (UL54)

Extracellular

Intracellular
UL97 functional domains and resistance mutations

**Codon**

337 345 357 453 481 462 483 520 574 527 579 707

- **Kinase subdomain**
- **Putative function**
  - ATP binding
  - P-Transfer
  - Substrate binding

**UL97 variants show different levels of GCV resistance**

<table>
<thead>
<tr>
<th>Amino Acid Change</th>
<th>GCV IC&lt;sub&gt;50&lt;/sub&gt; ratio</th>
<th>Level of GCV Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>M460V/I, H520Q, A594V, L595S, C603W</td>
<td>5-10</td>
<td>Higher level resistance, Alternate therapy indicated</td>
</tr>
<tr>
<td>C592G, A594T</td>
<td>2-3</td>
<td>Low level resistance</td>
</tr>
<tr>
<td>A591V, N597D</td>
<td>&lt;2</td>
<td>Insignificant resistance</td>
</tr>
<tr>
<td>Q449K, H469Y, D605E</td>
<td>&lt;1.5</td>
<td>Baseline polymorphisms, No GCV resistance</td>
</tr>
</tbody>
</table>

**Most common UL97 mutations detected in GCV-resistant CMV isolates**

1. Frequency in set of 79 GCV-resistant CMV isolates
GCV/FOS/CDV Mechanism of Action

Viral Protein Kinase (UL97)

Inhibits Viral DNA Polymerase (UL54)

FOSCARNET

CIDOFOVIR

Extracellular

Intracellular
CMV Resistance: Proposed Treatment Algorithm

At least 2 weeks of adequate dose of ganciclovir with increasing or unchanged viral load

Reduce immunosuppression. Send for genotypic resistance testing

Severe CMV disease

Switch to or add foscarnet at full dose

Non-severe CMV disease

Increase ganciclovir dose up to 10 mg/kg BID or full dose foscarnet

Alter therapy based on genotypic resistance testing and clinical response. Adjunctive unproven therapy may be required.

Razonable and Humar; AST Guidelines. Am J Transplant 2013
NEW Antiviral Options

- Letermovir (AIC246; Merck)
- Maribavir (ViroPharma)
- CMX-001 (Brincidofovir; Chimerix)
Letermovir (AIC246)

- **po (once daily)**

- CMV viral terminase enzyme inhibitor (ie inhibits cleavage and packaging of DNA into capsids)

- No significant adverse events noted in studies
**Letermovir Phase II Kidney Study**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Viral Clearance at day 15</th>
<th>No Viral Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letermovir 40mg BID (n=4)</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Letermovir 80mg QD (n=8)</td>
<td>28.6%</td>
<td>71.4%</td>
</tr>
<tr>
<td>Standard of Care (n=7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Graph:**
- **Log change in CMV DNA copies**
- **40 mg BID (n=7)**
- **80 mg QD (n=9)**
- **SOC (n=9)**

*Stoelben et al., Transpl Int 2014*
Maribavir

- po drug
- Inhibits UL97 kinase (viral encapsidation and nuclear egress)
- No bone marrow suppression
Maribavir for CMV prophylaxis in D+/R- liver transplant

- RCT of GCV po 1g TID vs. Maribavir 100mg BID
- 307 patients
- Any CMV (disease or infection) at 100 days: 20% vs. 60%, p<0.0001
- Any CMV at 6 months: 53% vs. 72%, p=0.005

Winston et al., AJT 2013
Maribavir – future indications?

• Higher dose studies: 400-1200mg BID

• Refractory or resistant CMV
**DNA POLYMERASE INHIBITOR CMX001**

- CMX001 is a lipid conjugated cidofovir (po drug given twice weekly)

- After po dose absorbed in SI, penetrates target cells before being cleaved to free the antiviral, cidofovir

- Aim – increase potency, decrease toxicity and allow for oral formulation

CMV, adenovirus, BK, other herpesviruses
Randomized, Double-Blind, Placebo-Controlled Trial of CMX001 for CMV Prevention after Allogeneic SCT

- Evaluate ability of different doses of CMX001 to prevent or control CMV infection in CMV-seropositive allogeneic SCT recipients
- 27 transplant centers in USA
- 3:1 allocation (CMX001:placebo)
- 40mg weekly; 100mg weekly; 200mg weekly; 200mg twice weekly

Marty et al. NEJM 2013
Time to Onset of CMV DNAemia >1000c/mL

CMV events less in 100mg BIW than placebo (10% vs 37%, p=0.002)
Diarrhea most common AE
Summary

• Need for alternate antivirals
  – Less toxicity
  – Better efficacy
  – GCV-resistant CMV

• Prophylaxis and treatment indications for new antivirals will need to be better defined
CMV Vaccine
# CMV Vaccines

<table>
<thead>
<tr>
<th>Construct</th>
<th>Clinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Towne / Live attenuated</td>
<td>Seroconversion w/ neutralizing abs but no impact on infection rate, reduced CMV risk post KTx (1991)</td>
</tr>
<tr>
<td>Towne/Toledo – Live attenuated</td>
<td>No significant changes in humoral and CMI in seropositive persons</td>
</tr>
<tr>
<td>gB subunit + MF59 adjuvant (Sanofi w/ Novartis adjuvant)</td>
<td>Induced neutralizing abs and reduced maternal CMV</td>
</tr>
<tr>
<td>gB subunit + MF59 adjuvant (Sanofi w/ Novartis adjuvant)</td>
<td>SOT study</td>
</tr>
<tr>
<td>gp65/gB DNA plasmid vaccine (Transvax by Vical/Astellas)</td>
<td>Humoral and CMI in seroneg. Decreased duration and # of CMV viremia episodes in HSCT</td>
</tr>
<tr>
<td>HLA-restricted pp65 T-cell epitope fused with PanDR epitope (given with CpG adjuvant)</td>
<td>T cell responses and safety in healthy volunteers</td>
</tr>
<tr>
<td>Peptide epitope vaccines – loaded into DCs</td>
<td>Cellular response in tx</td>
</tr>
<tr>
<td>HCMV polyepitope encoding T cell epitopes from IE-1, IE-2, pp28, pp50, pp65, pp150, gH, gB</td>
<td>Mouse models show humoral and CMI responses</td>
</tr>
<tr>
<td>Alphavirus vaccines encoding gB, IE-1, pp65 (Novartis)</td>
<td>Phase I showing good B&amp;T cell immunity</td>
</tr>
<tr>
<td>MVA/canarypox encoding gB, IE-1, pp65</td>
<td>Rhesus models / Human studies</td>
</tr>
</tbody>
</table>

Adapted from Smith/Khanna Human Vaccines 2010
Cytomegalovirus glycoprotein-B vaccine with MF59 adjuvant in transplant recipients: a phase 2 randomised placebo-controlled trial


A novel therapeutic cytomegalovirus DNA vaccine in allogeneic haemopoietic stem-cell transplantation: a randomised, double-blind, placebo-controlled, phase 2 trial

Mohamed A Kharfan-Dabaja, Michael Boeckh, Marissa B Wilck, Amelia A Langston, Alice H Chu, Mary K Wloch, Don F Guterwill, Larry R Smith, Alain P Rolland, Richard T Kenney
gB-MF59 vaccine in SOT

- IM at 0, 1, 6 months pre-transplant

Griffiths, Lancet 2011
Transvax

- DNA vaccine;
- Two plasmids: gB + pp65
- RCT Vaccine vs. Placebo before conditioning and at 1,3, and 6 months post HSCT
p=0.016, HR 0.362 (95% CI 0.154-0.850)

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Vaccine group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>16</td>
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<tr>
<td></td>
<td>21</td>
<td>14</td>
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<td>13</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>13</td>
</tr>
</tbody>
</table>
T-cell response [SPU] pp65

T-cell response [SPU] gB
Summary: Future of CMV Management (next 5 years)

- **CMV D+/R-SOT Patient**

  - Administer Vaccine
  - Measure Vaccine Response [CMI]

  - **No need for prophylaxis/monitoring**
  - **Give prophylaxis or monitor viral load**
Thank you! Merci!

- deepali.kumar@uhn.ca

Updated International Consensus Guidelines on the Management of Cytomegalovirus in Solid-Organ Transplantation

Camille N. Kotton, Deepali Kumar, Angela M. Caliendo, Anders Åsberg, Sunwen Chou, Lara Danziger-Isakov, and Atul Humar, on behalf of The Transplantation Society International CMV Consensus Group

Cytomegalovirus in Solid Organ Transplantation

R. R. Razonable, A. Humar and the AST Infectious Diseases Community of Practice

AJT Transplant ID Guidelines 2013