Prevention of CMV in Solid Organ Transplantation

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Disclosure

- Advisory Board: GSK, Pfizer, Atara, Qiagen, Oxford Immunotec
- Clinical Trial: GSK, Merck, Oxford Immunotec, Qiagen
- Honoraria: Shire, Merck, Pfizer
Objectives

• Examine the direct and indirect effects of CMV post-SOT
• Explore current and future approaches to CMV prevention
• Review case-based scenarios to illustrate various prevention approaches
CMV is the most common viral infection in SOT

- Genetic composition
  - 2 unique regions of DNA – $U_L$ and $U_S$ and flanking terminal repeat regions (TR) and internal repeat regions (IR)
  - Encodes 168 + unique functional genes (exact number unknown)
  - Gene expression occurs in a temporal cascade (IE, early, and late)

What leads to CMV replication post-transplant

- **Viral factors**
  - Replication dynamics
  - Immune evasion
  - Viral heterogeneity
  - Viral co-infections

- **Host factors**
  - CD4+, CD8+ T-cell
  - NK cell, B-cell
  - Exogenous immunosuppression
  - D/R serostatus

CMV PATHOGENESIS
### Serologic Risk Profile for CMV

<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+

Humar et al., AJT 2009; Fishman et al., Clin Transplant 2007
Effects of CMV Infection post-transplant

**Direct Effects**

**CMV Viral Syndrome**
- Fever, malaise, myalgias
- Leukopenia, thrombocytopenia, and other laboratory abnormalities

**Tissue Invasive Disease**
- Hepatitis
- Pneumonitis
- Colitis
- Carditis
- Nephritis
- Pancreatitis
- Retinitis

**Indirect effects**
Indirect Effects of CMV

- Immuno-suppressive effects of viral infection
- Pro-inflammatory effects
- Alloreactivity
- Direct interaction with other herpesviruses

Graft rejection; graft dysfunction
Opportunistic infections: Bacterial fungal superinfection
Decreased graft and patient survival
Herpesvirus interactions: EBV/PTLD
55 y.o. woman deceased donor kidney transplant CMV D+/R-
ATG induction, is on Tac/Pred/MPA
For CMV prevention you would use:
For CMV prevention you would use (adjusted for renal function)

a) Valganciclovir 900mg/d x 3 months
b) Valganciclovir 900mg/d x 6 months
c) Preemptive strategy (VL monitoring)
d) 3 months prophylaxis followed by pre-emptive strategy
CMV PREVENTION: Universal Prophylaxis

• Antiviral therapy from the time of transplant to all patients or a subgroup of patients (3-6 months of antiviral prophylaxis in all D+/R- transplant patients)

• Prophylaxis very successful in multiple clinical trials for CMV prevention
RCT of oral GCV vs. VGCV

n=364 D+/R- kidney,liver,heart

Viremia very common after prophylaxis

Paya, et al AJT 2004
Impact Trial: RCT of 100d vs 200d VGCV

International RCT
Kidney recipients, D+/R-, N=316

**VGCV-100 days:**
- Valganciclovir 900 mg od*
- Placebo

**VGCV-200 days:**
- Valganciclovir 900 mg od*
- Valganciclovir 900 mg od*

* dose adjusted for renal function

Impact Trial

Event-free probability

Study day

Valganciclovir 200 days

Valganciclovir 100 days

CMV disease 36.8 vs 16.1% p<0.0001

Higher rates of leukopenia (38% vs 26%)

Number of patients assessed

Valganciclovir 100 days: 163, 161, 157, 151, 125, 110, 104, 102, 101, 95, 94, 83, 4

Valganciclovir 200 days: 155, 154, 152, 150, 149, 147, 145, 143, 136, 130, 125, 122, 120, 7

Extended Valganciclovir Prophylaxis to Prevent Cytomegalovirus After Lung Transplantation
A Randomized, Controlled Trial

Scott M. Palmer, MD, MHS; Ajit P. Limaye, MD; Missy Banks, BS; Dianne Gallup, MS; Jeffrey Chapman, MD; E. Clinton Lawrence, MD; Jordan Dunitz, MD; Aaron Milstone, MD; John Reynolds, MD; Gordon L. Yung, MD; Kevin M. Chan, MD; Robert Aris, MD; Edward Garrity, MD; Vincent Valentine, MD; Jonathan McCall, BA; Shein-Chung Chow, PhD; Robert Duane Davis, MD; and Robin Avery, MD
The patient is placed on Valganciclovir. At 2.5 months post-transplant the patient develops low WBC of 1.7 with ANC of 0.9. Septra is held. You would

a) Hold Valganciclovir
b) Hold MPA
c) Hold both a) and b)
d) Not hold anything but give GCSF
Issues with Prophylaxis

1. Drug toxicity

2. After discontinuation of prophylaxis – viremia and disease often develops
   - “Late onset CMV disease”
     - May present with atypical symptoms (no fever – malaise, fatigue); diagnosis can be missed
Maribavir

- Inhibits UL97 (viral kinase)
- Does not cover HSV / VZV
- Some overlap with GCV-resistant mutations
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
Letermovir

• Terminase complex inhibitor
  • Binds at UL56
• Generally good safety profile
• Drug interactions with CyA, tacrolimus, voriconazole, others
• Covers CMV only
  • Need acyclovir for HSV/VZV prevention
• High-grade resistance mutations in UL56 terminase gene are readily selected in vitro under letermovir; clinical correlation needed (not UL97/UL54) (Chou 2015)


CyA, cyclosporine A; VZV, varicella zoster virus.
Letermovir Study: SOT

Kidney D+/R-

Arm 1
Letermovir 6 months 480 mg/d

Arm 2
Valganciclovir 6 months 900 mg/d

600 patients
Non-inferiority trial
Placebo controlled
Acyclovir used in Letermovir arm

Clinicaltrials.gov
CMV PREVENTION: Pre-emptive Therapy

Could have initiated pre-emptive therapy
Either oral or IV can be used for pre-emptive therapy

Valganciclovir (N) 133 130 128 123 123 124 124 122 118 115 117
IV Ganciclovir (N) 125 122 123 123 124 121 120 120 119 118 116

Issues with Pre-emptive therapy

• Weekly monitoring (needs patient compliance and physician review)

• Short viral doubling time in some patients

• Thresholds for treatment not established (likely different for D+/R- vs. R+)

• Effect of low level replication on graft not fully defined
Combination strategy: Surveillance after Prophylaxis

CMV disease

Could have initiated pre-emptive therapy
<table>
<thead>
<tr>
<th></th>
<th>Prophylaxis</th>
<th>Pre-emptive</th>
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</thead>
<tbody>
<tr>
<td>Evidence of efficacy</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Indirect effects/mortality</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Other viruses</td>
<td>+ for some</td>
<td>-</td>
</tr>
<tr>
<td>Ease</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Late onset disease</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Resistance</td>
<td>Low</td>
<td>Low</td>
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</tbody>
</table>
# CMV Guidelines

<table>
<thead>
<tr>
<th>Serostatus</th>
<th>Transplant</th>
<th>Prophylaxis vs. Pre-emptive</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>D+/R-</td>
<td>Kidney, liver, pancreas, heart</td>
<td>Universal prophylaxis preferred Preemptive strategy is an option</td>
<td>3-6 months 6 months for kidney Some add CMV Ig for heart</td>
</tr>
<tr>
<td>R+</td>
<td>Kidney, liver, pancreas, heart</td>
<td>Prophylaxis or pre-emptive therapy</td>
<td>3 months</td>
</tr>
<tr>
<td>D+/R- or R+</td>
<td>Lung</td>
<td>Universal prophylaxis recommended</td>
<td>3-12 months for R+ 6-12 months for R- Some add CMV Ig</td>
</tr>
</tbody>
</table>

AST Guidelines 2019, International Guidelines 2018
Prophylaxis versus Preemptive Therapy for the Prevention of CMV in High-Risk D+/R- Liver Transplant Recipients

[CMV Antiviral Prevention Strategies in D+R- Liver Transplants (“CAPSIL”)]

Clinicaltrials.gov: NCT01552369

Objectives: To conduct a Phase II randomized controlled trial comparing prophylaxis with preemptive therapy using valganciclovir in D+/R- liver recipients with the primary endpoint of CMV disease. The secondary endpoints include: CMV-specific immunity, toxicity, and indirect outcomes.
Pre-emptive vs. Prophylaxis RCT

N=205 D+/R- liver transplant patients randomized at 6 centers
CMV disease: 9% in pre-emptive therapy and 19% in prophylaxis (p=0.04)
Stratifying Risk by CMV-specific Cell-mediated Immunity

Assays based on measurement of IFN-γ production by cells stimulated with CMV peptides, whole proteins or CMV whole virus

CMI could be used to stratify who needs prophylaxis or pre-emptive therapy

- CMV D+/R-
- Antiviral prophylaxis
- Monitor CMI
- Time Post-Transplant

D/C Prophylaxis

Prolong Prophylaxis or Monitor VL more closely
CMV viremia detected (≥1000 IU/mL) → Antiviral Therapy (until one negative PCR or two PCR <137 IU/mL) → CMV CMI Assay at End of Antiviral Therapy (within 48 hours)

- Negative CMI: Antiviral prophylaxis for 2 months
- Positive CMI: No Antiviral Prophylaxis

After CMI result:
- CMV viral load testing q2weeks for 3 months
- 6 month follow-up

Am J Transplant 2017
CMI negative at end of therapy (n=13); Received additional 2 months of secondary prophylaxis But still had a high rate of relapse

CMI positive at end of therapy (n=14); No secondary prophylaxis But still had a low rate of relapse
CMV Vaccines

- **Attenuated Virus**
  - Towne/Toledo Chimeric
  - V160 replication defective

- **Recombinant Subunit or Recombinant VLP**
  - gB/MF59
  - gB/ASO3
  - VBI-1501A

- **DNA vaccines**
  - gB/pp65 (ASP0113)

- **Vectored vaccines**
  - Alphavax
  - HCMV – MVA (pp65, UL123 / IE-1 exon 4, UL122 / IE-1 exon 5)
  - HB-101 (gB, pp65)
  - Alvac – pp65

- **Peptide Vaccines**
  - CMV pp65 – T cell epitope fused to tetanus epitope

Anderholm et al. Drugs, 2016
The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation

Camille N. Kotton, MD, Deepali Kumar, MD, Angela M. Caliendo, MD, PhD, Shirish Huprikar, MD, Sunwen Chou, MD, Lara Danziger-Isakov, MD, MPH, and Atul Humar, MD on behalf of the 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

Transplantation 2018

Clinical Transplantation 2019
Thank you!

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