CMV EN TRANSPLANTATION RÉNALE: TRAITEMENT PRÉVENTIF OU PRÉEMPTIF ET NOUVELLES ALTERNATIVES

Hannah Kaminski
STRUCTURE, TRANSMISSION

Herpesvirus
Double strain DNA
235 KB et 165 genes
180-200 nm
Icosahedral capsid
Transmission: exclusively inter-human
83% (95%UI: 78-88) in the general population, 86% (95%UI: 82-89) in donors of blood or organs, 86% (95%UI: 82-89) in women of childbearing age, and European region 66% (95%UI: 56-74).
POPULATIONS AT RISK OF CMV DISEASE

Solid-Organ Transplant Recipients
► 126,670 transplanted organs in 2015 (+5.8%) worldwide

Hematopoietic-Cell Transplant Recipients
► more than 50,000 transplants each year

AIDS Patients
► 36.7 million

Newborns (congenital infections)

www.transplant-observatory.org
www.wbmt.org
ANTI-CMV IMMUNE RESPONSE

Healthy individuals

Dissemination and CMV disease in immunocompromised individuals
DEFINITIONS OF CMV INFECTION

- **CMV antigenemia** is defined as the detection of CMV pp65 antigen in PBMC.

- **CMV DNAemia** is defined as the detection of CMV DNA in samples of plasma, serum, whole blood.

Ljungman, Clin Infect Dis. 2017;64(1):87-91 (CMV Drug Development Forum)
CMV QUANTITATIVE ACID NUCLEIC TESTING (QNAT)

- Must be calibrated with the **WHO International Standard** for **Human CMV**
- Reported as **IU/ml**, and termed as **DNAemia** rather than viremia.
- **Highly sensitive QNAT** : < 200 IU/ml (results given as $\log_{10}$ IU/ml)
- Sensitivity: whole blood > plasma

- **In our center** : whole-blood : sensitivity for positivity : 250 IU/ml (WHO: since June 19, 2012)

Kotton, Transplantation. 2018 Jun; 102(6): 900-931
DEFINITIONS OF CMV INFECTION AND DISEASE

- **CMV infection** is defined as virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen, regardless of symptoms (i.e., CMV DNAemia ± symptoms)

- **CMV disease**: Evidence of CMV infection with attributable symptoms. CMV disease can be further categorized as:
  - Viral syndrome
  - Tissue-invasive disease

Ljungman, Clin Infect Dis. 2017;64(1):87-91 (CMV Drug Development Forum)
DEFINITIONS OF CMV DISEASE:
TISSUE INVASIVE (OR END-ORGAN) DISEASE

- CMV retinitis
- CMV cholecystitis
- CMV colitis
- CMV encephalitis
- CMV pneumonia
- CMV pancreatitis
RISK FACTORS OF CMV DISEASE

- **Risk of cytomegalovirus (CMV) infection** in solid organ transplant recipients is defined by:
  - Donor and recipient **CMV serostatus**
    - $D^+R^- > D^+R^+ > D^-R^+ > D^-R^-$

- **The transplanted organ**
  - **Lung** > others

- **Additional immunosuppressive therapy**
  - **Induction:** ATG > anti-IL2R in R+ patients but not in D+R-
  - *Webster, The Cochrane Database of Systematic Reviews, 2010*
  - Kaminski, J Inf Dis, 2019, 220(5):761-771

- **Rejection**
  - Santos, Transplantation. 2014;98(2):187-194
Risk of CMV infection in solid organ transplant recipients is defined by:

- donor and recipient **CMV serostatus**
- the **transplanted organ**
- and **additional immunosuppressive therapy**.

- These parameters are used to design the preventive strategy.
CMV PREVENTION: FOUR STRATEGIES

1. UNIVERSAL PROPHYLAXIS
2. PREEMPTIVE STRATEGY
3. HYBRID APPROACH
4.ailORi?
CMV PREVENTION: UNIVERSAL PROPHYLAXIS

No CMV QNAT

- **Universal prophylaxis**
- **VGCV 900 mg/day**
- **VGCV 900 mg/day**

D0  M3  M6  M12

- **Valganciclovir**: most commonly used
- **High-dose valacyclovir** (=valganciclovir)

Humar, Am J Transplant. 2010 May;10(5):1228-37

VGCV : Valganciclovir; GCV : Ganciclovir
CMV PREVENTION: PREEMPTIVE THERAPY

Preemptive strategy

CMV QNAT 1/week J0-M3, 1/month M3-M12

IV GCV / VGCV IF CMV PCR +

D0 M3 M6 M12

Kotton, Transplantation. 2013 Aug 27;96(4):333-60

VGCV : Valganciclovir; GCV : Ganciclovir
# SUMMARY ON THE RATE OF INFECTION/DISEASE FOLLOWING STRATEGY

<table>
<thead>
<tr>
<th></th>
<th><strong>No treatment</strong></th>
<th><strong>Universal prophylaxis</strong></th>
<th><strong>Preemptive strategy</strong></th>
<th>Références</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>D+R-</strong></td>
<td><strong>D+R+</strong></td>
<td><strong>D-R+</strong></td>
<td>(1, 2, 3, 5, 8)</td>
</tr>
<tr>
<td><strong>Infection/Disease</strong></td>
<td>68 %</td>
<td>63 %</td>
<td>50 %</td>
<td>(1, 2, 3, 5, 6, 9)</td>
</tr>
<tr>
<td><strong>Universal prophylaxis</strong></td>
<td></td>
<td></td>
<td></td>
<td>(1, 6, 9)</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>3 month : 51 %</td>
<td>3 mois : 25 %</td>
<td>3 mois : 23 %</td>
<td>(1, 2, 3, 5, 6, 9)</td>
</tr>
<tr>
<td></td>
<td>6 month : 37 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td>3 month : 37 %</td>
<td>3 mois : 7 %</td>
<td>3 mois : 2 %</td>
<td>(1, 6, 9)</td>
</tr>
<tr>
<td></td>
<td>6 month : 16 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Preemptive strategy</strong></td>
<td></td>
<td></td>
<td></td>
<td>(1, 2, 3, 5, 8)</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>68 %</td>
<td>63 %</td>
<td>50 %</td>
<td>(1, 2, 3, 5, 8)</td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td>20 %</td>
<td>5 %</td>
<td>2 %</td>
<td>(1, 3, 6, 7, 8)</td>
</tr>
</tbody>
</table>

5. Van der Beek, Transplantation. 2010, 3:320-6
6. Couzi, Am J Transplant. 2012, 1:202-
# UNIVERSAL PROPHYLAXIS VERSUS PREEMPTIVE THERAPY

<table>
<thead>
<tr>
<th></th>
<th>Prophylaxis</th>
<th>Pre-emptive therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early CMV DNAemia/infection</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Prevention of CMV disease</td>
<td>Good efficacy</td>
<td>Good efficacy</td>
</tr>
<tr>
<td>Late CMV (infection/disease)</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Resistance</td>
<td>Uncommon</td>
<td>Uncommon (with weekly testing)</td>
</tr>
<tr>
<td>Ease of implementation</td>
<td>Relatively easy</td>
<td>More difficult</td>
</tr>
<tr>
<td>Prevention of other herpes viruses</td>
<td>Prevents HSV, VZV</td>
<td>Does not prevent</td>
</tr>
<tr>
<td>Other opportunistic infections</td>
<td>May prevent</td>
<td>Unknown</td>
</tr>
<tr>
<td>Costs</td>
<td>Drug costs</td>
<td>Monitoring costs</td>
</tr>
<tr>
<td>Safety</td>
<td>Drug side effects</td>
<td>Less drug toxicity</td>
</tr>
<tr>
<td>Prevention of rejection</td>
<td>May prevent</td>
<td>Unknown</td>
</tr>
<tr>
<td>Graft survival</td>
<td>May improve</td>
<td>May improve</td>
</tr>
</tbody>
</table>

CMV PREVENTION: FOUR STRATEGIES

1. UNIVERSAL PROPHYLAXIS
2. PREEMPTIVE STRATEGY
3. HYBRID APPROACH
4. mTORi?
SURVEILLANCE AFTER PROPHYLAXIS (OR “HYBRID APPROACH”)

Surveillance after prophylaxis

VGCV 900 mg/day

CMV QNAT

D0 M3 M6 M12

VGCV : Valganciclovir; GCV : Ganciclovir
SURVEILLANCE AFTER PROPHYLAXIS
(OR “HYBRID APPROACH”)

- No RCT to support the use of a surveillance after prophylaxis approach

- Use of surveillance after prophylaxis may be considered in patients at increased risk for post-prophylaxis CMV disease. The value is probably greatest if done weekly for 8-12 weeks.

Kotton, Transplantation. 2018 Jun;102(6):900-931  
RCT : randomized control trial
CURRENT EPIDEMIOLOGY OF CMV INFECTION IN KIDNEY TRANSPLANT PATIENTS

CMV Mutant: 6%

Clinical relapse: 20.7%

Persistence: 28.5%

CMV requiring treatment: 17.5%

N= 1207 /2004 -2015/at least two years of follow-up. Personal unpublished data
P.Pfimmann-B.Taton-H.Kaminski

313 events among 1792 KTR 2004-2017
Personal unpublished data
M.Acquier-H.Kaminski-L.Couzi
CMV PREVENTION: COULD IMMUNOMONITORING HELP?

1. UNIVERSAL PROPHYLAXIS
2. PREEMPTIVE STRATEGY
3. HYBRID APPROACH
4. mTORi?
CELLULAR IMMUNITY TO PREDICT THE RISK OF CMV INFECTION IN R+ KIDNEY TRANSPLANTATION

CMV-specific T cell response

No CMV-specific T cell response

15-day post-transplant

CMV PREVENTION: FOUR STRATEGIES

1. UNIVERSAL PROPHYLAXIS
2. PREEMPTIVE STRATEGY
3. HYBRID APPROACH
4. mTORi?
First randomised, multicenter, open-label, parallel group study in CMV R+ kidney transplant recipients, comparing everolimus versus mycophenolic acid, with CMV DNAemia as a primary end-point.

First draft : 2012...
**Main inclusion criteria:**
- CMV R+ recipients
- No DSA

**Basiliximab + Ciclosporin and Steroids**

**EVEROLIMUS**

<table>
<thead>
<tr>
<th>CsA C₀: 100–200 ng/mL</th>
<th>CsA C₀: 75–150 ng/mL</th>
<th>CsA C₀: 50–100 ng/mL</th>
<th>CsA C₀: 25–50 ng/mL</th>
</tr>
</thead>
</table>

**MYCOPHENOLIC ACID**

<table>
<thead>
<tr>
<th>CsA C₀: 150–220 ng/mL</th>
<th>CsA C₀: 100–150 ng/mL</th>
</tr>
</thead>
</table>

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Time post-Tx:
- D0
- M2
- M3
- M4
- M6
- M12

**Primary endpoint**

**End of study**

Inclusion: May 2014 - October 2017

Preemptive therapy for CMV (n=186)
PRIMARY ENDPOINT AT 6 MONTHS POST-TRANSPLANTATION

Kaminski et al, in prep.
7.4% of patients with ONGOING EVR undergo CMV DNAemia requiring treatment

Kaminski et al, in prep.
CMV PREVENTION: ALTERNATIVE DRUGS

1. UNIVERSAL PROPHYLAXIS
2. PREEMPTIVE STRATEGY
3. HYBRID APPROACH
4. mTORi?
LETTERMOVIR FOR CMV PROPHYLAXIS IN HEMATOPOIETIC-CELL TRANSPLANTATION (PHASE II)

n=133

Failure of prophylaxis against CMV infection
- Virologic failure (detectable CMV antigen/DNA)
- Any other reason

LETTERMOVIR FOR CMV PROPHYLAXIS IN HEMATOPOIETIC-CELL TRANSPLANTATION (PHASE III)

Clinically significant infection

\[ P < 0.001 \text{ by log-rank test} \]

*No. at Risk*

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>170</th>
<th>169</th>
<th>135</th>
<th>96</th>
<th>85</th>
<th>77</th>
<th>70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letermovir</td>
<td>325</td>
<td>320</td>
<td>299</td>
<td>279</td>
<td>270</td>
<td>254</td>
<td>212</td>
<td></td>
</tr>
</tbody>
</table>

\[ n = 565 \text{ but } 495 \]

With undetectable CMV DNAemia at day 9


PHASE III in Kidney transplant recipients (MK-8228-002)

Sample size: 600 patients

Recruiting D+R-

ClinicalTrials.gov NCT03443869
MARIBAVIR: PROPHYLAXIS IN LIVER TRANSPLANTATION

- Oral maribavir (n= 147, 100 mg twice daily) – 14 days
- Vs Oral ganciclovir (n=156, 1 g three times daily) - 14 days
- D+R-

MARIBAVIR FOR PREEMPTIVE TREATMENT OF CYTOMEGALOVIRUS REACTIVATION (PHASE 2 STUDY)

MARIBAVIR FOR PREEMPTIVE TREATMENT OF CYTOMEGALOVIRUS REACTIVATION (PHASE 2 STUDY)

## UPDATE OF CMV GUIDELINES 2018

<table>
<thead>
<tr>
<th>Organ</th>
<th>Serostatus</th>
<th>Risk Level</th>
<th>RECOMMENDED</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>D-/R-</td>
<td>Low</td>
<td>Monitoring for clinical symptoms; consider antiviral prophylaxis against other herpes infections</td>
</tr>
<tr>
<td><strong>Kidney</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D+/R-</td>
<td>High</td>
<td>6 months of GCV/VGCV OR Preemptive therapy</td>
<td></td>
</tr>
<tr>
<td>R+</td>
<td>Intermediate</td>
<td>3 months of VGCV OR Preemptive therapy</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>D+R-</td>
<td>High</td>
<td>3 -6 months of VGCV OR Preemptive therapy</td>
</tr>
<tr>
<td></td>
<td>R+</td>
<td>Intermediate</td>
<td>3 months of VGCV (VGCV not FDA approved in liver) OR Preemptive therapy</td>
</tr>
<tr>
<td>Pancreas</td>
<td>D+R-</td>
<td>High</td>
<td>3 -6 months of VGCV</td>
</tr>
<tr>
<td></td>
<td>R+</td>
<td>Intermediate</td>
<td>3 months of VGCV OR Preemptive therapy</td>
</tr>
<tr>
<td>Islet</td>
<td>D+R-</td>
<td>Intermediate</td>
<td>3 months of VGCV</td>
</tr>
<tr>
<td></td>
<td>R+</td>
<td>Intermediate</td>
<td>3 months of VGCV OR Preemptive therapy</td>
</tr>
</tbody>
</table>

Kotton, Transplantation. 2018 Jun;102(6):900-931
## UPDATE OF CMV GUIDELINES 2018

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<thead>
<tr>
<th>Organ</th>
<th>Serostatus</th>
<th>Risk Level</th>
<th>RECOMMENDED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>D+/R-</td>
<td>High</td>
<td>3-6 months of GCV/VGCV</td>
</tr>
<tr>
<td></td>
<td>R+</td>
<td>Intermediate</td>
<td>3 months of GCV/VGCV OR Preemptive therapy</td>
</tr>
<tr>
<td>Lung</td>
<td>D+/R-</td>
<td>High</td>
<td>6-12 months of GCV/VGCV</td>
</tr>
<tr>
<td></td>
<td>R+</td>
<td>Intermediate</td>
<td>Minimum 6 months of GCV/VGCV</td>
</tr>
<tr>
<td>Intestinal, composite tissue</td>
<td>D+/R-</td>
<td>High</td>
<td>Minimum 6 months GCV/VGCV + surveillance after prophylaxis</td>
</tr>
</tbody>
</table>

**CMV Ig** is not generally recommended for use, although there may be specific circumstances, especially in thoracic organs, when used in combination with antivirals, in which some benefit has been demonstrated.

Kotton, Transplantation. **2018** Jun;102(6):900-931
The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation

THANK YOU FOR YOUR ATTENTION!
MARIBAVIR: INHIBIT UL97

Activities of the UL97 kinase:
- stimulate the cell cycle to support viral DNA synthesis
- enhance the expression of viral genes
- promote virion morphogenesis
- facilitate the egress of mature capsids from the nucleus

Frange, Med Mal Infect. 2018 Dec;48(8):495-502
LETTERMOVIR (AIC246): IMPACT ON HERPESVIRUS DNA REPLICATION

Formation of long, branched, head-to-tail DNA concatemers

\[ p_{ac} \] indicates the terminase cleavage site at the genome terminus

The HCMV terminase complex is responsible for the cleavage of concatemeric progeny DNA to unit-length genomes and the packaging of those genomes into preformed procapsids.

Essential for virus replication