CMV INFECTION IN KIDNEY TRANSPLANTATION

PIERRE MERVILLE

CHU BORDEAUX - UNIVERSITÉ BORDEAUX SEGALEN
UMR-CNRS 5164
SUMMARY:

1. Epidemiology in kidney transplantation
2. T cell response: $\alpha\beta$ and $\gamma\delta$ lymphocytes
4. Indirects effects: Clinical impact
5. Update on CMV guidelines
6. Perspectives
At the era of generalized prevention, the risk of infection depends on the treatment.

- **Universal Prophylaxis**: VGCV 900mg/day
- **Preemptive Therapy**: Whole blood CMV qPCR

Whole blood CMV qPCR: 1/week J0-M3, 1/month M3-M12

No threshold for anti-CMV therapy
MORE CMV INFECTIONS WITH THE PREEMPTIVE STRATEGY

<table>
<thead>
<tr>
<th>qPCR</th>
<th>D+R-</th>
<th>D+R+</th>
<th>D-R+</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRO 6 Mths</td>
<td>PRO 3 Mths</td>
<td>PREE</td>
<td>PRO</td>
</tr>
<tr>
<td>Khoury, 2006</td>
<td>44,0</td>
<td>54,0</td>
<td>18,0</td>
<td>54,0</td>
</tr>
<tr>
<td>Kliem, 2008</td>
<td>52,0</td>
<td>74,0</td>
<td>10,0</td>
<td>56,0</td>
</tr>
<tr>
<td>Reischig, 2007</td>
<td>75,0</td>
<td>83,0</td>
<td>56,0</td>
<td>96,0</td>
</tr>
<tr>
<td>Helentera, 2010</td>
<td>37,0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humar, 2010</td>
<td>37,4</td>
<td>50,9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van der Beek, 2010</td>
<td>52,0</td>
<td>69,0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Couzi, 2012</td>
<td>34,0</td>
<td>60,0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Witzke, 2011</td>
<td></td>
<td></td>
<td>15,6</td>
<td>53,8</td>
</tr>
<tr>
<td>Atabani, 2012</td>
<td></td>
<td></td>
<td>70,0</td>
<td>53,0</td>
</tr>
<tr>
<td>Mean (%)</td>
<td>37,2</td>
<td>51,3</td>
<td>68,3</td>
<td>24,9</td>
</tr>
</tbody>
</table>

PRO: Prophylactic
PREE: Preemptive
## Similar Incidence of CMV Diseases

<table>
<thead>
<tr>
<th>qPCR</th>
<th>D+R-</th>
<th>D+R+</th>
<th>D-R+</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRO 6 Mths</td>
<td>Proph 3 Mths</td>
<td>PREE</td>
<td>PRO</td>
</tr>
<tr>
<td>Khoury, 2006</td>
<td>19,0</td>
<td>8,0</td>
<td></td>
<td>5,0</td>
</tr>
<tr>
<td>Kliem, 2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reischig, 2007</td>
<td>9,0</td>
<td>6,0</td>
<td>13,0</td>
<td>0,0</td>
</tr>
<tr>
<td>Helentera, 2010</td>
<td>34,0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humar, 2010</td>
<td>16,1</td>
<td>36,8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van der Beek, 2010</td>
<td>0,0</td>
<td>0,0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Couzi, 2012</td>
<td>16,0</td>
<td>26,0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Witzke, 2011</td>
<td></td>
<td></td>
<td>4,4</td>
<td>19,2</td>
</tr>
<tr>
<td>Atabani, 2012</td>
<td>32,5</td>
<td>2,5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (%)</td>
<td>na</td>
<td>20,2</td>
<td>18,1</td>
<td>7,5</td>
</tr>
</tbody>
</table>

**PRO** : Prophylactic  
**PREE** : Preemptive  
**Na** : Not applicable
SUMMARY:

1. Epidemiology in kidney transplantation
2. T cell response: $\alpha\beta$ and $\gamma\delta$ lymphocytes
4. Indirects effects: Clinical impact
5. Update on CMV guidelines
6. Perspectives
DOMINATE THE MEMORY COMPARTMENTS OF EXPOSED SUBJECTS

70% of viral peptides are able to generate a T cell response

IN R+ INDIVIDUALS, ANTI-CMV RESPONSE ENGAGES 4-5 %
OF TOTAL CD4 AND CD8 LYMPHOCYTES

CONSEQUENCES OF CMV INFECTION: MEMORY INFLATION AND IMMUNE SENESCENCE?

- « CMV would represent the most important agent of effector T cell expansion and probably one of the most important causes for persistent immune activation in human aging »

Vescovini et al, J. Immunol., 2007; 179: 4283-4291
CMV-driven expansion of γδ T cells

**Organ recipients**

CMV

CMV-driven expansion of γδ T cells

**Innate-like features**
- massive expansion of Vδ2<sup>neg</sup> cells
- diverse TCR repertoire
- high expression of MHC-NKR
- high expression of CD16

*(JCI, 1999)*

**Adaptive-like features**
- very specific of CMV
- associated to infection resolution
- long-term blood signature of CMV
- TEMRA phenotype,
- concomitant to αβ expansion
- more rapid response in secondary infection

*(JID, 2001; Blood, 2008; JID, 2009, Blood 2012)*

**Mouse model**
- γδ protect αβ- mice from death
- γδ control virus

*(JEM, 2005; JASN, 2010; Cancer Res, 2009)*
CMV INFECTION, A RELEVANT MODEL TO UNDERSTAND $\gamma\delta$ T CELLS

**STRATEGY TO IDENTIFY NEW $\gamma\delta$ TCR LIGANDS**

Patients

Isolated T cell clones

Reported cell lines

- $\gamma\delta$
- TCR-Ligand identification
- TCR transfer
- Lentiviral transduction
- mAb screening
- CD69

CMV-infected or tumor cells

Immunisation

stress

**CMV**
DISCOVERY OF EPCR AS THE LIGAND OF THE CLONE “LES” (Vγ5Vδ5)

EPCR

Phospholipids

Involved in coagulation (activator of protein C)
→ MHC-I-like molecule
→ Crystallization: associated with phospholipids
→ expressed on endothelial cells (CMV targets)
→ Increased expression on carcinoma cells

sEPCR directly binds to LES sTCR

Kd = 100 μM

(Willcox et al, Nat Immunol 2012)
SUMMARY:

1. Epidemiology in kidney transplantation
2. T cell response: $\alpha\beta$ and $\gamma\delta$ lymphocytes
4. Indirects effects: Clinical impact
5. Update on CMV guidelines
6. Perspectives
WHY TO MONITORE SPECIFIC CMV IMMUNE RESPONSE?

Prophylaxis of CMV infection:
- D+/R- patients: Which patients require a prolongation of prophylaxis?
- R+ patients: Is a treatment necessary for all patients?

Treatment of CMV disease:
- Should we treat minor/transitory ADNemia?
- Following complete treatment of CMV disease, which patients require viral monitoring?

When this patient is really cured?
**HOW TO MONITORE SPECIFIC CMV IMMUNE RESPONSE?**

### SUMMARY OF THE STUDIES

<table>
<thead>
<tr>
<th>Assays</th>
<th>Correlation with ADNemia</th>
<th>Correlation with disease</th>
<th>Clinical impact on treatment decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>QuantiFERON-CMV (N=4)</td>
<td>Yes</td>
<td>Yes</td>
<td>No data</td>
</tr>
<tr>
<td>ELISPOT (N=5)</td>
<td>Yes</td>
<td>Yes</td>
<td>No data</td>
</tr>
<tr>
<td>Cytométry (N=9)</td>
<td>Yes</td>
<td>Yes</td>
<td>No data</td>
</tr>
<tr>
<td>Multimer HLA (N=1)</td>
<td>No</td>
<td>No</td>
<td>No data</td>
</tr>
</tbody>
</table>

- Limited number of patients (10-134), heterogeneous (R+ and D+R-)
- No clear predictive threshold, weak sensitivity, influence of treatment…
- Probably more a matter of kinetics of the response than an immune threshold.

![Graph showing Viral load and Anti-CMV response](image)
SUMMARY:

1. Epidemiology in kidney transplantation
2. T cell response: $\alpha\beta$ and $\gamma\delta$ lymphocytes
4. Indirects effects: Clinical impact
5. Update on CMV guidelines
6. Perspectives
INDIRECT EFFECTS OF CMV INFECTION

Fishman, NEJM, 2007; 357: 2601-14

Infection (D+R-) or Reactivation (R+)

CMV infection (DNAemia)

DIRECT effects
CMV disease

CMV Syndrome

Invasive disease
Hepatitis
Colitis,
Pneumonia,
Etc, ...

INDIRECTS effects of CMV

Rejection
down
Graft survival

IF/TA
down

Arterial stenosis

↑↑↑
↑↑↑
↑↑

↑↑↓
↓↓↓

↑↑
↓
↑

↑

↑

↑

↑

↑

Patient survival

Opportunistic infections

PTLD
CMV AND ACUTE REJECTION: AN OLD DEBATE

**PRO:**


**CONTRA:**


**Drawbacks:**

- Retrospective studies
- Timing between CMV and acute rejection
- Interplay between these two major events in kidney transplantation
EFFECT OF CMV VIREMIA ON SUBCLINICAL ACUTE REJECTION AND IFTA

Patients and methods:
- 118 kidney transplant recipients with
  - Prophylactic treatment (VACV 3 months)
  - Preemptive treatment (VGCV)
  - Protocol biopsy at M3

Résults:
- DNAemia incidence: 41%
- Subclinical acute rejection: 29%
- IFTA: 28%

Subclinical acute rejection:
- Is not associated to DNAemia

IFTA
- Is associated to DNAemia > 2000 copies (OR: 3.8, p=0.02)

Reischig et al, Transplantation 2009; 87:436-444
SOME YEARS LATER... LATE EFFECTS OF A PREEMPTIVE TREATMENT

Patients:

- Preemptive (VGCV) : N=34
- Preventive (VACV 3 mois) : N=36

Better patient survival in the preemptive group

With less late-onset CMV infections

Trend to less IFTA in the preemptive group (19 % vs 38 %)

EFFECT ON DNAEMIA ON GRAFT DYSFUNCTION AT 2 YEARS

- N=55 pediatric kidney transplants
- 22% of subclinical CMV DNAemia during the first two years
- Prophylactic treatment for 3 à 12 months

More IFTA on protocol biopsies in viremic patients
Unless the prophylactic treatment

INDIRECT EFFECTS AT THE LIGHT OF ECOLOGICAL IMMUNOLOGY: CONCEPT OF TOLERANCE TO A PATHOGEN

For each individual, a CMV infection has a fitness cost:

- Damage caused by the pathogen: direct effects
- Damage caused by host immune system: indirect effects

Tolerance is the magnitude of these direct and indirect effects

In transplantation, immunosuppressive treatment can differently modulate the level of tolerance

Ruslan Medzhitov, Disease Tolerance as a Defense Strategy, Science, 2012, 335, 936
Ayres and Schneider, Tolerance of Infections, Ann Rev Immunol 2012, 30:271-294
SUMMARY:

1. Epidemiology in kidney transplantation
2. T cell response: $\alpha\beta$ and $\gamma\delta$ lymphocytes
4. Indirect effects: Clinical impact
5. Update on CMV guidelines
6. Perspectives
International consensus guidelines on the management of cytomegalovirus in solid organ transplantation

Transplantation Society International CMV Consensus Group. Transplantation. 2010 Apr 15;89(7):779-95
Update October 2012
Both universal prophylaxis and pre-emptive strategies are viable approaches for prevention of CMV disease (D+R- and R+).

For centers or patients unable to meet the stringent logistic requirements required with a pre-emptive therapy strategy, prophylaxis is preferred.

Where possible, 6 months may be preferable for D+/R- kidney recipients

When a prophylaxis strategy is used for prevention in R+ patients (with either D+ or D-), 3 months of antiviral medication should be used

When a pre-emptive therapy strategy is used, a sufficiently low threshold for initiation of treatment during pre-emptive therapy is recommended.
Anti-viral medications used in kidney transplant: valganciclovir, intravenous ganciclovir, or high dose valacyclovir.

Treatment of rejection (ALG, high dose steroids) should result in reinitiation of prophylaxis or pre-emptive therapy for 1 to 3 months

The routine use of the hybrid strategy is not recommended at this time in any risk group

Immune monitoring assays should continue to be improved for ease of use and standardization.
WHO international standard +++ (UI/ML)

Clinical studies on immune monitoring are required

Maribavir and new medications (letermovir, cyclopropavir, CMX001) useful in anti-viral resistance

Vaccines (anti-Gb), humanized anti-CMV antibodies

Modulation of immunosuppression: anti-viral effects of mTOR inhibitors.
MERCI POUR VOTRE ATTENTION