CMV vaccine: phase II trial results

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Published clinical vaccine trials in healthy adults (March 2013)

**Phase 1**
- Towne CMV live virus
- Canary pox vector/CMV pp65
- Canary pox vector/CMV gB
- CMV gB + MF59 adjuvant
- Live Towne/Toledo chimeric recombinant CMV
- Trivalent CMV DNA vaccine (gB, IE1, pp65)
- Bivalent CMV DNA vaccine (pp65, gB)
- Towne CMV live virus + rIL-12
- Pan HLA DR-binding epitope CMV pp65 fusion peptide
- Tetanus CMV pp65 fusion peptide

**Phase 2**
- CMV gB + MF59 adjuvant
Congenital CMV infection

- Most common congenital viral infection (birth prevalence, 0.6%)
- USA - 38,000 babies with congenital cytomegalovirus annually
  - 13% signs of infection at birth (neurologic)
  - 14% develop signs during the first 5 years of life (sensorineural hearing loss)

Modes of transmission in congenital CMV disease

- CMV⁻: Primary infection
- CMV⁺: Reinfection with new strain/reactivation of latent CMV infection

CMV end-organ diseases in immunocompromised patients

- Solid-organ transplant recipients
- Bone-marrow transplant recipients
- Advanced HIV-infection
- Inflammatory bowel disease (TNF-, Thiopurine, Corticosteroids)
- Critically ill patients

Sources: M Thurnher, M Häfner, I Ruhswurm-Dejaco (Medical University of Vienna)

Potential immunological targets for a CMV vaccine

- >20 immunogenic CMV proteins
  - Envelope (glycoproteins B, H, O, UL128C)
  - Non-structural (pp52 - DNA binding phosphoprotein)
  - Tegument (pp65, pUL32/pp150)

Inhibition of immunomodulation
- IL-10 (Logsdon et al. PlosOne2011)

Source: Dr. Reschke, Institute of Virology, Marburg, Germany
## Phase 2 clinical trials of CMV vaccines (March 2013)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Type</th>
<th>Sponsor/manufacturer</th>
<th>Study cohort</th>
<th>No. of subjects</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Towne</td>
<td>Live, attenuated</td>
<td>Pasteur-Merieux</td>
<td>Solid-organ transplant patients</td>
<td>61</td>
<td>Plotkin et al. Transplantation 1994</td>
</tr>
<tr>
<td>gB-MF59</td>
<td>Subunit (gB)</td>
<td>Sanofi-Pasteur (Chiron/Novartis)</td>
<td>Post-partum women</td>
<td>464</td>
<td>Pass et al. 2009</td>
</tr>
</tbody>
</table>
# Phase 2 clinical trial of gB-MF59 in postpartum women

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aim</strong></td>
<td>Prevention of maternal CMV infection between pregnancies</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Double-blind, randomized, placebo-controlled</td>
</tr>
</tbody>
</table>
| **Endpoints** | I°: Time to CMV infection  
II°: Rate of CMV infection, congenital CMV infection in offspring of the immunized women, decline in antibody levels over time |
| **Population** | Healthy, CMV-seronegative women (ages 14-40 years), postpartum |
| **Groups** | Group I: 20 µg gB + 13.25 mg MF59 (n=234)  
Group II: placebo (n=230) |
| **Schedule** | 0, 1, 6 months |
| **Follow-up** | 42 months |
| **Enrollment** | August 1999 – April 2006 |

because most susceptible during this time! infection from child
Dr. Christoph Steininger; 08.03.2013
Efficacy of gB-MF59 in postpartum women

- Vaccine efficacy – 50% (95% CI, 7 to 73)
- Rate of congenital CMV infection:
  Vaccine: 1/81 (1%) – Placebo: 3/97 (3%, P = 0.41)

Desired vs. minimum effectiveness of a CMV vaccine

- Vast majority of vaccines introduced in the EU market have efficacies of at >80%

Threshold analysis of vaccine efficacy

Sterilizing immunity assumed for prevention of congenital infection

Viral load vs. hearing threshold

Dempsey et al. Vaccine 2012; Broder et al. MMWR 2006; Bilukha et al. MMWR 2005; Lu et al. BMC Infectious Diseases 2011; Shepard et al. Pediatrics 2005
Changing pattern of CMV infection in industrialized nations

- Primary routes of transmission: perinatal and breast-feeding
- Formula feeding reduced infection rates in infants
  - 30%–50% of women of childbearing age in the United States and Europe are susceptible to CMV infection
  - <10% of women of childbearing age in developing countries are susceptible

Phase 2 clinical trial of gB-MF59 in solid-organ transplant patients

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<th>Parameter</th>
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<tr>
<td>Aim</td>
<td>Moderation of end-organ disease by vaccine-induced immunity</td>
</tr>
<tr>
<td>Design</td>
<td>Double-blind, randomized, placebo-controlled</td>
</tr>
</tbody>
</table>
| Endpoints | I°: Immunogenicity  
 II°: Reduction in incidence/quantity of CMV-DNA detection in blood, immune protection, persistence of vaccine-induced neutralizing antibody, CD8 and CD4 responses |
| Population| Adults awaiting liver or kidney transplantation |
| Groups    | Group I: 20 µg gB + 13.25 mg MF59 (n=67)  
 Group II: placebo (n=73) |
| Follow-up period | Median, 95 days post transplantation |
| Enrollment | August 2006 –October 2008 |
Study population of gB-MF59 trial in solid-organ transplant patients

<table>
<thead>
<tr>
<th></th>
<th>Vaccine group</th>
<th></th>
<th>Placebo group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CMV positive</td>
<td>CMV negative</td>
<td>CMV positive</td>
<td>CMV negative</td>
</tr>
<tr>
<td>No. of patients</td>
<td>32</td>
<td>35</td>
<td>38</td>
<td>35</td>
</tr>
<tr>
<td>No. of patients with TX</td>
<td>18</td>
<td>23</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Number of doses of vaccine or placebo received before transplantation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>2</td>
<td>9 (50%)</td>
<td>16 (70%)</td>
<td>8 (36%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>3</td>
<td>9 (50%)</td>
<td>6 (26%)</td>
<td>13 (59%)</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>Cytomegalovirus status of donor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>7 (39%)</td>
<td>11 (48%)</td>
<td>15 (68%)</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>Negative</td>
<td>11 (61%)</td>
<td>12 (52%)</td>
<td>7 (32%)</td>
<td>10 (67%)</td>
</tr>
</tbody>
</table>

Griffiths et al. Lancet 2011
Immunogenicity of gB-MF59 in solid-organ transplant patients

CMV-seronegative

CMV-seropositive

Griffiths et al. Lancet 2011
Efficacy of gB-MF59 in solid-organ transplant patients

No. of patients with viremia, 27 of 78

Griffiths et al. Lancet 2011
Phase 2 clinical trial of Transvax in bone-marrow transplant recipients

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<tr>
<td>Aim</td>
<td>Safety and efficacy of a CMV therapeutic DNA vaccine</td>
</tr>
<tr>
<td>Design</td>
<td>Double-blind, randomized, placebo-controlled</td>
</tr>
</tbody>
</table>
| Endpoints       | I°: rates of cytomegalovirus viraemia resulting in initiation of CMV-specific antiviral therapy  
                    II°: ELISPOT responses to pp65 & gB, gB titers,                       |
| Population      | CMV-seropositive bone-marrow transplant recipients                          |
| Groups          | Group I: Transvax 5 mg/ml + CRL1005 i.m. (n=40)                             
                    Group II: placebo (n=34)                                              |
| Schedule        | Day -5, 21-41, 84, 196 post transplantation                                 |
| Follow-up period| 365 days post transplantation                                              |
| Enrollment      | June 2006 – December 2011                                                  |

Kharfan-Dabaja et al. Lancet Infect Dis 2012
Immune response to Transvax

Kharfan-Dabaja et al.
Lancet Infect Dis 2012
Protection from CMV infection and disease by the use of Transvax

<table>
<thead>
<tr>
<th></th>
<th>Vaccine (n=40)</th>
<th>Placebo (n=34)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median no. of CMV episodes</td>
<td>0</td>
<td>1</td>
<td>0.017</td>
</tr>
<tr>
<td>CMV viraemia (≥500 copies per mL)</td>
<td>33%</td>
<td>62%</td>
<td>0.008</td>
</tr>
<tr>
<td>Viraemia-free rate at 1 year, %</td>
<td>65%</td>
<td>36%</td>
<td>0.014</td>
</tr>
<tr>
<td>CMV-associated disease</td>
<td>8%</td>
<td>9%</td>
<td>1.000</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>8%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>CMV pneumonia</td>
<td>3%</td>
<td>3%</td>
<td></td>
</tr>
</tbody>
</table>
Prophylactic strategies in solid-organ transplant patients

Preemptive Therapy

Av

PCR

Immuno-suppression

Antiviral

Av

PCR

Immu

suppression

Prophylaxis

CMV disease

AV

PCR

Immu

suppression

Months after Transplantation

0 1 2 3 4 5 6 7 8 9 10 11 12
Next generation CMV vaccine candidates

Cui et al. Vaccine 2008
Pentameric virion complex (UL128C)
Glycoproteins gH/gL, UL128, UL130 & UL131A

Thanks for your attention!