Correlation between humoral and cellular immune responses after hepatitis A vaccination in low and high responder vaccinees

Ursula Wiedermann, MD, PhD
Institute of Specific Prophylaxis and Tropical Medicine, Medical University Vienna
www.meduniwien.ac.at/tropenmedizin

Viral Hepatitis Prevention Board Meeting, Antwerpen, 12-13 March 2009
Low- or no-responsiveness

- Occurs in 2-10% of vaccinees after routine vaccination
- Non responder rate is particularly high (10%) among hepatitis B vaccinees
- Risk factors: age, gender, obesity, smoking, chronic diseases (diabetes, renal failure etc)
- Association with HLADRB1; HLADQB1
- Low/no responsiveness is only defined on the basis of antibody levels
- The mechanisms of non-responsiveness are largely unknown
Questions to be answered:

• Is there a correlation between humoral and cellular immune responses in low responders?
• Are there characteristic changes of cellular parameters in low responders?
• Is there a cellular prediction marker of non-responsiveness?
• Are there consequences for vaccination recommendation?
• Is the infection risk higher in low/no-responders?
• Is low/no- responsiveness a generell or antigen-specific phenomenon?
Persistence of seroprotection 10 years after primary hepatitis
A vaccination in an unselected study population

Pamela Rendi-Wagner\textsuperscript{a,b}, Maria Korinek\textsuperscript{a}, Birgit Winkler\textsuperscript{a}, Michael Kundi\textsuperscript{c},
Herwig Kollaritsch\textsuperscript{a,b}, Ursula Wiedermann\textsuperscript{a,b,*}

\textsuperscript{a} Department of Specific Prophylaxis and Tropical Medicine, Center for Physiology and Pathophysiology,
Medical University Vienna, Vienna, Austria
\textsuperscript{b} Center for Travel Medicine, Vienna, Austria
\textsuperscript{c} Institute of Environmental Health, Center for Public Health, Medical University Vienna, Vienna, Austria

Received 31 July 2006; received in revised form 25 August 2006; accepted 29 August 2006
Study Design

Study population:
1016 healthy female and male adults; no upper age limit
(≥15 years at the time of primary vaccination)

Vaccine:
Havrix® 720 El.U (GSK)
0, 1, 6-12 months (i.m)

Control of immune responses (serology):
January 2003 to April 2006

Serology:
- ELISA (Anti-HAV Elecsys, Roche, Institute of Virology, MUW)
- Enzygnost HAV-ELISA (Dade Behring; ISPTM)
- Anti-HAV Titer Cut-Off: 10mIU/ml
Distribution of antibody titers (n=1016)

**Graph:**
- X-axis: Anti HAV [mIU/ml]
- Y-axis: Frequency [%]
- Chart shows a distribution with a peak around 100 mIU/ml, with a cut-off at 11,400 mIU/ml.

*Rendi-Wagner, Vaccine 2007*
Study population

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Anti-HAV &lt; 11400 mIU/ml</th>
<th>Anti-HAV &gt;11400 mIU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>1016 (100)</td>
<td>796 (78,35)</td>
<td>203 (19,98)</td>
</tr>
<tr>
<td>Age</td>
<td>54,67 (+12,95)</td>
<td>52,51 (+13,17)</td>
<td>63,23 (+7,72)</td>
</tr>
<tr>
<td>Interval</td>
<td>9,9 (+0,81)</td>
<td>9,88 (+0,8)</td>
<td>10,09 (+0,81)</td>
</tr>
<tr>
<td>gender (f)</td>
<td>52,9</td>
<td>51,8</td>
<td>56,2</td>
</tr>
<tr>
<td>Smoker/n-smoker (%)*</td>
<td>9,94/50,6</td>
<td>10,3/48,49</td>
<td>9,35/60,1</td>
</tr>
<tr>
<td>BMI (+ SD) (n= 863)</td>
<td>25,31 (+4,15)</td>
<td>25,17 (+4,13)</td>
<td>25,41 (+3,53)</td>
</tr>
</tbody>
</table>
Age category of hepatitis A immune subjects due to infection (> 11400 mIU/ml; n = 203)

Rendi-Wagner, Vaccine 2007
Vaccine induced GMTs according to categories
(< 11400 mIU/ml, n = 796)

p < 0.001
p < 0.001
n.s.

Rendi-Wagner, Vaccine 2007
Vaccine induced, gender-specific GMTs 10 years after primary vaccination

After 10 years GMTs are far above protective range – New booster recommendation: 20 years!
Vaccine induced seroprotection rate (n= 813)

- >= 10mIU/ml: 98%
- < 10mIU/ml: 2%

Non-responder

Is non-responsiveness due to a decline of antibodies or due to an intrinsic inability to respond to hepatitis A antigen?

<table>
<thead>
<tr>
<th>SPR nach Alter (j)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 Jahre</td>
<td>98,1</td>
</tr>
<tr>
<td>&gt;50 Jahre</td>
<td>97,8</td>
</tr>
</tbody>
</table>

Rendi-Wagner, Vaccine 2007
Immunological characterization of Low/no responsiveness

3 Groups (n=52):
- GROUP 1 (n=10): < 20 IU/l
- GROUP 2 (n=26): 21 – 100 IU/l
- GROUP 3 (n=16): 101-1000 IU/l

Mean age:
- Group 1: 61.4 yrs
- Group 2: 63.3 yrs
- Group 3: 54.5 yrs

Booster with Havrix 1440

Blood pre and 7 days after booster
Detailed immunological characterization of low/no-responsiveness after hepatitis A vaccination

Correlation between humoral and cellular immune responses and the expression of the hepatitis A receptor HAVcr-1 on T cells after hepatitis A re-vaccination in high and low-responder vaccinees

Erika Garner-Spitzer\textsuperscript{a}, Michael Kundi\textsuperscript{b}, Pamela Rendi-Wagner\textsuperscript{a}, Birgit Winkler\textsuperscript{a}, Gerhard Wiedermann\textsuperscript{c}, Heidemarie Holzmann\textsuperscript{d}, Christian Herzog\textsuperscript{e}, Herwig Kollaritsch\textsuperscript{a,c}, Ursula Wiedermann\textsuperscript{a,c,*}
Humoral immune responses pre and post hepatitis A booster

Anti-HAV IgG

Garner-Spitzer et al, Vaccine 2009
Cellular immune responses pre and post hepatitis A booster

*PBMCs were stimulated with HAV antigen; Cytokine production measured in supernatants

Garner-Spitzer et al, Vaccine 2009
Changes in T cell surface marker expression after booster vaccination

CD4+CD25+ T-cells after booster vaccination

CD62L+ on T cells after booster vaccination

Interpretation: in an attempt to overcome non-responsiveness, new/naive T-cells are being activated

Garner-Spitzer et al, Vaccine 2009
Expression of the HAV receptor on T cells

HAV receptor as possible cellular prediction marker of non-responsiveness against hepatitis A?

HAV receptor expression is significantly lower on T cells of non-responder than on T cells of high responder

Garner-Spitzer et al, Vaccine 2009
### Summary of immune parameters in non- and higher responder vaccinees

<table>
<thead>
<tr>
<th></th>
<th>Anti-HAV Ig (IU/l)</th>
<th>HAVcr-1 Ratio</th>
<th>HAVcr-1/CD4 Ratio</th>
<th>IFNγ (pg/ml)</th>
<th>IL-2 (pg/ml)</th>
<th>IL-10 (pg/ml)</th>
<th>(%) CD4</th>
<th>% CD62L of CD4</th>
<th>% CD25 of CD4</th>
<th>%CD4/CD25high</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>Pre 7.2</td>
<td>0.42</td>
<td>10.35</td>
<td>7.6</td>
<td>0</td>
<td>31</td>
<td>41</td>
<td>24.5</td>
<td>43.9</td>
<td>4.54</td>
</tr>
<tr>
<td></td>
<td>Post 11.4</td>
<td>0.31</td>
<td>6.29</td>
<td>8.8</td>
<td>8.4</td>
<td>45</td>
<td>50</td>
<td>40</td>
<td>34</td>
<td>4.67</td>
</tr>
<tr>
<td>N2</td>
<td>Pre 0.1</td>
<td>0.13</td>
<td>6.51</td>
<td>2.08</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>20.9</td>
<td>31</td>
<td>3.23</td>
</tr>
<tr>
<td></td>
<td>Post 19.3</td>
<td>0.18</td>
<td>6.10</td>
<td>6.3</td>
<td>9</td>
<td>14</td>
<td>30</td>
<td>29</td>
<td>52</td>
<td>3.88</td>
</tr>
<tr>
<td>N3</td>
<td>Pre 0.1</td>
<td>0.34</td>
<td>9.79</td>
<td>0.9</td>
<td>2.2</td>
<td>15</td>
<td>34.6</td>
<td>21.6</td>
<td>12.6</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>Post 0.1</td>
<td>0.26</td>
<td>5.69</td>
<td>1.1</td>
<td>1.5</td>
<td>10</td>
<td>45</td>
<td>42.6</td>
<td>15.2</td>
<td>0.69</td>
</tr>
<tr>
<td>H1</td>
<td>Pre 555.9</td>
<td>2.24</td>
<td>55.88</td>
<td>248.5</td>
<td>7.5</td>
<td>10.6</td>
<td>40</td>
<td>45.0</td>
<td>60.0</td>
<td>1.51</td>
</tr>
<tr>
<td></td>
<td>Post 1031.0</td>
<td>1.79</td>
<td>41.25</td>
<td>3000</td>
<td>18.1</td>
<td>25.9</td>
<td>43.5</td>
<td>55.2</td>
<td>61.2</td>
<td>1.91</td>
</tr>
<tr>
<td>H2</td>
<td>Pre 598.5</td>
<td>1.24</td>
<td>21.49</td>
<td>830</td>
<td>92.5</td>
<td>68.0</td>
<td>57.7</td>
<td>33.7</td>
<td>53.4</td>
<td>3.76</td>
</tr>
<tr>
<td></td>
<td>Post 1115.0</td>
<td>0.91</td>
<td>17.98</td>
<td>831</td>
<td>43.9</td>
<td>63.9</td>
<td>50.6</td>
<td>37.4</td>
<td>51.5</td>
<td>3.84</td>
</tr>
<tr>
<td>H3</td>
<td>Pre 266.5</td>
<td>3.98</td>
<td>86.33</td>
<td>209.6</td>
<td>23.4</td>
<td>138.1</td>
<td>46.1</td>
<td>20.1</td>
<td>55.4</td>
<td>3.15</td>
</tr>
<tr>
<td></td>
<td>Post 1488.0</td>
<td>1.57</td>
<td>32.71</td>
<td>515</td>
<td>32.0</td>
<td>144.5</td>
<td>47.9</td>
<td>20.2</td>
<td>51.6</td>
<td>2.62</td>
</tr>
</tbody>
</table>

Garner-Spitzer et al, Vaccine 2009
Conclusions

• National recommendation for 20 year hepatitis A booster interval in Austria (travellers)
• A small, but significant, percentage of „real“ hepatitis A non-responder
• Routinely performed immune response evaluation is not necessary, but
• Risk populations (frequent travellers, health care professionals, travellers staying for prolonged time in endemic areas) should be carefully observed!
• The hepatitis A receptor might function as a cellular prediction marker of non-responsivens in risk populations