HBV preventive and therapeutic vaccines: What is new?

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Vaccine protection against hepatitis B

1st mechanism: immediate viral neutralisation
- Neutralizing antibodies anti-HBs "a" (> 10 mUI/ml) prevent initial infection
- Efficient if antibodies persist > 10 mUI/ml (chimp.)

2nd mechanism: Induction of CD4+ T helper response
- Activation of B lymphocytes secreting anti-HBs antibodies
- Activation or recall of memory B cell response

Exposure → Initial Replication → Acute Infection → Control of infection → recovery
- chronic Infection → Cirrhosis HCC
Impact of anti-hepatitis B vaccination: where we are 25 yrs later

• Decrease in the number of acute and fulminant hepatitis
  • $5.4/10^5$ (1975-1984) $>>$ $1.7/10^5$ (1985-1998) = 68% decrease in fulminant hepatitis in Taiwan
• Decrease in HBsAg prevalence and in HBV reservoir
• Decrease in hepatitis delta virus infections
• Decrease in mother-child transmission
• Decrease in the number of deaths related to cirrhosis and HCC
  • $0.7/10^5$ (1981-1986) $>>$ $0.36/10^5$ (1990-1994) $>>$ $0.16/10^5$ HCC in 6-14 yr old children in Taiwan

  Failure to prevent hepatocellular carcinoma results mostly from unsuccessful control of HBV infection transmitted by highly infectious mothers and/or from incomplete HBV vaccination.
Reduction of HCC in childhood by vaccination against HBV for infants born to HBV-carrier mothers (Japan)
Tajiri H et al., 2011

- Start 1986: 494 babies born to HBV-infected mothers vaccinated
- 93.5% protection efficacy
- HBV carrier rate decreased from 0.8% (1985) to 0.005% (2005)

<table>
<thead>
<tr>
<th>Period</th>
<th>HB cases</th>
<th>Total HCC</th>
<th>Ratio to HB</th>
<th>HBV+ HCC</th>
<th>Ratio to HB</th>
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<tbody>
<tr>
<td>1981-1985</td>
<td>124</td>
<td>20</td>
<td>0.161</td>
<td>11</td>
<td>0.089</td>
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<tr>
<td>1986-1990</td>
<td>119</td>
<td>25</td>
<td>(0-4yr)</td>
<td>10</td>
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<tr>
<td>1991-1995</td>
<td>147</td>
<td>22</td>
<td>(0-9yr)</td>
<td>9</td>
<td>0.061</td>
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<td>1996-2000</td>
<td>133</td>
<td>15</td>
<td>(0-14yr)</td>
<td>7</td>
<td>0.053</td>
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<td>2001-2005</td>
<td>133</td>
<td>8</td>
<td>(0-19yr)</td>
<td>1</td>
<td>0.008</td>
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<tr>
<td>2006-2008</td>
<td>84</td>
<td>5</td>
<td>(0-22yr)</td>
<td>0</td>
<td>0.000 (p&lt;0.0001)</td>
</tr>
</tbody>
</table>

incidence of HBV-HCC / hepatoblastoma (HB) among HCC (JCCR)
hepatitis B vaccination: Unresolved issues

• Decline in anti-HBs titers: Is a booster dose required?
  – No (countries with low HBV endemicity, subjects with low infection risk)
  – Yes (immunocompromised subjects & subjects with high risk to HBV exposure)

• Anamnestic effect of booster dose on a-HBs Ab: stimulation of memory B cells
  – Few significant breakthrough infections (Ni YH et al. Gastroenterology 2007)
  – Unusual clinical courses of HBV infection in previously vaccinated subjects: transient viremia and no biochemical hepatitis after infection resulting from sexual contact or blood transfusion (Stramer SL et al. NEJM 2011; Liu et al. J Hepatol 2006)

• Eliminating HBV through neonatal vaccination?
  – Overall post-vaccination HBsAg carrier rate <1%
  – HBsAg carrier rate 7-17% or occult HBV found in infants from mothers with high titer viremia (HBeAg+)
  – Administration of anti-viral agents (Lam, Tfv, Telb) to pregnant mothers
hepatitis B vaccination: Unresolved issues

- Emergence of HBV envelope mutants ? sG145R (*Lai MW Gastroenterology, 2012; Hsu HY JID 2010*)
- Non-responder to hepatitis B vaccine (a-HBs Ab response linked to HLA DRB1*0301, DRB1*07 )
- Hypo-responders (<100mIU/ml): additional vaccinations, double dose, ID injection, preS-antigens, bivalent vaccine (hepB/hepA), adjuvants (CpG, AS02…)
- Implementation of a multivalent vaccine in infants
- catch-up of adolescents (2 doses)
- is a “one shot” vaccine feasible?
HBV INFECTIONS: STRONG NEED FOR DEVELOPMENT OF NEW THERAPEUTIC INTERVENTIONS

Existing vaccine

Worldwide HBV chronic carriers
>350 Millions

Inactive carriers of HBsAg
HBV DNA < 2000 UI/ml
not treated

Peg-IFN-alpha successful in 30%
Side effects

Antiviral treatments

“e” Ag~ mutants increase

Lamivudine/ Adefovir therapy
Low rate of anti-HBe+
emergence of resistant virus

Entecavir/ Tenofovir therapy
Low rate of resistance
Persitence of cccDNA+
Low rate of HBsAg loss
Vaccine therapy in chronic HBV infection:

Rationale:

• HBV infection is successfully controlled by natural immune responses in #90% of individuals infected as adults

• resolution of chronic HBV infection can be achieved by bone marrow transplantation from an immune donor (Lau GK, Gastroenterology 2002)
Acute self-limited HBV infection: Co-ordinated immune responses

- HBV Infection = high viral replication ($10^{10}$ copies /ml) all hepatocytes are infected
- IFN-γ production by NK et NK T cells
- non cytolytic control of viral replication (IFN-γ / TNF-α)
- Strong multi-specific CD8 T cells
- Strong proliferation of CD4+ T cells
- HBV-specific CD8+ T recruited in liver
- Hepatic lysis = >ALT

(Rehermann Nat. Rev. Immunol., 2005)
Chronic HBV infection: uncontrolled viral replication and ongoing liver damage

Low frequency HBV-specific CD8 T-cell responses
- with exhausted phenotype (PD-1, CTLA-4)

Impaired IL-2/proliferation of T cells
- increase in Tregs and IL-10-secreting T cells

Impaired NK cell responses
(Bertoletti & Maini, Antiviral. Ther., 2010).
Vaccine therapy in chronic HBV infection:

Goals:

• To increase the strength of HBV-specific T cell responses to levels found in patients recovering from acute infection
• To increase or activate Innate immunity/ NK cells
• To restore functional HBV-specific T-cell responses able to control viral replication
• To prime HBV-specific T cells in the periphery and to target vaccine-activated T cells to liver avoiding liver immuno-pathology…
• To induce long term maintenance of activated T cells and their differentiation into memory T cells
Identifying patients with immunological profile for immune-therapy

1. Restoration of dysfunctional HBV-T cells
   - Decrease in viral or/and Antigen loads
   - Blocking inhibitory mechanisms in liver
     3. Blocking inhibitory mechanisms in liver
        a-PD-1 MoAb (MDX-1106)
        a-CTLA4 MoAb (ipilimumab)

2. Targeting the virus
   - Elimination of cccDNA (HDAC inh.)
   - Blocking HBsAg Secretion (NAPs)

3. Stimulating host-innate immunity
   - TLR stimulation
     GS-9620 (TLR-7)

4. Adapted from Grimm D et al.
Not all patients are susceptible to immunotherapy.

Select patients on the basis of:
- route of transmission
- age of HBV infection
- duration of infection or treatment.
- HBsAg level
- presence/absence of HBeAg.

<table>
<thead>
<tr>
<th>Immune tolerance</th>
<th>Immune clearance</th>
<th>Low replicative phase</th>
<th>Reactivation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg positive</td>
<td>HBeAg negative/ anti-HBe positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV-DNA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$10^9-10^{10}$ cp/mL</td>
<td>$10^7-10^8$ cp/mL</td>
<td>$&lt;10^4$ cp/mL</td>
<td>$&gt;10^5$ cp/mL</td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal/ mild Hep</td>
<td>Moderate/severe CH</td>
<td></td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>HBeAg positive</td>
<td>Inactive-carrier state CHB</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<10^4 cp/ml = <2000 IU/ml

Adapted from Fattovich.

Kennedy et al. Gastro, 2012
Restoration of dysfunctional HBV-T cells:
Inhibition of viral replication and decline in HBV Ags

Viral persistence in chronic HBV infection

Restoration of antiviral immunity and viral control

**NUC treatment**
- HBV DNA decrease
- Poor HBsAg+ HBeAg elimination

**Vaccine therapy**

**T cell defects**
- CTL -
- IFN-γ -/+ 
- TNF-α -
- IL-2 -
- Prolif. -/+ 

Poor viral control

**Stimulation of HBV-specific T cells in periphery**
- + Induction of α-HBs Ab

**Functional T cells**
- CTL ++
- IFN-γ ++
- TNF-α ++
- IL-2 ++
- Prolif. ++

Effective viral control
Vaccine therapy for chronic hepatitis B

Inducing strong specific CD4+ and CD8+ T cell responses

- peptide vaccines
- DNA vaccines
- viral vectors (MVA, AdenoV)
- prime-boost (DNA or protein + vv)
- HBV gene therapy
- +/- Cytokines (IFN-γ, IL-2, IL-12)
- +/- anti-virals

Inducing CD4+ T and B-cell responses a-HBs Ab

- Protein vaccines (HBsAg +HBcAg)+adj.
- HBsAg-Ab complexes

Inducing multi-specific T cells

- envelope (preS+S)
- core
- polymerase
- # HBV genotypes?
Blocking interactions between PD1 and/or CTLA-4 and theirs ligands

- α-PD-1 MoAb (MDX-1106) = phase I for HCV
- α-CTLA4 MoAb (ipilimumab) = effective immune response to tumors Phase III, melanoma

Expected effects:
- Proliferation
- Cytokine production
- CTL
- IFNγ/TNFα cytolyis

Exhausted CD8 T cell

Target all activated T cells, non-HBV specific T cell expansion,

Risks: auto-immunity (depending on the dose)

Consequence on T-cell homeostasis, not all HBV T-cell specificities are restored
Vaccine therapy in chronic HBV infection: What we learned from previous trials?

- To better define patients candidate for vaccine therapy
  - naive of treatment or recently NUC-treated patients
  - Mostly HBeAg+

- To restore functional T-cell responses able to control viral replication
  - by reducing viral load by NUC treatment (but no effect on HBsAg level)
  - by reducing viral antigen load by extra hepatic priming with protein vaccines?

- To improve the vaccine approach
  - by boosting T cell responses primed by DNA using viral vectors encoding HBV proteins?
  - by increasing diversify the T cell response (add core, pol)?

- To set up a less stringent read-out?
  - by increasing the time between last vaccine injection and stop of treatment

Michel ML et al. J. hepatol 2011
therapeutic vaccination

Unresolved issues

select patients?

NUC treatment

Immune active or reactivation phases

shortly after start of treatment

Block inhibitory factors

Vaccine route & schedule

To be improved

Not fully understood?