Immunotherapy of HBV vaccine

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Chronic infection with hepatitis B virus (HBV) affects 350 to 400 million individuals worldwide and is the leading cause of liver cirrhosis and hepatocellular carcinoma (HCC) worldwide.

More than 780,000 people die every year due to the consequences of hepatitis B (WHO 2014)
HBV Map

Na-Taurocholate Cotransporting Polypeptide (NTCP)
# HBV Vaccines

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Manufacturer</th>
<th>Envelope antigen</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma derived</td>
<td>Hepatavax-B® (Merck &amp; Co.)</td>
<td>SHBs</td>
<td>HBsAg, 5–40 μg/dose, licensed worldwide (not in use)</td>
</tr>
<tr>
<td></td>
<td>Hevac B® (Pasteur M., France)</td>
<td>SHBsAg, (± MHBs)</td>
<td>HBsAg, 5–20 μg/dose, licensed in France (not in use)</td>
</tr>
<tr>
<td></td>
<td>KGC® (Korea Green Cross)</td>
<td>SHBs</td>
<td>HBsAg, licensed in East Asia</td>
</tr>
<tr>
<td>Recombinant, yeast</td>
<td>RECOMBIVAX® HB (Merck &amp; Co., USA)</td>
<td>SHBs</td>
<td>HBsAg, small S, 2.5–10 μg/dose, licensed worldwide</td>
</tr>
<tr>
<td>derived</td>
<td>Engerix-B® (GSK, Belgium) Iran, Pasteur</td>
<td>SHBs³</td>
<td>HBsAg, small S, 10–20 μg/dose, licensed worldwide</td>
</tr>
<tr>
<td></td>
<td>TGP 943™ (Takeda Chem, Japan)</td>
<td>SHBs³, MHBs</td>
<td>HBsAg (small S, Pre-S2) 10 μg/dose, licensed in Japan</td>
</tr>
<tr>
<td>Recombinant, mammalian cell derived</td>
<td>Gen Hevac B® (Pasteur M., France)</td>
<td>SHBs, MHBs</td>
<td>HBsAg (S, Pre-S2), 20 μg/dose, licensed in France</td>
</tr>
<tr>
<td></td>
<td>AG-3™ (Hepagene™) (Medeva, UK)</td>
<td>SHBs, MHBs, LHBs</td>
<td>HBsAg, small S, Pre-S1, Pre-S2, 10–20 μg/dose, licensed worldwide</td>
</tr>
</tbody>
</table>

- SHBs-p24
- Contain non-glycosylated p24 and glycosylated gp27, gp33, gp36
- Contain non-glycosylated p24 and p39, and glycosylated gp27, gp33, gp36, gp42
HBV Vaccines

- All the Human hepatitis B vaccine, HBsAg gene expressed in the yeast *Saccharomyces cerevisiae*
- HBsAg of subtype adw, ayw, adr
- Vaccinated chimpanzees were totally protected when challenged intravenously with either homologous or heterologous subtype adw, adr and ayw virus of human serum source.
History of HBV vaccine in immunotherapy.
• Vaccine based on HBsAg, preS-1, preS2, HBcAg, X + IL12 result in Polyfunctional T-cell responses thus enhance synthesis of specific IFN-γ+, TNF-α+, and CD107a+ and are very important in preventing the HBV infection, capable to clear HBV and now used in immunotherapy of chronic HBV infection.

• CD8+ Cytotoxic T lymphocytes (CTLs) are crucial for eliminating hepatitis B virus (HBV)
CD8+ Cytotoxic T lymphocytes (CTLs) are crucial for eliminating hepatitis B virus (HBV)


• 1- S Pol- Paris, France

32 consecutive chronic HBsAg carriers with chronic hepatitis and detectable serum HBV DNA were given 3 standard injections of the GenHevac B® vaccine at 0, 1 and 2 months, then 6 months after the first injection, 12 patients (37.5%) had undetectable HBV DNA while 3 others showed significant decrease in HBV DNA titers. 8/15 responders received a standard course of α-interferon (5 MU thrice weekly subcutaneously for 4 months) and all still had undetectable HBV replication. By contrast, among 13/17 of non responders to vaccine who were given α-interferon, only 3 stopped HBV replication. In summary, serum HBV DNA disappeared in 18 of the 32 patients (53.1%) who were given vaccine therapy, with or without interferon. Vaccination was uneventful.

• Active immune therapy against HBV appears as efficient and less expensive than antiviral therapies in stopping HBV replication.

Kendal Yalcin et al, Turkey. Immunized 30 immune tolerant chronic HBV patients with three doses of rHEVAC (France) vaccine at 0, 1, 6 months. They found r-HB vaccine has no far effect in suppression of viral replication and in enhancing the rate of HBeAg seroconversion in immune tolerant patients. Based on these results, future approach for treatment of HBV in this patient population may include combination of potent antiviral agents29–32 and more efficient HBV-specific vaccines33 (e.g., pre-S1/pre-S2/S epitopes).

• Xiangming Li et al. Designed a DNA vaccine using pCI vector (Promega, Madison, WI, USA encoding multiple T cell epitopes four HBsAg CTL epitopes (S28–39, S198–209, S172–191 and S208–216). They found that it induced stronger CTL responses than the vaccine encoding the single antigen in Female BALB/c (H-2d), C57BL/6 (H-2b) . Interestingly, heat shock protein 70 as an adjuvant not only enhanced CTL response to the viral antigen but also overcame this epitope suppression. Furthermore, the polytope DNA vaccine resulted in a long-term down-regulation of hepatitis B virus surface antigen and inhibition of HBV DNA replication in a HBV transgenic mouse model. They indicate that it is practicable and feasible to design a DNA vaccine for chronic hepatitis B immunotherapy.
• Zeng Z, using a hepatitis B virus (HBV)-carrier mouse model, reported that IL-12-based vaccination therapy can efficiently reverse systemic tolerance toward HBV. HBV-carrier mice lost responsiveness to hepatitis B surface Ag (HBsAg) vaccination, and IL-12 alone could not reverse this liver-induced immune tolerance. However, after IL-12-based vaccination therapy, the majority of treated mice became HBsAg(-) in serum; hepatitis B core Ag was also undetectable in hepatocytes. HBV clearance was dependent on HBsAg vaccine-induced anti-HBV immunity. Further results showed that IL-12-based vaccination therapy strongly enhanced hepatic HBV-specific CD8(+) T cell responses, including proliferation and IFN-γ secretion. Conclusion, IL-12-based vaccination therapy may induce robust hepatic HBV-specific CD8(+) T cell responses, and facilitating the generation of HBsAg-specific humoral immunity; thus, this therapy may become a viable approach to treating patients with chronic hepatitis B.

vectors used in HBV vaccine Therapy

• Using DNA vaccine ,pVax vector encoding encoding HBsAg and HBcAg + IL-12(current study conducted in USA started 2015 finishing 2018)

• 1-Recombinant Yeast-Based Therapeutic Vaccine elicits HBV X, S, Core CorKing TH et al. (2014) A Whole Recombinant Yeast-Based Therapeutic Vaccine Elicits HBV X, S and core Specific T Cells in Mice and Activates Human T Cells Recognizing Epitopes Linked to Viral Clearance. PLoS ONE 9(7): e101904e King

• 2-recombinant vaccinia virus (Tiantan) containing the S+PreS1 fusion antigen (RVJSS1) combined with the HBV particle-like subunit vaccine Chen H, (2012) Optimisation of Prime–Boost Immunization in Mice Using Novel Protein-Based and Recombinant Vaccinia (Tiantan)-Based HBV Vaccine. PLoS ONE 7(9): e43730.

• 3-Vesicular Stomatitis Virus-Based Hepatitis B Virus Vaccine Vector

• Melissa A et al, A Vesicular Stomatitis Virus-Based Hepatitis B Virus Vaccine VectorProvides Protection against Challenge in a Single Dose JOURNAL OF VIROLOGY. 2010; 84,(15): 7513–7522

• 4- DNA vaccine pCI vector

• Xiangming Li A novel HBV DNA vaccine based on T cell epitopes and its potential therapeutic effect in HBV transgenic mice .International Immunology,2005;17(10): 1293–1302
Conclusion mentioned studies
They have designed yeast-based immunotherapy (Tarmogen) vaccine that expressed S, Core, X (X-S-Core). They found all the antigens can activate, Cytotoxic T Lymphocyte CD8+ to enhance synthesis of specific IFN-γ+, TNF-α+, and CD107a+ by CD8+ T and by CD4+ to produce IFN-γ IL12 result in Polyfunctional T-cell responses thus enhance synthesis of specific IFN-γ+, TNF-α+, and CD107a+
pVAX1 Vector

Invitrogen, USA
Trigrid delivery system
• Present research protocol using PVAX encoding HBsAg and HBcAg gene as HBV immunotherapy, USA, (2015-2018)

• Phase I Study of INO-1800 (DNA plasmids encoding HBsAg and HBcAg) With or Without INO-9112 (DNA plasmid encoding human interleukin 12) delivered by electroporation (EP) in Chronic Hepatitis B Subjects

Supported by NIH and Inovio Pharmaceuticals
Start: January 2015, Expected completion date: December 2018

The aimed to evaluate the safety, tolerability, and immunogenicity of dose combinations of INO-1800 (DNA plasmids encoding HBsAg and HBcAg) and INO-9112 (DNA plasmid encoding human interleukin 12) delivered by electroporation (EP) in 126 (one hundred twenty six) entecavir and/or tenofovir treated patients.
• Group A: (DNA plasmids encoding HBsAg and HBcAg) alone delivered by EP

Group B: (DNA plasmids encoding HBsAg and HBcAg) + INO-9112 (DNA plasmid encoding human interleukin 12) delivered by EP

Drug: Entecavir/Tenofovir
Composite outcome measure consisting of multiple measures, including:

1- Relationship between immunogenicity and antiviral response

2- Expression of individual markers potentially predictive of immunogenic and antiviral responses

Eligibility

Ages Eligible for Study: 18 Years to 65 Years (Adult)
Genders Eligible for Study: Both
INCLUSION CRITERIA:

• 1-Chronic Hepatitis B virus infection
2-Negative for Hepatitis A IgM, C, D and HIV
3-Liver biopsy, Fibroscan® or equivalent elastography-based test obtained within the past 6 months demonstrating liver disease without evidence of bridging fibrosis or cirrhosis
4-Positive for Hepatitis B surface antigen
5-Nucleos(t)ide treatment for at least 1 year with ongoing entecavir or tenofovir at randomization and for 3 months prior to randomization
6-HBV DNA <90 IU/mL for ≥6 months prior to randomization
7-ALT ≤1.5x upper limits of normal ULN from 2 measurements separated by at least 14 days during the 6 months prior to randomization and ALT at screening ≤1.5x ULN
8-AST, TBili, DBili, Alk Phos and albumin within normal range or judged to be not clinically significant by PI and medical monitor at screening
9-For men and women who are not postmenopausal [i.e. ≥ 12 months of non-therapy-induced amenorrhea, confirmed by follicle stimulating hormone (FSH), if not on hormone replacement] or surgically sterile (vasectomy in males or absence of ovaries and/or uterus in females) agreement to remain abstinent or use 1 highly effective or combined contraceptive methods that result in a failure rate of < 1% per year during the treatment period and at least through week 12 after last dose
EXCLUSION CRITERIA:

1- Pregnant or breastfeeding females
2- Positive serum pregnancy test at screening or positive urine pregnancy test at randomization
3- Use of topical corticosteroids at or near the intended administration site
4- Autoimmune disorders, transplant recipients, other immunosuppression including any concurrent condition requiring 5- the use of immunosuppressive/immunomodulating agents (eye drop-containing and infrequent inhaled corticosteroids are permissible)
5- Need for systemic antiviral treatment (other than ETV and/or TDF)
6- Documented history or other evidence of decompensated liver disease (e.g., ascites, bleeding from esophageal varices, Child-Pugh clinical classification B or C)
7- History of other evidence of a medical condition associated with chronic liver disease [e.g., hemochromatosis, autoimmune hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis (NASH), toxin exposure, thalassemia, etc.]
8- Documented history or other evidence of metabolic liver disease within 1yr of randomization
9- Abnormal renal function including serum creatinine >ULN (Upper limit of normal)
10- History of or suspicion of HCC
11- Screening alpha fetoprotein greater than 13 ng/mL
12- History of significant medical conditions [e.g., cardiac (including ventricular or supraventricular arrhythmias), renal disease, pulmonary, gastrointestinal, neurological]
13- Significant acute infection (e.g., influenza, local infection) or any other clinically significant illness within 2 weeks of randomization
14- Administration of any blood product within 3 mon of randomization
15- History of seizures (unless seizure free for 5yrs)
Thank You