Safety and Efficacy of a Candidate rHEV Vaccines

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**Candidate vaccine**

- Truncated capsid protein (aa 112-607) of Sar 55 strain of HEV (genotype 1)
- Produced w/ BVES in Sf-9 cells
- Purified by column chromatography
- 20 μg protein adsorbed to 0.5 mg alum (0.5 mL of saline)
- Pilot lot of vaccine
  - Protected non-human primates
  - Phase I dose range study in adults (USA) selected 20 μg dose
  - Phase II study confirmed safety, immunogenicity in adults in Nepal

1. Tsarev, Vaccine 1997
2. Safary, Intervirology 2001
3. Scott, Shrestha, unpublished data
Rationale for the study

- **Primary objective** → To evaluate the efficacy of the HEV candidate vaccine among healthy adults in Nepal

- **Why Nepal?**
  - Hepatitis E → public health research priority
  - Documented disease epidemiology
  - Medical infrastructure is in place to monitor the safety of subjects

- **Expected outcomes:**
  - Proof of concept
  - Further assessment of candidate vaccine’s safety
  - Information regarding anti-rHEV as a correlate of protection
  - Information regarding true burden of disease (from active surveillance)

Study design

- Population: healthy men and non-pregnant women, from Nepalese Army units in Kathmandu
  - Initial screening for anti-rHEV Ig < 2.5 WHO U/mL (presumed susceptible to hepatitis E)

- Randomized (1:1), double-blind
  - Vaccine (0, 1, 6 months)
  - Placebo (0.5 mg alum in saline; same schedule)

- Active surveillance for hepatitis E for ~ 2 years

- Reactogenicity and immunogenicity evaluated in a random subset

- Safety evaluated in all (spontaneous adverse events during 30 days after any dose and Serious Adverse Events during the entire study)
Clinical case definition: acute viral hepatitis

- **Jaundice or illness for at least 3 days** comprised of at least 3 symptoms:
  - fatigue, loss of appetite, abdominal discomfort, right upper quadrant pain, nausea, vomiting

AND

- **Peak ALT > 2.5 times** the upper limit of normal or peak **total bilirubin > 2 mg/dl**
Case definition and diagnostic algorithm

Consistent w/ clinical & lab-confirmed acute viral hepatitis

PCR for HEV RNA on acute specimens*

Possible Hep E, needs serological confirmation

Possible Hep E, needs serological confirmation

Not Hepatitis E

Any positive

* Acute specimens include 2 fecal specimens collected as soon after hospital admission as possible, and 4 serum specimens collected 0, 1, 2, and 4 weeks after hospital admission

Definite hepatitis E

IgM >100 WR U/ml

WRAIR HEV IgM test

or

WRAIR HEV Ig test

Ig >2500 WR U/ml

Ig <2500 WR U/ml

Not definite hepatitis E

IgM <100 WR U/ml and Ig <2500 WR U/ml

Not Hepatitis E

(rule-out probable hepatitis E, i.e. Total Ig >1000 WR U/ml)
Outcomes in the screened cohort

- 66.3% of 5323 screened considered susceptible with anti-rHEV Ig < 2.5 WHO U/mL
- This population is at high risk if exposed to HEV

Age of randomized cohort

<table>
<thead>
<tr>
<th>Gender</th>
<th>N</th>
<th>Mean age</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>8</td>
<td>29.6</td>
<td>10.07</td>
<td>20</td>
<td>47</td>
</tr>
<tr>
<td>M</td>
<td>1992</td>
<td>25.2</td>
<td>6.23</td>
<td>18</td>
<td>62</td>
</tr>
<tr>
<td>Total</td>
<td>2000</td>
<td>25.2</td>
<td>6.25</td>
<td>18</td>
<td>62</td>
</tr>
</tbody>
</table>
Outcomes in the randomized cohort

- Equal loss to follow-up
- 90% in per-protocol efficacy analysis
  - Exclusion only for incomplete vaccination
- DSMB reviewed 111 episodes of acute hepatitis
  - 87 had hepatitis E
  - 24 not hepatitis E
Cumulative hazard of hepatitis E (Total vaccinated cohort)

Placebo

Vaccine

No. at Risk
Placebo 1000 985 970 944 901 851 807 775 539 0
Vaccine 1000 986 972 948 924 905 864 851 577 2

Estimated as minus-log transformation of the Kaplan-Meier survival curve from receipt of dose 1

Median follow-up: 804 days from dose 1

Viral Hepatitis Prevention Board Mtg 12-13 Mar 2009
## Vaccine efficacy estimates

<table>
<thead>
<tr>
<th>Period of observation (endpoint category)</th>
<th>Vaccine</th>
<th>Placebo</th>
<th>Vaccine efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>No. in cohort</td>
<td>No. of Cases</td>
</tr>
<tr>
<td>From 14 days after dose 3 onwards (a priori primary endpoint)</td>
<td>3</td>
<td>898</td>
<td>66</td>
</tr>
<tr>
<td>From 14 days after dose 2 until dose 3 (a priori secondary endpoint)</td>
<td>1</td>
<td>960</td>
<td>7</td>
</tr>
<tr>
<td>From 14 days after dose 2 until 14 days after dose 3 (a posteriori secondary endpoint)</td>
<td>1</td>
<td>960</td>
<td>8**</td>
</tr>
<tr>
<td>From dose 1 onwards (exploratory endpoint)</td>
<td>9</td>
<td>1,000</td>
<td>78</td>
</tr>
</tbody>
</table>

Efficacy estimated as 1-relative risk, with the 95% confidence interval based on the Mantel Haenszel confidence interval for relative risk.
Antibody responses

![Graphs showing antibody responses](image)

- **Vaccines doses:**
  - Placebo
  - Vaccine
  - Positive cut-off

- **Chart:**
  - % Subjects with anti-HEV Ig
  - GMC of anti-HEV Ig (WHO U/mL)

- **Days:**
  - 0
  - 60
  - 180
  - 210
  - 720

Viral Hepatitis Prevention Board Mtg 12-13 Mar 2009
Reactogenicity (Days 0-7 in N=200, any dose)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Intensity *</th>
<th>Number and percent reporting indicated finding (95% CI for percent)</th>
<th>p-value **</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Vaccine (N=100)</td>
<td>Placebo (N=100)</td>
</tr>
<tr>
<td>Injection Site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>Any</td>
<td>82 (73.1, 89.0)</td>
<td>68 (57.9, 77.0)</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>1 (0, 5.4)</td>
<td>0 (0, 3.6)</td>
</tr>
<tr>
<td>Redness</td>
<td>Any</td>
<td>24 (16.0, 33.6)</td>
<td>19 (11.8, 28.1)</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>0 (0, 3.6)</td>
<td>0 (0, 3.6)</td>
</tr>
<tr>
<td>Swelling</td>
<td>Any</td>
<td>20 (12.7, 29.2)</td>
<td>17 (10.2, 25.8)</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>0 (0, 3.6)</td>
<td>0 (0, 3.6)</td>
</tr>
<tr>
<td>Systemic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Any</td>
<td>43 (33.1, 53.3)</td>
<td>47 (36.9, 57.2)</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>0 (0, 3.6)</td>
<td>0 (0, 3.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>Any</td>
<td>46 (36.0, 56.3)</td>
<td>46 (36.0, 56.3)</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>0 (0, 3.6)</td>
<td>0 (0, 3.6)</td>
</tr>
<tr>
<td>Fever</td>
<td>Any</td>
<td>30 (21.2, 40.0)</td>
<td>36 (26.6, 46.2)</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>1 (0, 5.4)</td>
<td>1 (0, 5.4)</td>
</tr>
</tbody>
</table>

* Grade 3 pain, headache or fatigue prevented normal activities; grade 3 redness or swelling had diameter >50 mm; grade 3 fever was temperature >39.0ºC  ** Two-sided Fisher’s exact test  *** Rate difference: 14.0 % (95% CI: 2.0 to 25.8 %)
Vaccine was well-tolerated and no safety signal was identified.
Summary

- This PoC study established the following:
  - rHEV antigen (BVES; aa 112-607; 20 mcg adsorbed to 0.5mg alum) offered 95% protection against hep E on a 3-dose schedule
  - Protection after 2 doses not determined (insufficient AR)
  - Vaccine elicited an immune response in all subjects; but seropositivity by indirect ELISA declined to ~50% at 800 days
    - During period of antibody decline → continuing protection, suggesting protective memory had been established
  - Vaccine was well-tolerated and no safety signal was identified
  - Antibody neg males in Nepal Army (18-62 yrs) were at sustained high risk for hepatitis E, confirming the potential benefit of vaccination vaccine
Acknowledgements

Supported by US Army Medical Research and Materiel Command, US NIAID, GSK Biologicals, 1999-2004

- **Walter Reed Army Inst of Research:**
  - MP Shrestha, RM Scott, MP Jr. Mammen, KSA Myint, RA Kuschner, SK Shrestha, J Seriwatana, DW Vaughn, TP Endy

- **Nepalese Army:**
  - DM Joshi, GB Thapa, N Tapa

- **GSK Biologicals:**
  - M Fourneau, MP David, A Safary, BL Innis