Status and Potential Role of Human Challenge/Protection studies

Anna P. Durbin, M.D.
Associate Professor
Center for Immunization Research
Department of International Health
Johns Hopkins Bloomberg School of Public Health
6 June 2016
Why a ZIKV human challenge model?

• Accelerate vaccine development
  - Down-select vaccine candidates prior to evaluation in endemic areas
  - Establish immune correlates?
  - Possible regulatory pathway in the face of decreased transmission

• Learn more about ZIKV
  - Duration of viremia
  - Duration of shedding in urine/semen/vaginal secretions
    • Infectious virus vs PCR-isolates
  - Effect of known pre-existing antibodies
Human challenge model experience

• Dengue human challenge model (DHCM) developed by scientists at NIH and JHU to better inform development of the NIH LATV dengue vaccine and to try to identify correlates of protection for dengue

• Parent strains used were initially chosen for dengue vaccine development
  - “naturally attenuated” – caused more mild disease in outbreak settings
  - Failed as vaccine candidates: were not attenuated in NHP compared to parent strain
Challenge strains manufactured under cGMP
First evaluated in small number of subjects (n=10 with 4 controls)
Goal was to induce reproducible clinical and virologic endpoints in high proportion of individuals without inducing dengue fever or severe dengue
Two DENV challenge strains have been evaluated at $10^3$ PFU
  - rDEN2Δ30
  - rDEN3Δ30
rDEN2Δ30 has been used as a challenge virus in 4 clinical trials
- Assess the protective efficacy of TV003
- Assess the protective efficacy of TV005
- Evaluate the role of heterotypic antibody to protection by administering a trivalent admixture then challenging
- Evaluate the clinical and immunological response to sequential heterologous DENV infection

rDEN3Δ30 will be used to assess the protective efficacy of TV005

There have not been any SAEs due to either challenge virus observed to date
Consistency of challenge strain rDEN2Δ30¹

<table>
<thead>
<tr>
<th>Clinical sign/symptom</th>
<th>rDEN2Δ30 (n=52)</th>
<th>Control (n=48)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viremia</td>
<td>52 (100%)</td>
<td>0 (0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fever</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>n/a</td>
</tr>
<tr>
<td>Rash</td>
<td>45 (87%)</td>
<td>0(0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Headache</td>
<td>22 (42%)</td>
<td>10 (21%)</td>
<td>0.0179</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>9 (17%)</td>
<td>0 (0)</td>
<td>0.0019</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>4 (8%)</td>
<td>1 (2%)</td>
<td>0.2071</td>
</tr>
<tr>
<td>Myalgia</td>
<td>12 (23%)</td>
<td>3 (6%)</td>
<td>0.0173</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6 (12%)</td>
<td>0 (0%)</td>
<td>0.0171</td>
</tr>
<tr>
<td>Retro-orbital pain</td>
<td>15 (29%)</td>
<td>0 (0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9 (4%)</td>
<td>0 (0)</td>
<td>0.2683</td>
</tr>
</tbody>
</table>

¹ Combined results from 3 clinical trials (CIR286, 287, & 299)
Selection of Zika human challenge strain

- Specimens from multiples patients with acute uncomplicated Zika virus infection have been received by the Laboratory of Infectious Diseases (LID) at the NIH
  - Nicaragua (4)
    - All from uncomplicated Zika cases
  - Brazil (4 - 6)
    - All from uncomplicated Zika cases

- Development of ZIKV challenge strain will follow DEN challenge development plan
Development of Zika human challenge

• Viruses will be recovered directly from primary serum samples using GLP-like processes

• Individual viruses will be evaluated for different characteristics *in vitro* and in NHP to choose strain for manufacture under cGMP
  - Growth characteristics in tissue culture
  - Sequence
  - Level of viremia in NHP

• 1 – 2 strains will be manufactured under cGMP for use as challenge strain
Challenge studies

• Candidate challenge virus will be evaluated in small number of subjects in a dose-ranging study
  - ~10 ZIKV recipients/4 controls
  - Start at $10^3$ PFU and escalate dose depending on incidence of viremia, level of viremia, incidence and severity of adverse events

• Studies to be conducted as inpatient studies

• Exclusion criteria to include partner who is pregnant

• All potential subjects will receive extensive education on pregnancy prevention and risks of sexual transmission
ZIKV challenge study

- Evaluation of challenge strain candidate will include collection of samples to evaluate the incidence, peak titer, and duration of ZIKV recovered from:
  - Blood
  - Urine
  - Semen
  - Vaginal secretions
  - Possibly saliva
- Samples will be tested for ZIKV by direct culture and by PCR
- GBS and other neurological adverse events will be collected as adverse events of special interest for duration of the study
Status of ZIKV challenge strains

• Isolates have been recovered from all 4 samples from Nicaragua under cGLP-like conditions at LID/NIH

• Serum samples were from Brazil were received last week and isolate-recovery is underway at LID/NIH

• Funding for ZIKV challenge strain development and evaluation has been committed

• Clinical trial of ZIKV challenge strain will likely begin Q4 2016
ZIKV vaccine-challenge studies

• The LID has plans to develop and manufacture multiple ZIKV candidates using its current platform DENV vaccine development
  - Δ30 mutation in the 3´ UTR
  - Chimerization (replacing the prM and E of rDEN Δ30 with those of ZIKV)

• The Vaccine Research Center (VRC) at the NIH is developing a DNA-based ZIKV candidate

• As early evaluation of efficacy, clinical evaluation of these candidates will include ZIKV challenge
**ZIKV challenge studies**

- Subjects would receive ZIKV vaccine as outpatients.
- LID ZIKV vaccine candidates are live attenuated viruses which would be given as a single dose.
- Challenge would be done 6 months post-vaccination.
  - Depending on clinical and virologic profile of challenge virus, challenge portion will be done either as an inpatient or an outpatients study.
- Challenge phase is also part of the VRC clinical development plan for the candidate ZIKV DNA vaccine.
- Initial vaccine evaluation and evaluation of challenge strains will be done in parallel.
Challenge of the challenge

• Clinical and virologic characteristics of the challenge virus will determine the ability to conduct challenge studies as outpatient studies
  - Risk of transmission by mosquitoes (*Aedes albopictus* common in Maryland, less common in Vermont)
  - Risk of sexual transmission

• Depending on length of shedding of ZIKV in semen, it may be difficult to keep subjects inpatient for the duration of the shedding period
Challenge of the challenge

• Guillain-Barre and adverse events of special concern
  - Risk possibly as high as 1 in 5,000 (likely lower than this)
  - How to minimize risk
    • Enroll younger subjects (< 35 years of age)
    • Exclude those with history of autoimmune disease, previous GBS
    • Provide care for those who experience adverse events
  - Continue to collect data on risk of GBS
  - Consult with bioethicists
Other considerations

• Long-term ZIKV vaccine development plan includes a pentavalent DENV/ZIKV vaccine
  - Plan to challenge recipients of pentavalent DENV/ZIKV vaccine

• Consider vaccination/challenge in flavivirus-experienced population