Passive Immunization with RSV F Vaccine-Induced Polyclonal Antibodies Protect Cotton Rats From RSV A Challenge

R. Raghunandan, G. Smith, L. Fries, B. Zhou, H. Lu, D. Flyer, G. M. Glenn, MD — Novavax, Inc., Rockville, MD

Abstract

Background: A candidate RSV F-protein nanoparticle vaccine has been evaluated in 3 human trials, towards development of a maternal vaccine to passively protect against RSV. High levels of palivizumab-competing antibodies (PCA) were observed in vaccine recipients1. Preclinical studies3 with the RSV A neutralizing titer (MN) of 400, and an flg l Specifies 2.4 x 104 and PCA equivalent of 844 µg/mL2. Female CRs 4-8 weeks of age were passively immunized with 0.4, 0.1 or 0.04 mL of vaccine-induced immune serum, 0.4 mL of pre-immune serum, or 1, 0.25, or 0.625 mg/kg of palivizumab, given IM. One day after, animals were challenged intranasally with 105 pfu of RSV A, Long strain. Lung samples were harvested on day 4 and homogenized for virus plaque assay.

Methods: RSV F-positive immune sera given IM at an 0.4 mL dose protected CRs against infection in the cotton rat model and human PK studies. In these studies trough levels of anti-F antibodies were detected in passively-treated CR sera pre-challenge, and 50 µg/mL PCA and MN of 30 were associated with ~2 log reduction in viral load were successful used as guide for efficacy testing. The RSV F nanoparticle vaccine has been evaluated in clinical studies and the induction of palivizumab competing antibodies (PCA) suggests that the vaccine may be effective. Evaluation of anti-a from immunized cotton rats and RSV F nanoparticle given passively in the challenge model presents an opportunity to test whether the RSV F nanoparticle vaccine-induced antibodies associated with protection and thus may be useful as a marker for protection in future efficacy studies.

Conclusions: Passive immunization with RSV F nanoparticle vaccine-induced polyclonal antibodies protected CRs from RSV challenge. PCA levels that were associated with ~2 log reduction in viral load were successful used as guide for efficacy testing. This study suggests that PCA induced by the RSV F nanoparticle vaccine completely inhibited viral replication in the lung.

Results:

- RSV continue to be a leading cause of respiratory illness related hospitalization in infants, children and the elderly. Passive prophylaxis using anti-F polyclonal and monoclonal antibodies has been shown to reduce disease severity and hospitalization in infants. A vaccine that generates similar immune responses may be effective in combating RSV disease.

- In clinical studies, the inactivated RSV F nanoparticles vaccine candidate has been shown to induce PCA to palivizumab antibodies. Similar responses are seen using the RSV F nanoparticles vaccine in cotton rats, which induce complete protective immunity to live viral challenge. The vaccine appears to be particularly effective in the induction of anti-F antibodies that compete with palivizumab, a site II (Asn 258-Val 278) binding monoclonal antibody, currently used in passive prophylaxis in infants.

- The RSV F nanoparticle vaccine is being developed in the context of maternal immunization, where placental transfer of antibody may protect young infants against severe RSV disease. The development of palivizumab was guided by the cotton rat model and human PK studies. In these studies trough levels of palivizumab at 25-30 µg/mL were successful used as guide for efficacy testing.

- The RSV F nanoparticle vaccine has been evaluated in clinical studies and the induction of palivizumab competing antibodies (PCA) suggests that the vaccine may be effective. Evaluation of anti-a from immunized cotton rats and RSV F nanoparticle given passively in the challenge model presents an opportunity to test whether the RSV F nanoparticle vaccine-induced antibodies associated with protection and thus may be useful as a marker for protection in future efficacy studies.

- This study suggests that PCA induced by the RSV F nanoparticle vaccine completely inhibited viral replication in the lung.

Study Objectives:

- To establish if passively administered anti-F antibodies could reconstitute active immunity in naive cotton rats.
- To establish if prophylactically administered anti-F antibodies could protect naive cotton rats against viral live viral challenge.
- To establish an inverse predictive response curve for anti-F passive prophylaxis in comparison to palivizumab.

Study Design:

Table 1: Palivizumab-competing and neutralizing antibodies and lung viral titers from cotton rats passively treated with vaccine-induced antibodies or Palivizumab

<table>
<thead>
<tr>
<th>Antibody Group</th>
<th>Lung Titer (Log2)</th>
<th>Palivizumab-Competing Antibody (Log2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-RSV F Serum (0.4 mL)</td>
<td>5.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Anti-RSV F Serum (0.4 mL)</td>
<td>5.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Palivizumab (5 mg/kg)</td>
<td>5.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Palivizumab (0.625 mg/kg)</td>
<td>5.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Palivizumab (0.04 mL)</td>
<td>5.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Phadoxin</td>
<td>5.2</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Table 2: Study Design

<table>
<thead>
<tr>
<th>Group</th>
<th>Antibody</th>
<th>Antibody Dose</th>
<th>Target Dose (µg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Anti-RSV F</td>
<td>0.4 mL</td>
<td>—</td>
</tr>
<tr>
<td>B</td>
<td>Anti-RSV F</td>
<td>0.1 mL</td>
<td>—</td>
</tr>
<tr>
<td>C</td>
<td>Anti-RSV F</td>
<td>0.04 mL</td>
<td>—</td>
</tr>
<tr>
<td>D</td>
<td>Palivizumab</td>
<td>—</td>
<td>5 mg/kg</td>
</tr>
<tr>
<td>E</td>
<td>Palivizumab</td>
<td>—</td>
<td>1.25 mg/kg</td>
</tr>
<tr>
<td>F</td>
<td>Palivizumab</td>
<td>—</td>
<td>0.625 mg/kg</td>
</tr>
<tr>
<td>G</td>
<td>Normal Cotton Rat Sera</td>
<td>0.15 mL</td>
<td>Negative Control</td>
</tr>
</tbody>
</table>

Figure 1: Study Design

Figure 2: Palivizumab Competing and MN Antibodies After Passive Immunization

Immunogenicity Results

Passive immunization with vaccine-induced anti-F polyclonal antibody resulted in measurable anti-F PCA, IgG and MN antibodies that were similar to those observed after palivizumab administration.

Figure 4: Protection in Lung

Challenge Results

Passive immunization with polyclonal sera from animals immunized with the RSV-F nanoparticle vaccine completely inhibited viral replication in the lung.

Conclusion: Passive immunization with 105 µL of polyclonal sera resulted in a 2.0 log reduction in lung viral load and was associated with a palivizumab-like antibody of 51 µg/mL and MN titer of 3.0 log2. Passive immunization with 50µg/ml palivizumab completely inhibited viral replication in the lung and was associated with a palivizumab-like antibody of 68 µg/mL and MN titer of 5.5 log2.

References:


RSV continues to be a leading cause of respiratory illness related hospitalization in infants, children and the elderly. Passive prophylaxis using anti-F polyclonal and monoclonal antibodies have been shown to reduce disease severity and hospitalization in infants. A vaccine that generates similar immune responses may be effective in combating RSV disease.

In clinical studies, the inactivated RSV F nanoparticles vaccine candidate has been shown to induce PCA to palivizumab antibodies. Similar responses are seen using the RSV F nanoparticles vaccine in cotton rats, which induce complete protective immunity to live viral challenge. The vaccine appears to be particularly effective in the induction of anti-F antibodies that compete with palivizumab, a site II (Asn 258-Val 278) binding monoclonal antibody, currently used in passive prophylaxis in infants.

The RSV F nanoparticle vaccine is being developed in the context of maternal immunization, where placental transfer of antibody may protect young infants against severe RSV disease. The development of palivizumab was guided by the cotton rat model and human PK studies. In these studies trough levels of palivizumab at 25-30 µg/mL were successful used as guide for efficacy testing.

The RSV F nanoparticle vaccine has been evaluated in clinical studies and the induction of palivizumab competing antibodies (PCA) suggests that the vaccine may be effective. Evaluation of anti-a from immunized cotton rats and RSV F nanoparticle given passively in the challenge model presents an opportunity to test whether the RSV F nanoparticle vaccine-induced antibodies associated with protection and thus may be useful as a marker for protection in future efficacy studies.

This study suggests that PCA induced by the RSV F nanoparticle vaccine completely inhibited viral replication in the lung.

Passive immunization with 105 µL of polyclonal sera resulted in a 2.0 log reduction in lung viral load and was associated with a palivizumab-like antibody of 51 µg/mL and MN titer of 3.0 log2. Passive immunization with 50µg/ml palivizumab completely inhibited viral replication in the lung and was associated with a palivizumab-like antibody of 68 µg/mL and MN titer of 5.5 log2.

References:
