Influenza Vaccine and Possible Neurological Complications: Intranasal Vaccines

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Overview of Presentation

• Cold-adapted, live, attenuated vaccine
  – Summary of Studies and Safety Results

• Virosomal vaccine with heat-labile toxin
  – Summary of published safety reports
Live, Attenuated Cold-Adapted Influenza Vaccine

- Developed in 1960’s by Dr. Maassab
- Cold adapted
  - serial passage in tissue culture at successively lower temperatures
  - will grow in the nose (32-35°C)
- Temperature sensitive
  - ceases replication at 37°C
- Induces local mucosal immunity
Production of CAIV from Master Strain

H3N2, wild

H2N2, CA

Tissue culture

H3N2, CA
CAIV Development

NIH studies 1976-
NIH / Wyeth 1991-93
NIH / Aviron 1995 – 2002
Medimmune 2002 - present
Randomized Controlled Trial of Inactivated and Cold-Adapted Vaccines for the Prevention of Influenza A

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Vanderbilt University
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Methods

• Randomized, controlled trial of cold-adapted and inactivated vaccines
• Subjects between ages of 1-65 years
• Safety and immunogenicity studied
• Subjects completed a vaccine reaction form to indicate any systemic or local symptoms for 5 days after vaccination
Results

• During the 5 years of the study, 5210 subjects participated in the trial and received a total of 12,500 doses of vaccine
• This included 791 children < 16 years of age who received 1,809 doses of vaccine
• Both cold adapted and inactivated vaccines were both well-tolerated with no serious adverse events noted
<table>
<thead>
<tr>
<th>Reaction</th>
<th>Control N=1738</th>
<th>CAIV N=1733</th>
<th>TIV N=1739</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt;38°</td>
<td>3.7</td>
<td>3.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Redness</td>
<td>8.3</td>
<td>7.8</td>
<td>10.5</td>
</tr>
<tr>
<td>Coryza</td>
<td>19.8</td>
<td>26.2</td>
<td>19.9</td>
</tr>
<tr>
<td>Lethargy</td>
<td>16.7</td>
<td>21.7</td>
<td>18.4</td>
</tr>
<tr>
<td>Myalgia</td>
<td>13.3</td>
<td>15.3</td>
<td>14.1</td>
</tr>
<tr>
<td>Cough</td>
<td>8.4</td>
<td>9.5</td>
<td>9.6</td>
</tr>
</tbody>
</table>
FluMist

• Influenza Virus Vaccine consisting of 3 strains of live, attenuated, cold-adapted, temperature-sensitive influenza viruses
• Each dose contains $10^7$ TCID$_{50}$ of each strain; two influenza A and one influenza B
## Number of Subjects Given FluMist

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>5963</td>
<td>3145</td>
<td>3323</td>
</tr>
<tr>
<td>5-8</td>
<td>4418</td>
<td>2643</td>
<td>1970</td>
</tr>
<tr>
<td>9-17</td>
<td>5903</td>
<td>1028</td>
<td>1371</td>
</tr>
<tr>
<td>18-49</td>
<td>3322</td>
<td>38</td>
<td>1495</td>
</tr>
<tr>
<td>50-64</td>
<td>511</td>
<td>0</td>
<td>209</td>
</tr>
<tr>
<td>&gt;65</td>
<td>111</td>
<td>0</td>
<td>101</td>
</tr>
<tr>
<td>Total</td>
<td>20,228</td>
<td>7354</td>
<td>8469</td>
</tr>
</tbody>
</table>
Studies Conducted with FluMist

- 20 studies submitted to the FDA
- 14 randomized, double-blinded, placebo controlled and 6 non-controlled studies
- For purposes of safety assessment, four trials will be summarized
  - AV019 Pediatric Safety Trial
  - AV012 Herd Immunity Trial
  - AV006 Pediatric Efficacy Trial
  - AV009 Adult Effectiveness Trial
AV019

- Randomized, double-blinded, placebo-controlled study of the safety of FluMist
- Healthy children (1-17 yrs); no asthma
- 2:1 randomization to FluMist or placebo
- Children < 9 years received 2 doses
- Medically attended events obtained from Northern California Kaiser database
AV019 Safety Methods

- No active monitoring for solicited reactions
- NCKP database searched for Serious Adverse Events (SAE) and Medically Attended Events (MAE)
- 9689 subjects (6473 FluMist, 3216 control)
  - 58% between 1-8 years
  - 42% between 9-17 years
## AV019 Results: % MAE by Setting

<table>
<thead>
<tr>
<th>Setting</th>
<th>FluMist N=6473</th>
<th>Placebo N=3216</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>ED</td>
<td>2.9</td>
<td>3.2</td>
</tr>
<tr>
<td>Clinic</td>
<td>35.6</td>
<td>37</td>
</tr>
</tbody>
</table>
AV019 Results: SAE

• No deaths reported
• 20 Severe Adverse Events reported- 0.02% in both vaccine and placebo groups
• Events included 11 hospitalizations, 6 psychiatric admissions, 1 ED, 1 clinic, 1 outpatient surgery
AV019 Neurologic Events

- No cases of encephalitis, encephalopathy, Guillain-Barre or Reye’s Syndrome, or other influenza-associated disorders
- 10 subjects (7 FluMist, 3 placebo) reported seizure events
- RR of seizures =1.16 (90% CI .38, 4.09)
AV012 Texas HMO Trial

- Open-label, non-randomized
- Subjects 18 mos-18 years of age
- History of mild asthma permitted
- Vaccine single dose each year
- Planned to assess herd immunity
- Safety monitoring was secondary
- 9549 doses administered to 7448 subjects
AV012 Safety Assessment

- Severe adverse events captured for 42 days after vaccination by postcards and database review
- No deaths reported
- 24 SAEs but 15 occurred after day 21
- Only 2 SAE related to CNS in first 21 days
  - 1 hospitalization for depression
  - 1 hospitalization for aseptic meningitis
• Phase 3 randomized, double-blind, placebo-controlled study in healthy children aged 15-71 months of age
• 2:1 randomization
• Year 1 enrolled 1602 subjects
• Year 2 enrolled 1358 subjects
• Efficacy of culture-confirmed influenza

% Post-vaccination Reactions in Children: AV006

<table>
<thead>
<tr>
<th></th>
<th>Dose 1</th>
<th></th>
<th>Dose 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FluMist</td>
<td>Control</td>
<td>FluMist</td>
<td>Control</td>
</tr>
<tr>
<td>Any rx</td>
<td>74</td>
<td>66</td>
<td>69</td>
<td>62</td>
</tr>
<tr>
<td>URI</td>
<td>59</td>
<td>48</td>
<td>51</td>
<td>46</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Fever ≥ 101°C</td>
<td>16</td>
<td>12</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>
AV009

- Phase 3 randomized, double-blind, placebo controlled study in 18-64 yr olds
- 2:1 randomization to FluMist or controls
- 4561 subjects enrolled in one year
- Endpoint was effectiveness in reducing influenza-like illness, absenteeism, health care utilization in adults

Nichol et al JAMA 1999;282:137-44
% Post-vaccination Reactions in Adults: AV009

<table>
<thead>
<tr>
<th></th>
<th>FluMist</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Rx</td>
<td>71</td>
<td>62</td>
</tr>
<tr>
<td>URI</td>
<td>44</td>
<td>27</td>
</tr>
<tr>
<td>Sore throat</td>
<td>27</td>
<td>16</td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Myalgia</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Fever $\geq 101^\circ \text{C}$</td>
<td>0.6</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Rare Adverse Events Seen in 20 Studies of FluMist

- No reported cases of encephalitis, encephalopathy, Guillain Barre, Reyes
- No increase in the Relative Risk for CNS events, including seizures following the receipt of FluMist
Nasalflu Berna: Intranasal Virosomal Influenza Vaccine

- Consists of influenza virosomes (small suspended spheres with a lipid bilayer) formulated to contain influenza hemagglutinin and neuraminidase from three contemporary influenza strains
- Vaccine contains E. coli heat-labile toxin as an adjuvant
- Safety studies conducted in 5400 subjects
Studies of Nasalflu

- Elicited both local and systemic immunity
- Well tolerated locally and systemically by most of the vaccinated subjects
- Four SAE seen during development
- One subject had hypotension after vaccine, possibly related to vaccine
Efficacy of Virosomes for Prevention of Acute Otitis in Children

- Children aged 1-5 years with history of recurrent acute otitis media enrolled
- Single center, prospective, randomized single blind study conducted in Italy in 1999-2000 influenza season
- Children randomly assigned to vaccine or placebo group
- Parents recorded local and systemic symptoms for 4 days after vaccination
<table>
<thead>
<tr>
<th>Local Events</th>
<th>After dose 1</th>
<th>After dose 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal irritation</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Sneezing</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>Stuffy nose</td>
<td>43</td>
<td>33</td>
</tr>
<tr>
<td>Runny nose</td>
<td>43</td>
<td>40</td>
</tr>
<tr>
<td>&gt; 1 local event</td>
<td>64</td>
<td>49</td>
</tr>
</tbody>
</table>

Marchiso et al. CID; 2002; 35: 168-74
<table>
<thead>
<tr>
<th>Systemic Event</th>
<th>After dose 1</th>
<th>After dose 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever $\geq 38.1^\circ$C</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Shivering</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Irritability</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Earache</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cough</td>
<td>43</td>
<td>28</td>
</tr>
<tr>
<td>$\geq 1$ event</td>
<td>54</td>
<td>49</td>
</tr>
</tbody>
</table>

Marchiso et al. CID; 2002; 35: 168-74
Summary

• Studies of cold-adapted, live, attenuated influenza vaccine in children and adults have not demonstrated a significant increase in adverse neurologic events in the subjects studied.

• Studies of virosome influenza vaccine with heat-labile toxin adjuvant have been less extensive.