Role of nasal IgA in children vaccinated with live attenuated influenza vaccine (LAIV)

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The First WHO Integrated Meeting on Development and Clinical Trials of Influenza Vaccines that Induce Broadly Protective and Long-Lasting Immune Responses

24-26 January 2013
Ann Arbor LAIV background

- Live attenuated influenza virus vaccine
- $10^{7.0\pm0.5}$ FFU of each strain/dose
- 0.2 mL intranasal spray (0.1 mL per nostril)
- Approved in multiple countries for eligible individuals 2-49 years
  - EU for 2-17 years only; Canada 2-59 years
- 65 million doses distributed since 2003
- No immunologic correlate of efficacy established
- 9 pediatric efficacy studies conducted during development
  - 6 placebo-controlled
  - 3 inactivated vaccine (IIV) controlled
Efficacy relative to placebo in children 2-7 years
5 Randomized Studies; Year 1 Efficacy, Matched Strains

Any strain: 87%
(95% CI: 83, 91)

A/H1N1: 87%
(95% CI: 78, 93)

A/H3N2: 86%
(95% CI: 79, 91)

B: 93%
(95% CI: 83, 97)

## Numerous assays evaluated in search for correlate of protection for LAIV

<table>
<thead>
<tr>
<th>Assay</th>
<th>Number of studies*</th>
<th>Evaluated in adults</th>
<th>Evaluated in children</th>
<th>Evaluated in efficacy study</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAI</td>
<td>34</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nasal IgA</td>
<td>9</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>IFN-γ ELISPOT</td>
<td>7</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum IgG</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Microneutralization</td>
<td>4</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>NAI</td>
<td>1</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Saliva IgA</td>
<td>1</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>mRNA transcription</td>
<td>1</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Other**</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*Studies sponsored by Aviron, Wyeth or MedImmune  ** Includes intracellular IFN-γ, cytotoxic T lymphocytes, lymphocyte subsets and serum IgM

HAI = hemagglutination inhibition; NAI = neuraminidase inhibition
Objectives of current analysis

- Describe strain-specific IgA responses observed in randomized, placebo-controlled clinical studies of LAIV in young children
- Examine relationship between IgA and the incidence of influenza illness
Study methods

◆ Studies: 3 randomized, 2-year, placebo-controlled studies
◆ Subjects: 6-35 months of age at enrollment, previously unvaccinated
◆ Dosing: 2 doses 1 month apart in year 1, 1 dose in year 2
  – Studies 1&2, year 1: vaccine/vaccine vs. pbo/pbo
  – Study 3, year 1: vaccine/vaccine vs. vaccine/pbo vs. pbo/pbo
◆ Nasal wash samples collected on subset (new cohort each year)
  – Before vaccination and 1 month after final dose
  – Total IgA and strain-specific IgA to A/H1N1, A/H3N2, and B vaccine strains determined by ELISA
    • Plates coated with purified influenza glycoproteins
Analysis methods

◆ Evaluated IgA responses in LAIV vs. placebo recipients

◆ Endpoints:
  – Ratios of strain-specific to total nasal IgA
  – Prevaccination to postvaccination geometric mean fold-rises (GMFRs)

◆ Relationship between IgA and influenza illness:
  – Mean postvaccination IgA ratios were compared for subjects with and without confirmed influenza illness by study and in pooled analyses
## Results: Available subjects

<table>
<thead>
<tr>
<th>Subjects, n</th>
<th>Study 1</th>
<th></th>
<th>Study 2</th>
<th></th>
<th>Study 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 1</td>
<td>Year 2</td>
<td>Year 1</td>
<td>Year 2</td>
<td>Year 1</td>
<td>Year 2</td>
</tr>
<tr>
<td>LAIV</td>
<td>107</td>
<td>94</td>
<td>64</td>
<td>24</td>
<td>226</td>
<td>528</td>
</tr>
<tr>
<td>Placebo</td>
<td>76</td>
<td>81</td>
<td>37</td>
<td>17</td>
<td>107</td>
<td>263</td>
</tr>
</tbody>
</table>

LAIV = live attenuated influenza vaccine.
Results: IgA responses, studies 1 and 2

Subjects with ≥ 2-fold rise in nasal IgA ratio, post dose 2

Percentage

**Study 1**

- Year 1
- Year 2

**Study 2**

- Year 1
- Year 2

* = p < 0.05

Ambrose et al, Vaccine 30:6794-6801, 2012
Results: IgA responses, study 3

Subjects with ≥ 2-fold rise in nasal IgA ratio, post each dose

Percentage

Study 3
Year 1: Dose 1

LAIV/LAIV
LAIV/Placebo
Placebo/Placebo

LAIV
Placebo

* = p < 0.05

Ambrose et al, Vaccine 30:6794-6801, 2012
Results: Additional findings on IgA responses

- When 4-fold responses were evaluated, similar but lower proportions were observed
  - High response rate in placebo subjects remained

- Postvaccination GMFRs:
  - Year 1: 1.4 to 6.2 for LAIV vs. 0.5 to 2.0 for placebo
  - Year 2: 1.2 to 4.6 for LAIV vs. 0.8 to 2.2 for placebo

- Similar responses in baseline seronegative and seropositive subjects by HAI

- Increases in total IgA were observed
  - Among LAIV and placebo recipients, total IgA increased from by 1.0- to 2.4-fold in year 1 and 0.7- to 1.2-fold in year 2.
  - In study 3, total IgA in year 1 prevaccination samples increased over calendar time (P = 0.002 by linear regression).
**IgA ratios higher among vaccinees without influenza illness compared to those with influenza**

Postvaccination strain-specific IgA ratio by incidence of culture confirmed influenza: LAIV recipients

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Subjects without any influenza</th>
<th>Subjects with vaccine-matched influenza</th>
<th>Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>IgA ratio</td>
<td>N</td>
<td>IgA ratio</td>
</tr>
<tr>
<td><strong>Year 1 pooled</strong></td>
<td>793</td>
<td>0.18</td>
<td>32</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Year 2 pooled</strong></td>
<td>1323</td>
<td>0.09</td>
<td>46</td>
<td>0.04</td>
</tr>
</tbody>
</table>

- By study and type/subtype, mean IgA ratios were consistently higher among LAIV recipients with no evidence of influenza illness

- No such trend was observed for placebo recipients

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Ambrose et al, Vaccine 30:6794-6801, 2012
Limitations

- Small size of the study cohorts
- Variability in nasal specimen collection
- Averaging of IgA ratios across studies can be problematic because of inter- and intra-study variation
  - However, conclusions of pooled analyses were supported by similar and consistent trends by study and type/subtype.
- Assay did not evaluate nasal IgM or IgG antibody, which can also contribute to mucosal immunity
Conclusions

◆ IgA can provide evidence of vaccine-induced immunity and appears to contribute to efficacy of LAIV
  – Postvaccination strain-specific IgA ratios consistently higher among those without influenza illness
  – IgA responses boosted with revaccination, consistent with clinical efficacy data
  – Heterogeneity in nasal antibody levels and nasal specimen collection hinders precise evaluation of mucosal responses
◆ Consistent with hypothesis that LAIV induces protection through local B-cell responses in the upper respiratory tract
◆ Studies have also demonstrated LAIV-induced protection is partially explained by T-cell immunity, serum antibody, and innate immunity
  – Consistent with multifaceted nature of immunity to wild-type influenza and other live virus vaccines
Thank you for your attention

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