HUMAN CHALLENGE STUDIES IN HEALTHY VOLUNTEERS: PRACTICAL CONSIDERATIONS AND OUTCOMES OF INFLUENZA TRIALS

J. K. MFOPOU, G. MEMOLI, H. PILLU, H. DE SWERT, P. DE COCK

Clinical Pharmacology Unit, Antwerp, Belgium
Influenza challenge studies in healthy volunteers

- Disease modeling ⇒ testing novel therapies.
- Synchronized disease onset ⇒ timed intervention
- Non seasonal influenza ⇒ "à volonté" ⇒ Clinical development

Optimal model: virulent species

- high infectivity - relevant symptoms
- no safety concerns
Optimal methods
- virus preparation and inoculation
- sample management and data analysis

Experience of SGS/CPU with influenza trials
- Viral Challenge Unit / CPU Antwerpen
- Challenge agents manufacturing project (CHAMP)
**METHODS**

- 2 influenza A challenge models investigated

<table>
<thead>
<tr>
<th>Immunity to challenge agent</th>
<th>H1N1 (Phase 2a)</th>
<th>H3N2 (Phase 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hemagglutination inhibition (HAI) ≤ 10</td>
<td>Microneutralisation (MNT) ≤ 20</td>
</tr>
<tr>
<td>Adventitious agents: day -2</td>
<td>Biofire FilmArray Respiratory Panel</td>
<td></td>
</tr>
<tr>
<td>Challenge agent inoculation</td>
<td>0.25 mL/nostril ($10^5$-$10^7$ TCID$_{50}$/mL)</td>
<td></td>
</tr>
<tr>
<td>ILI twice daily</td>
<td>Symptoms Score Card (SSC)</td>
<td></td>
</tr>
<tr>
<td>Nasal mucus weight</td>
<td>Tissue paper collection</td>
<td></td>
</tr>
<tr>
<td>Viral shedding in airways</td>
<td>Nasopharyngeal swabs: qPCR, qCulture</td>
<td></td>
</tr>
</tbody>
</table>

qPCR: quantitative polymerase chain reaction / qCulture: quantitative viral culture
METHODS

- Regulatory framework (CA, IEC, Biosafety)
- State of the art VCU: keep in / keep out ⇒ key to success
- Rescue medications
- Well-trained staff: data collection, sample manipulation
RESULTS

HAI - H1N1 study

<table>
<thead>
<tr>
<th>HAI titer</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>105</td>
<td>73%</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>143</td>
<td>58%</td>
</tr>
<tr>
<td>1000</td>
<td></td>
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</tr>
</tbody>
</table>

Screened subjects

MNT - H3N2 study

<table>
<thead>
<tr>
<th>MNT titer</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>130</td>
<td>85%</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>52</td>
<td>31%</td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Screened subjects

Screening HAI MNT

- H1N1 (HAI)
- H3N2 (MNT)
RESULTS

- Success rate 1st screen
  - 42% HAI
  - 71% MNT
  - No / Low Ab titer: likelihood symptoms development
RESULTS

- Inoculation
  - H1N1: Eppendorf pipette
  - H3N2: VaxINator device

- VaxINator device
  - sprays challenge agent
  - handy lock-system => 0.25 mL
  - much appreciated
RESULTS

- dose-dependent ILI observed 3 to 5 days post-inoculation
RESULTS

- dose-dependent viral loads

**H3N2 viral load in NPS**

**Viral shedding H3N2 culture**

**Viral shedding qPCR H3N2**
**RESULTS**

- **Concordant biology**

![Graphs showing C-Reactive Protein and Monocytes levels for low, mid, and high dose groups over time.](image-url)
RESULTS

- Segregation of Treated vs Placebo subjects by 3 methods
RESULTS

- Segregation of Treated vs Placebo subjects by biology (% abnormaly high)

Bar chart showing:
- Mono: absolute monocytes counts
- Mono/Leuco: monocytes to leucocytes ratio
- CRP: C-reactive protein

Legend:
- Blue: Treated
- Red: Placebo
Human challenge studies

- intensive processes
- close monitoring and optimal techniques
- delivery of reliable data

Both influenza trials provided expected outcomes while following standardized methods.

A new interventional H3N2 trial is currently initiated, and its recruitment is consistent with current data.
ACKNOWLEDGEMENTS

- Volunteers
- SGS/CPU staff (RO, CTA, CTN, CRC, PM, CRA, CRP)
- Sponsors
- Labs

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CLINICAL PHARMACOLOGY UNIT, ANTWERP, BELGIUM
RESULTS

MNT - H3N2 study

Screened subjects

MNT titer

n = 52
29%
n = 130
RESULTS

<table>
<thead>
<tr>
<th></th>
<th>VENTALEON</th>
<th>CHAMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success rate MNT</td>
<td>32.1%</td>
<td>70.4%</td>
</tr>
<tr>
<td>Failure rate MNT</td>
<td>67.9%</td>
<td>29.6%</td>
</tr>
<tr>
<td>MNT threshold</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Effect threshold swap on success rate MNT</td>
<td>+7 (+13%)</td>
<td>-18 (-10.5%)</td>
</tr>
</tbody>
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