Immunomodulatory Therapy for Severe Influenza
Going Beyond Antivirals

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Pharmacy Grand Rounds
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Objectives

• Review the mechanisms of benefit in using immune therapies for influenza virus

• Determine the role of immune therapies in the treatment of severe influenza

• Identify safety concerns of immune therapies
Influenza Virus

- Surface glycoproteins
  - Hemagglutinin
  - Neuraminidase

- Viral mutation
  - Genetic drift
  - Antigenic shift

- Airborne (droplet), surfaces
  - Inhalation
  - Mouth, nose by touch
Pathobiology
Respiratory Compromise

- Bronchial hyper-reactivity
- Distal airway obstruction
- Bacterial superinfection
- Severe alveolar inflammation
- Impaired diffusion capacity

Severe Influenza Disease

- Minor bronchiolar infection
  Normal lungs

- Diffuse pulmonary infection, ↑↑cytokines
  Alveolar hemorrhage

Question 1

• I am familiar with and have recommended the use of blood products and/or derived immunoglobulins in the treatment of infectious diseases
  • True
  • False
Immunotherapy
Immune Therapies

- Convalescent Plasma
- Intravenous Immunoglobulin
- Hyperimmune Globulin
Convalescent Plasma (CP)

- Whole blood collected from individuals suffering illness during the recovery phase
- Immunogenicity measured by hemagglutinin-inhibition (neutralizing antibody inhibition)
- Use dates back to the 1918 Spanish influenza pandemic
- Utilized in many other infectious diseases (Ebola, SARS coronavirus, RSV)

SARS = severe acute respiratory syndrome
RSV = respiratory syncytial virus

CP in H5N1

- 31 y/o healthy male
  - Fever, chills, cough, clear sputum
  - Large opacities left lower lung

- Tracheal aspirate PCR

- Convalescent plasma donor
  - A/chicken/Hong Kong/282/2006
  - >99% homology of hemagglutinin genes
  - Hemagglutinin inhibition, 1:80


PCR = polymerase chain reaction
CP in H5N1

Viral load (copies x 100/ml)

Temperature (°C)

Day

Symptom onset
Oseltamivir
Convalescent plasma

**Design**

- Prospective cohort (n = 93)

**Population**

- Deterioration despite optimal antiviral therapy
- ICU admission within 7d of symptom onset

**Exclusion**

- Minors
- Hypersensitivity to Ig or known IgA deficiency

**Intervention**

- Standard antiviral therapy **PLUS**
  - CP with HA inhibition titer ≥ 1:160 (n = 20)
  - No CP (n = 73)

HA = hemagglutinin

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2009 H1N1 Pandemic Results

- Demographics
  - Middle-aged
  - Minimal comorbidities

- Severity of illness
  - Mechanical ventilation (93%)
  - Stress dose steroids (41%)
  - ECMO (13%)

<table>
<thead>
<tr>
<th></th>
<th>Dead (n = 44)</th>
<th>Alive (n = 49)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convalescent Plasma</td>
<td>4 (9%)</td>
<td>16 (33%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>17 (40%)</td>
<td>8 (18%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

CP associated with reduced viral load and inflammatory markers

ECMO = extracorporeal membrane oxygenation

## CP Phase II

<table>
<thead>
<tr>
<th><strong>Design</strong></th>
<th>Multicenter, randomized, phase II (n = 98)</th>
</tr>
</thead>
</table>
| **Population** | • Severe Influenza  
  • Hypoxia (SaO₂ < 93%)  
  • Tachypnea (RR > 20 bpm) |
| **Exclusion** | • ABO-compatible CP not available or allergy  
  • Condition not able to tolerate 500cc fluid  
  • Influenza not primary reason for acute illness |
| **Intervention** | • Standard of care **PLUS**  
  • CP 2 units, HA inhibition titer ≥ 1:40 (n = 49)  
  • No CP (n = 49) |

HA = hemagglutinin

## CP Phase II Results

### Demographics
- Middle-aged
- Moderate comorbidities

### Severity of illness
- O₂ requirement (82%)
- ARDS (38%)
- ICU admission (58%)

<table>
<thead>
<tr>
<th></th>
<th>CP (n = 49)</th>
<th>No CP (n = 49)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dismiss home without home health</td>
<td>21 (50%)</td>
<td>14 (33%)</td>
<td>0.029</td>
</tr>
<tr>
<td>Not hospitalized, resume normal activities</td>
<td>17 (40%)</td>
<td>8 (18%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

No differences in ICU admission, ICU or hospital LOS, need for supplemental O₂, mechanical ventilation, or adverse events

ARDS = acute respiratory distress syndrome
LOS = length of stay
Early Administration

Limitations

• Underpowered, un-blinded
• Non-pandemic setting
• Both groups received neuraminidase inhibitors
• Variability in hemagglutinin inhibition of plasma
  • Effects of hemagglutinin inhibition unknown
  • Effective titer/dose unknown
• Did not evaluate bacterial super-infection
Safety Considerations

Convalescent Plasma

Transfusion reactions

Transfusion-related lung injury

Antibody-dependent enhancement

Blood borne infections

Thromboembolism

Volume expansion

Intravenous Immunoglobulin (IVIg)

• Pooled serum IgG from thousands of donors

• Initially thought to contain anti-influenza antibodies

• Found to have protective effects independent of hemagglutinin inhibition
  • Large amounts of carbohydrate-binding antibodies
  • Sialylated antibody decoys

IVIg in H1N1

- 59 y/o healthy male
  - High-grade fever, sore throat, fatigue

Day 1
Antibiotics for pneumonia

Day 3
Worsening, required intubation
Oseltamivir started

Day 6
↑ventilatory requirements
IVIg 0.4 gm/kg x 5d

Day 8
↓ventilatory requirements

Day 14
Extubated

Cross-Reactive Neutralizing Antibodies

**IVIg concentration (g/dL)**

**Geometric Mean Titer**

**One Dose**

**MN titer**

**HA titer**

**Two Doses**

**MN titer**

**HA titer**

MN = microneutralization
HA = hemagglutinin

Hyperimmune Globulin (hIVIg)

- Polyclonal antibodies obtained from vaccinated patients or those recovered from disease
  - Usually fractionated from convalescent blood products
- High-titer hemagglutinin antibodies
- Frequently used in other viral diseases (e.g., cytomegalovirus globulin)
# hIVIg During H1N1 2009 Pandemic

<table>
<thead>
<tr>
<th>Design</th>
<th>Multicenter, randomized, double-blind (n = 34)</th>
</tr>
</thead>
</table>
| **Population** | • Deterioration despite standard of care (antiviral)  
• ICU admission & positive pressure ventilation  
  • Within 7d of symptom onset |
| **Exclusion** | • Minors  
• Hypersensitivity to Ig or known IgA deficiency  
• Moribund |
| **Intervention** | • hIVIg 0.4 gm/kg, HA antibody titer 1:640 (n = 17)  
• IVIg 0.4 gm/kg, HA antibody titer ≤ 1:20 (n = 17) |
2009 H1N1 Pandemic Results

- **Demographics**
  - Middle-aged
  - Minimal comorbidities

- **Severity of illness**
  - Mechanical ventilation (94%)
  - ECMO (35%)

Viral Load (log_{10} copies/cc)

- **Day 5**
  - IVIg: p = 0.04
  - hIVIg: p = 0.02

- **Day 7**
  - IVIg: p = 0.02

Survival

- **p = 0.02**

Limitations

• Small sample size
• Many excluded for late ICU admission
• No report of adverse reactions
• Long-term outcomes unknown
• Ideal dosage of hIVIg not determined
• Immune response not measured
INSIGHT FLU Group

- Pharmacokinetic analysis of evolution of HA inhibition antibody titer with hIVIg (n = 31)
  - hIVIg 0.25 gm/kg vs. placebo
  - 3 different strains/titers (1:640, 1:320, 1:160)

rGMT = reciprocal geometric mean

*significant, no p-value
IVIg Safety Considerations

- Infusion-related reactions
- Acute kidney injury
- Anaphylaxis
- Hemolytic anemia
- Thromboembolism
Question 2

Which of the following is NOT a proposed mechanism of immune therapies in treating influenza disease?

A. Prevent release of newly formed virions
B. Inhibit activating proteases
C. Direct damage to viral RNA
D. Inhibit viral fusion and internalization
E. Block binding to sialic acid receptors
Convalescent Plasma

- Greatest experience in influenza
- Potentially best option during a pandemic
  - Issues with blood products
  - Type & crossmatch required

Ongoing trials

- Demonstrated immune response
- Most time consuming production
- Potentially dangerous for laboratory personnel

**HAI****

Quicker availability

- Readily available
- Well-known safety profile
- Benefit extrapolated from theoretical mechanisms

↑↑IgG

Hyperimmune Globulin

Quicker availability

- Readily available
- Well-known safety profile
- Benefit extrapolated from theoretical mechanisms

Intravenous Immunoglobulin

HAI = hemagglutinin inhibition

**** = Not compared as monotherapy
Should We Use Them?

• Proposed mechanisms suggest benefit in severe disease
  • Limited scope experiences show potential benefit in varying outcomes

• May be most attractive for pandemic scenario resulting from new mutant strains
  • Convalescent plasma may be most realistic

• Infrastructure to operationalize may be biggest challenge moving forward
Question 3

- Which of the following are safety concerns with the use of convalescent blood products?
  A. Thromboembolic disease
  B. Blood borne infection
  C. Transfusion-related lung injury
  D. Volume overload
  E. All of the above
Conclusion

- Immune therapies may provide multifactorial benefit for treating influenza disease
- Immunomodulatory therapies are potentially a viable therapeutic option for severe influenza in a pandemic situation
- Limited safety data exist for immune therapies in influenza and must be extrapolated from other indications
“The worst pandemic in modern history was the Spanish flu of 1918, which killed tens of millions of people. Today, with how interconnected the world is, it would spread faster.”

*Bill Gates, 2014*
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